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Research article

Detecting normal pediatric brain development with diffusional kurtosis imaging

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ABSTRACT

Purpose: To characterise the pattern of change of diffusional kurtosis imaging (DKI) parameters (including kurtosis and diffusion parameters) in both white matter and gray matter in normal brain development with a large sample of subjects from term-born neonates to 14-years old children.

Methods: Two hundred and eighteen normal children (136 male, 82 female) underwent conventional magnetic resonance imaging and DKI. Regions of interest (ROIs) were placed in 7 white matter areas and 4 gray matter areas. Then the DKI-derived parameters were automatically calculated, including fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (Da), radial diffusivity (Dr), mean kurtosis (MK), axial kurtosis (Ka) and radial kurtosis (Kr). The correlation between the DKI parameters and ages were analyzed using nonlinear fit, and the rate of parameter change was computed compared to the baseline value of the neonates.

Results: For all ROIs in the white matter and gray matter, the FA, MK, Kr, Ka values increased with age, while the MD and Dr values decreased with age. The correlations were good to excellent, which changed rapidly within the first 2 years and relatively slowly after 2 years. The Da values in peripheral white matters and some gray matter structures (caudate nucleus and putamen) decreased with age. The amplitude of kurtosis parameters variation was greater than that of the diffusion parameters in both white matter and gray matter.

Conclusions: The DKI parameters correlated well with age, and kurtosis parameters showed a potential advantage in detecting the normal brain development of children.

1. Introduction

Magnetic resonance imaging (MRI) has become a standard imaging technique to assess the brain development of children due to its outstanding ability to provide high resolution brain images noninvasively [1–6]. Normal brain maturation in childhood is accompanied by gradually reduced water content and increased density of large molecules such as myelin [6,7], which change the signal of T1WI and T2WI that can be observed by the naked eye. Moreover, these microstructure changes can be measured quantitatively and assessed more objectively with functional magnetic resonance imaging.

The diffuse freedom of water molecules is influenced by axon growth, myelination development and change of axon membrane permeability [5]. The water distribution of diffusion tensor imaging (DTI) is based on the Gaussian dispersion model, calculating the water molecular diffusion along at least 6 different directions [8]. The main DTI parameters include the apparent diffusion coefficient (ADC) and fractional anisotropy (FA). The increased density of the cell membrane, interstitial cells and axons of myelination during brain maturation result in a decline in the ADC values and a rise in the FA values of the white matter. Multiple DTI studies [9–19] have reported non-linear increases in FA and decreases in diffusivities, especially during the first two years of life, consistent with the asynchrony maturation of myelination of the fiber bundles. However, the complexity of the biological tissue microstructure, especially the myelin package around axons, makes free water molecule diffusivity deviate away from the Gaussian distribution [20], thus limiting the theoretical sensitivity and accuracy of DTI measurement.

Diffusional kurtosis imaging (DKI) is an extension of DTI, which is based on non-Gaussian characteristics and can be used to assess the

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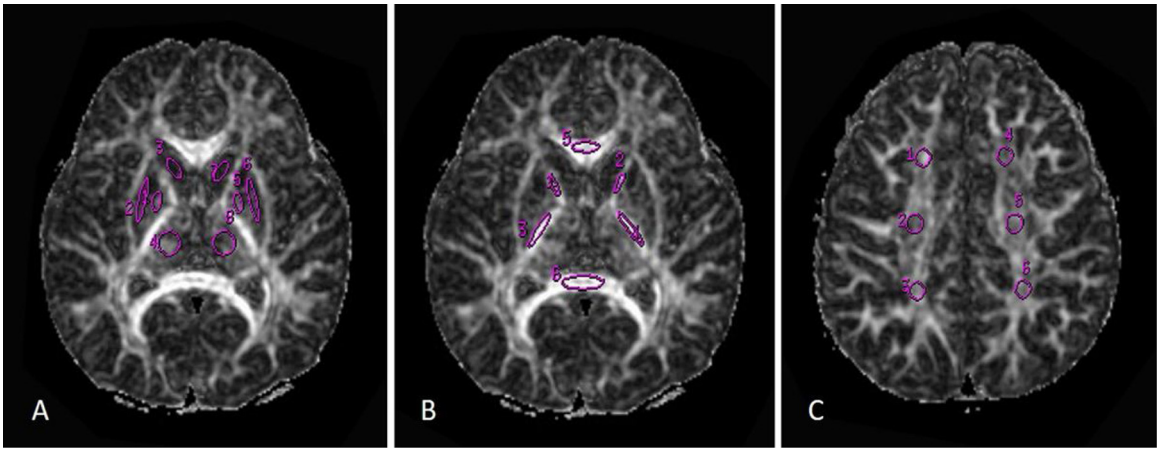

Fig. 1. A, Gray matter areas; B, Central white matter areas; C, Peripheral white matter areas.

complex changes within the microenvironment [21–23]. DKI is gradually being applied to human brain development. An initial DKI study of the developing brain from newborns to age 4.5 years reveals the changing pattern of FA and mean kurtosis (MK) values, MK values rise to a plateau at a later age than FA in all studied white matter areas, thus indicating further development of isotropic diffusion barriers [24]. Another recent study investigates how DKI-derived parameters change between childhood (average age 10.3 years) and middle adult age (average age 54.3 years), and unravels developmental differences in major association fibres, such as the cingulum and superior longitudinal fasciculus [25]. Other studies demonstrate kurtosis parameters show higher sensitivity than DTI parameters in preschool children or adults [26–30]. These studies have preliminarily confirmed the feasibility and application value of DKI in brain development, but the literature lacks a large sample evaluation from the neonatal to the adolescent period.

The purpose of this study is to assess the changing pattern of DKI parameters (including kurtosis and diffusion parameters) in both white matter and gray matter in normal brain development with a large sample of subjects from term-born neonates to 14-year old children.

2. Methods

2.1. Subjects

Two hundred and eighteen normal children (136 male, range from 2 days to 14 years old) were consecutively enrolled in our study from November 2014 to May 2016 in Wuhan Children's Hospital. These subjects had no central nervous system disease, and mainly attended hospital for the treatment of oculopathy, neck hemangioma, facial paralysis, etc. The informed consents were obtained from their parents before the examination, and this research was approved by the Women and Children Health Care Center ethics committee in Wuhan city. All the subjects had normal brain MRI examinations. These cases could be divided into 8 groups according to the age range: group 1 for 2days–28days as term newborn group (N = 24); Group 2 for 1month–1y group (N = 40); Group 3 for 1y–2y group (N = 35); Group 4 for 2y–3y group (N = 20); Group 5 for 3y–4y group (N = 17) ; Group 6 for 4y–5y group (N = 11); Group 7 for 5y–6y group (N = 13); Group 8 for 6y–14y group (N = 58).

2.2. Image acquisition

The children underwent MR scan after natural sleep or after oral sedation with 6% chloral hydrate (0.2 ml/kg). The conventional T1-FLAIR, T2, T2-FLAIR and DKI were performed in a 3 T scanner (Discovery 750, General Electric Medical System, USA) with an 8-channel head coil. Medical cotton ball and spongy pads were used for hearing protection and motion artifact prevention. DKI was carried out by 15 directions, number of excitation = 2, TR/TE = 4800/92.9 ms, slice thickness = 3 mm, slice space = 0, field of view = 240 × 240 mm^2, matrix = 128 × 128 (voxel size = 1.9 × 1.9 × 3 mm^3), b value = 0, 1000, 2000 s/mm^2. DKI scan time: 6 min 29 s. Conventional MR data were obtained with the following imaging parameters: T1 Flair (TR/TE = 1750/24 ms), T2 (TR/TE = 7859/96 ms) and T2 Flair (TR/TE ms = 8000/140). The total scanning time is approximately 15 min.

2.3. Data analysis

The post processing of DKI data was performed on an ADW 4.6 Function Tool off-line workstation, with well-established algorithms in a package according to previous studies [21,31,32]. All images were reviewed to avoid significant distortion by an experienced pediatric radiologist prior to the voxel-by-voxel calculation of DKI data. Regions of interest were defined on FA images and then transferred to the anatomically co-registered mean diffusivity (MD), axial diffusivity (Da), radial diffusivity (Dr), mean kurtosis (MK), axial kurtosis (Ka) and radial kurtosis (Kr) images in each subject. Regions of interest (ROI, Fig. 1) were placed by two professional pediatric radiologists separately, in both gray and white matter structures bilaterally on the transverse section through the level of the basal ganglia and the centrum semiovale, including: Gray matter areas [head of caudate nucleus (CN); globus pallidus (GP); putamen (PUT); the thalamus (TH)]; Central white matter areas [posterior limbs of internal capsule (PLIC); anterior limbs of internal capsule (ALIC); splenium of the corpus callosum (SCC); genu of the corpus callosum (GCC)]; Peripheral white matter areas [frontal white matter (FWM), parietal white matter (PWM), central white matter (CWM) of the centrum semiovale level]. The sizes of ROIs were ranged from 10-120mm^2 according to age and position size, and were kept identical for the symmetrical ones. All analyses were performed using SPSS 18.0 software (SPSS for Windows, Chicago III) with a 5% significance level. Each value of DKI parameter for one anatomical structure was calculated by averaging the values of both symmetrical ROIs for further analysis. Two researchers did the measurement separately blind to the clinical data, and the results were tested using intra-class correlation (ICC) analysis. The relationships between DKI-derived parameters and age were obtained using non-linear logarithmic fit, and the formula was $Y = b0 + b1 * \ln X$. We assumed the DKI parameter values of the neonatal group as the baseline value, and the rate of parameter change between each age group was computed by $P_{rate} = (P_{group} - P_{baseline})/P_{baseline}$.

3. Result

The two datasets measured by the two observers demonstrated good

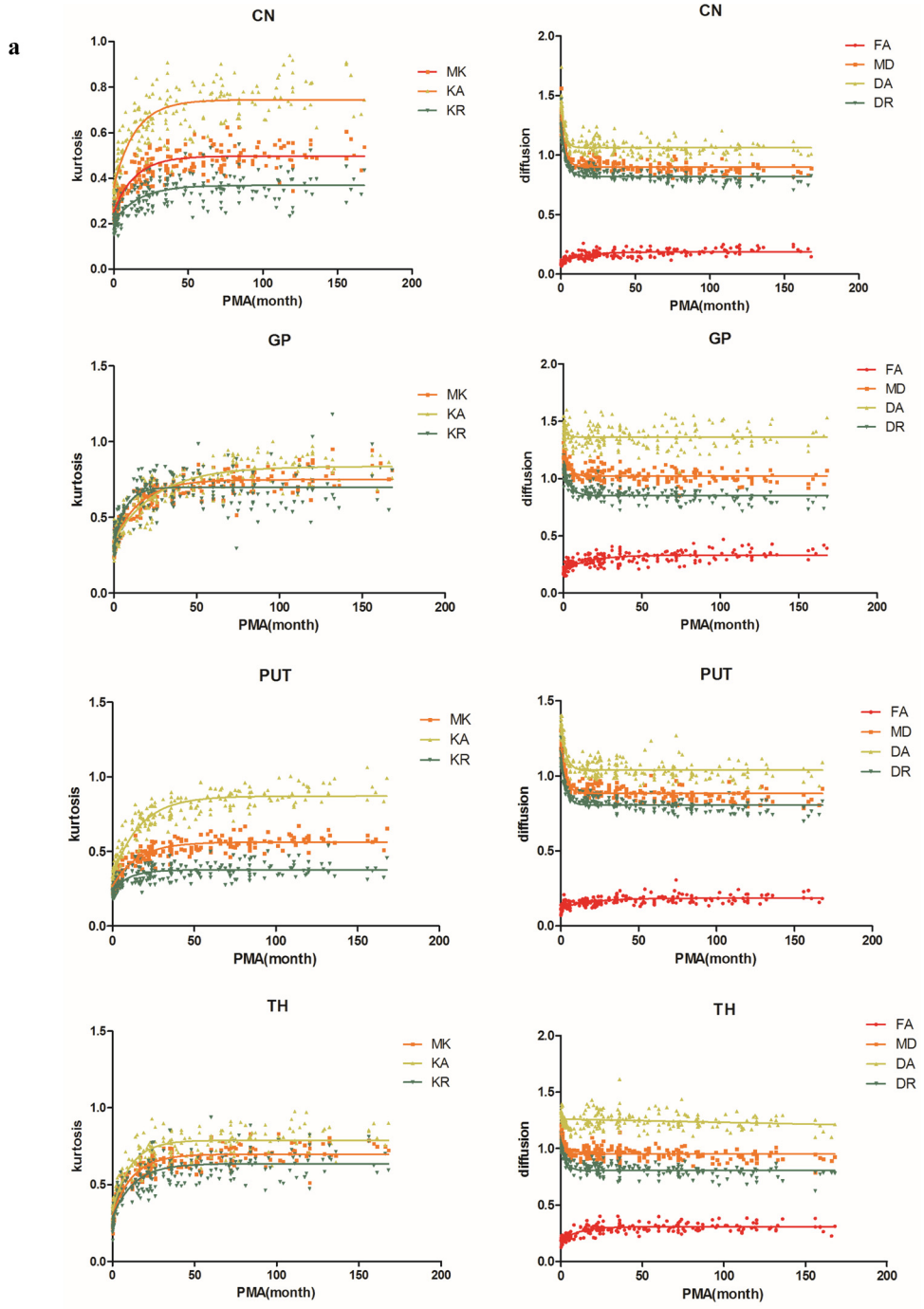

Fig. 2. a–c The scatter diagram of DKI-derived parameters of different ROIs with the logarithmic fitting curve. DKI-derived parameters had good correlation with age, which significantly increased within 2 years, and after 2 years the increase rate got reduced relatively. The units of MD, Da and Dr were mm^2/s.

consistency (ICC > 0.7). In all ROIs, as presented Fig. 2a–c and Supporting Fig. S1a–c, FA, MK, Ka and Kr values had good positive correlation with age, which significantly increased within 2 years, and after 2 years the rate of increase reduced; MD, Da and Dr values decreased with age, which also reduced obviously within 2 years, then declined more slowly. Fig. 3 and Supporting Fig. S2 show this trend visually.

In the neonatal period, the FA value of the SCC (0.57 ± 0.07) was the highest amongst the white matter areas, slightly higher than that of GCC with no statistical significance ($p > 0.05$). The FA values of the corpus callosum were significantly higher than the central white matter ($p < 0.05$), such as PLIC (0.50 ± 0.03) and ALIC (0.33 ± 0.03). The FA values of central white matter were higher than that of the periphery white matter (from the back to the front, in turn, was 0.26 ± 0.06, 0.20 ± 0.05, 0.20 ± 0.05; $p < 0.05$). Unlike FA values, the MK value of PLIC (0.47 ± 0.04) was highest, followed by the SCC (0.44 ± 0.06), then the GCC (0.35 ± 0.08), ALIC (0.33 ± 0.05), and the periphery white matter (from the back to the front, in turn, was 0.28 ± 0.05, 0.21 ± 0.03, 0.18 ± 0.02) in the order of decrease. The remaining DKI-derived parameter values of other age scopes is detailed in Supporting Table S1.

The rate of DKI parameter change in the same anatomical site was different with age. In white matter areas, as shown in the column chart, the variation range of diffusion values was around 50% compare to the

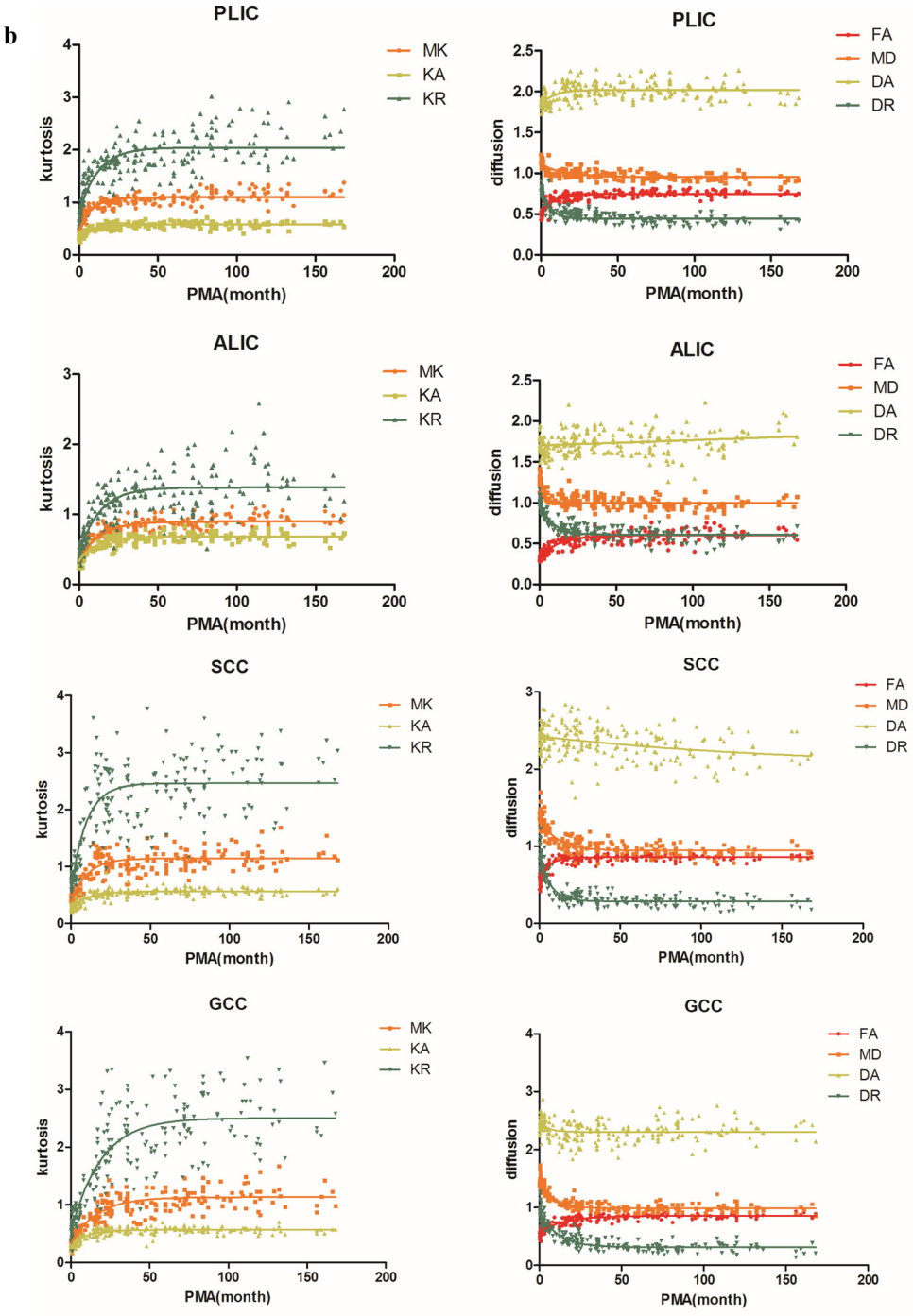

Fig. 2. (*continued*)

baseline value of the neonatal group, which was lower than the corresponding kurtosis values. For kurtosis and diffusion values, parameters perpendicular to the axon direction changed more obviously than the parallel direction. In the PLIC, ALIC and FWM, CWM, PWM of the centrum semiovale level, the amplitude list of the DKI-derived values from high to low was Kr, MK, Ka, FA, Dr, MD, and Da. The change rate of the white matter in the centrum semiovale level appeared greater than other areas, and the Kr value of FWM increased 394% from neonatal age to 2 years old, 147% can be seen from 2 years old to 5 years old, and 26% after 5 years old. The rest of the ROIs manifested similar changes. The increase of parameters of the corpus callosum from high to low, in turn, were Kr, MK, Ka, Dr, FA, MD and Da, of which the GCC changed slightly faster with Kr values increased 209% from neonatal age to 2 years old, 55% from 2 years old to 5 years old, and 84% after 5 years old.

In the gray matter areas, the change pattern of DKI parameters was different from the white matter. In general, the kurtosis values changed faster, while in the head of the caudate nucleus and the putamen, Ka value changed more obviously than Kr value; in the globus pallidus, Kr changed slightly more obviously upto 2 years old, and Ka more obviously after 2 years old; in the thalamus, Kr and Ka values had similar change rate. The Dr value in all these four gray matters changed faster than Da value. In the head of the caudate nucleus, the amplitude of the DKI-derived values increase from high to low was Ka, FA, MK, Kr, Dr,

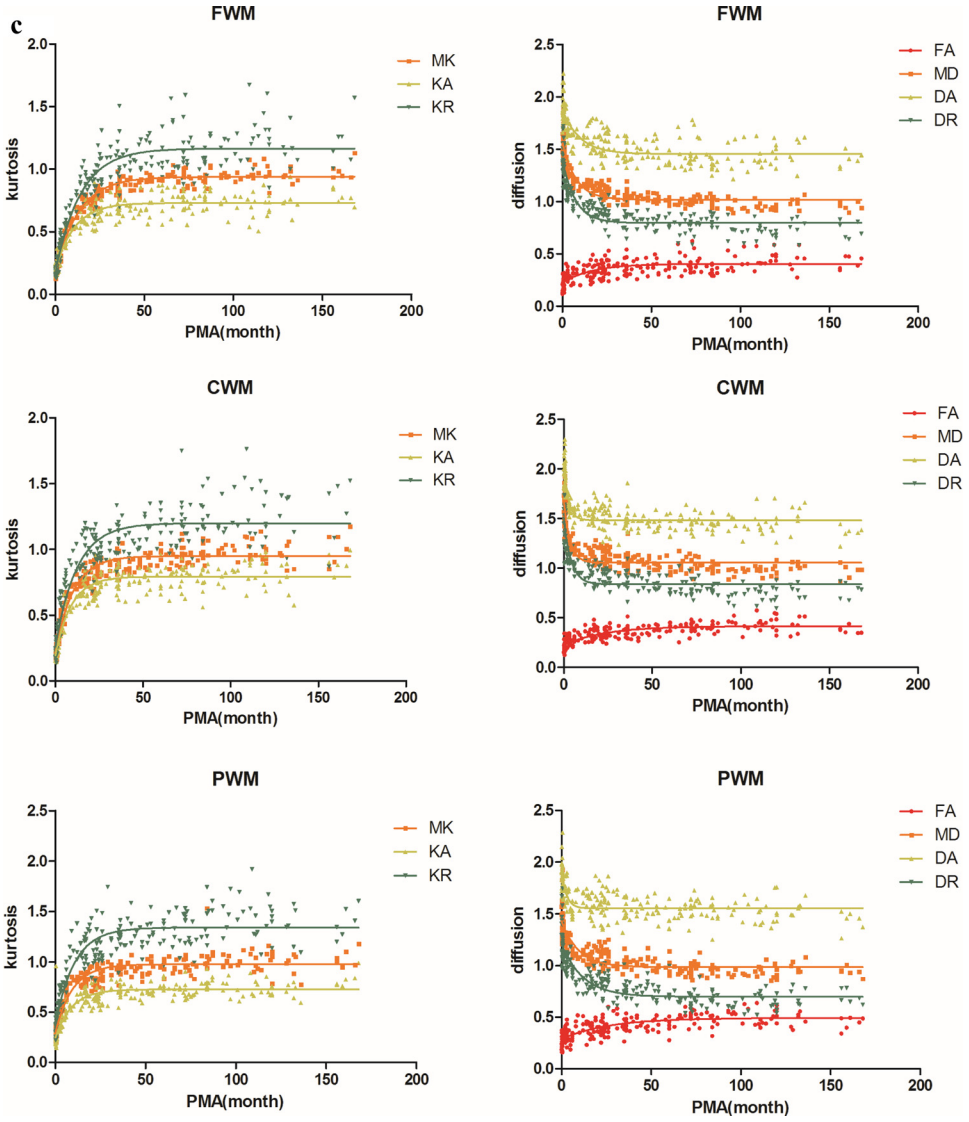

Fig. 2. (*continued*)

MD and Da. The Ka value increased 82% from neonatal age to 2 years old, 11% can be seen from 2 years old to 5 years old, and 28% after 5 years old. Similar change could be found in the putamen, from high to low was Ka, MK, Kr, Dr, FA, MD and Da. The Ka value increased 120% from neonatal age to 2 years old, 38% can be seen from 2 years old to 5 years old, and 22% after 5 years old. In the globus pallidus, the amplitude of the DKI-derived values increase from high to low was Kr, MK, Ka, FA, Dr, MD and Da. The Kr value increased 103% from neonatal age to 2 years old, then no obvious increase, while the Ka value increased 84% from neonatal age to 2 years old, 40% from 2 years old to 5 years old, and 28% after 5 years old. In the thalamus, the amplitude of the DKI-derived values increase from high to low was MK, Ka, Kr, FA, Dr, MD and Da. The MK value increased 106% from neonatal age to 2 years old, 22% from 2 years old to 5 years old, and 25% after 5 years old. The rate of the rest DKI parameters change in different age groups is shown in Fig. 4a–c and Supporting Table 2a–g.

4. Discussions

DKI can obtain diffusion and kurtosis parameters at the same time and these parameters had non-linear correlation with ages, which changed rapidly within the first 2 years, then showed a slowing trend after age 2. Kurtosis parameters showed higher variety rate in both white and gray matter, and may more sensitively depict the phenomenon of brain development.

Many DTI studies have demonstrated the non-linear changes of diffusion parameters as age increased [9,10,12,33]. In recent DKI studies, Paydar [24] found that the MK values continued to increase after 2 years old which might indicate some delayed isotropic changes. In our study, we also found this development pattern and extended the age range to 14 years. The FA values continued to increase in all the white matter regions as the process of myelination of the fiber tracts, and in all age groups, the FA value of the corpus callosum were the highest, which might be due to the accumulation of the closely packed fibers in the corpus callosum [7,8,34]. The increased density of cell and axon membrane during the brain development process might also account for the regional inhomogeneity that increased the MK value and decreased MD value. In addition, the reduction of water content would also affect MD value in the same direction. Comparing these two parameters, the MK value was more sensitive in detecting the micro-change process of white matter. Da value did not show significant change in the central white matter, which might be because the number of fiber bundles increased the Da value but this positive effect was offset by the reduction of water content, which decreased it at the same time. As a comparison, the increase of Ka value might be more sensitive to reflect the axial diffusion limited. Along with the increase of the thickness of

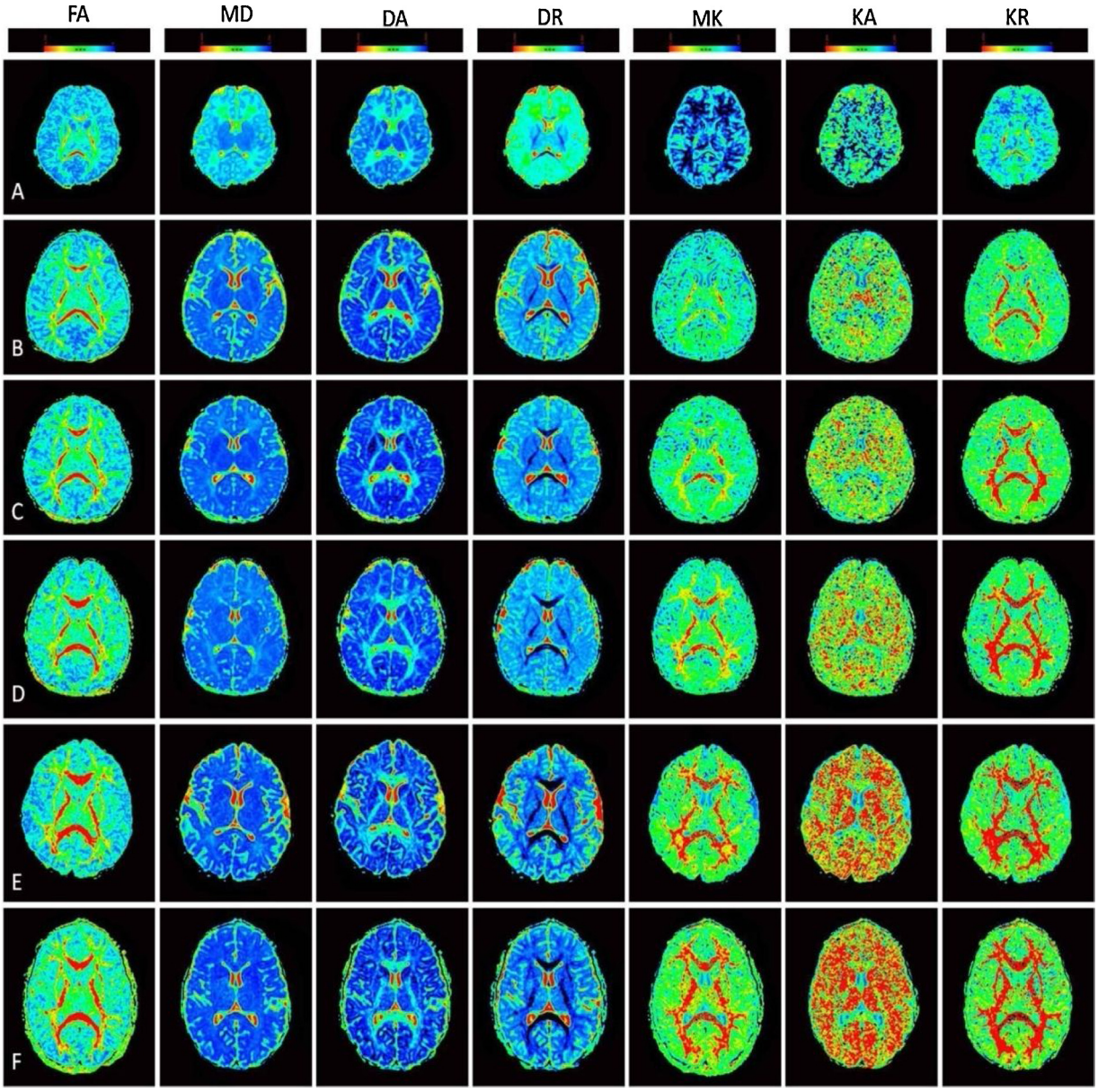

Fig. 3. A–F represented cases of different age groups (6d, 6m, 1y, 2y, 6y, 11y) respectively at the basal ganglia level. FA, MK, Ka and Kr values increased with age while MD, Da and Dr values decreased with age.

myelin sheath and axon diameter, the Dr value decreased and Kr value increased [22]. The Kr value changed more rapidly than Dr value. In the gray matter areas, DKI parameter change might be related to the mature neuronal macromolecular concentration increase and tissue water content decrease [19], or other special structures appearing in the development of gray matter, such as increased cell membranes and organelles, radial glial cells into astrocytes neuropil, increased dendrites [16,19,22]. In the thalamus, a large part of white matter fiber tracts also increase the anisotropy [27].

In the neonatal period, the DKI-derived parameters were different in different regions, which might be due to the early brain development, such as the brain white matter premyelination, synaptic formation and gray matter neuron migration [15]. White matter development followed certain rules from inferior to superior, central to peripheral, projection fibers faster than commissural and association fibers [3,35]. In our study in the neonatal period, the MK value of the PLIC was higher compared to the CC, and both of them were larger than that of the peripheral white matter areas, which is consistent with the regular developmental pattern of the brain. After 2 years old, DKI parameters changed relatively slowly, consistent with prior reports. Paydar [24] found that between 2 to 4.5 years old, MK value was still increasing compared with FA value. MK value reached a plateau later than FA value. Our results confirm that the kurtosis parameters' values at the age of 2–5 years old change distinctly from diffusion parameters' values. The most obvious parts occurred in the frontal white matter of the centrum semiovale level with 147% increase of Kr value, 98% increase of Ka value and 42% increase of MK value. Less increase occurred in the PLIC with 16% increase of Kr value, 7% increase of Ka value and 16% increase of MK value. The probable reason might be that myelination process in white matter of the centrum semiovale level predominants more than central white matter in this time period. The diffusional parameters also showed slight changes in these regions, such as frontal white matter FA value increased by 19%. Moreover, we analyzed the DKI parameters changes beyond the age of five. With similar results, more obvious changes in centrum semiovale and the genu corpus callosum were found. The asynchronous development resulted in the different change speed peak of DKI parameters [35].

As the brain grows from neonate to 14 years old, the kurtosis values

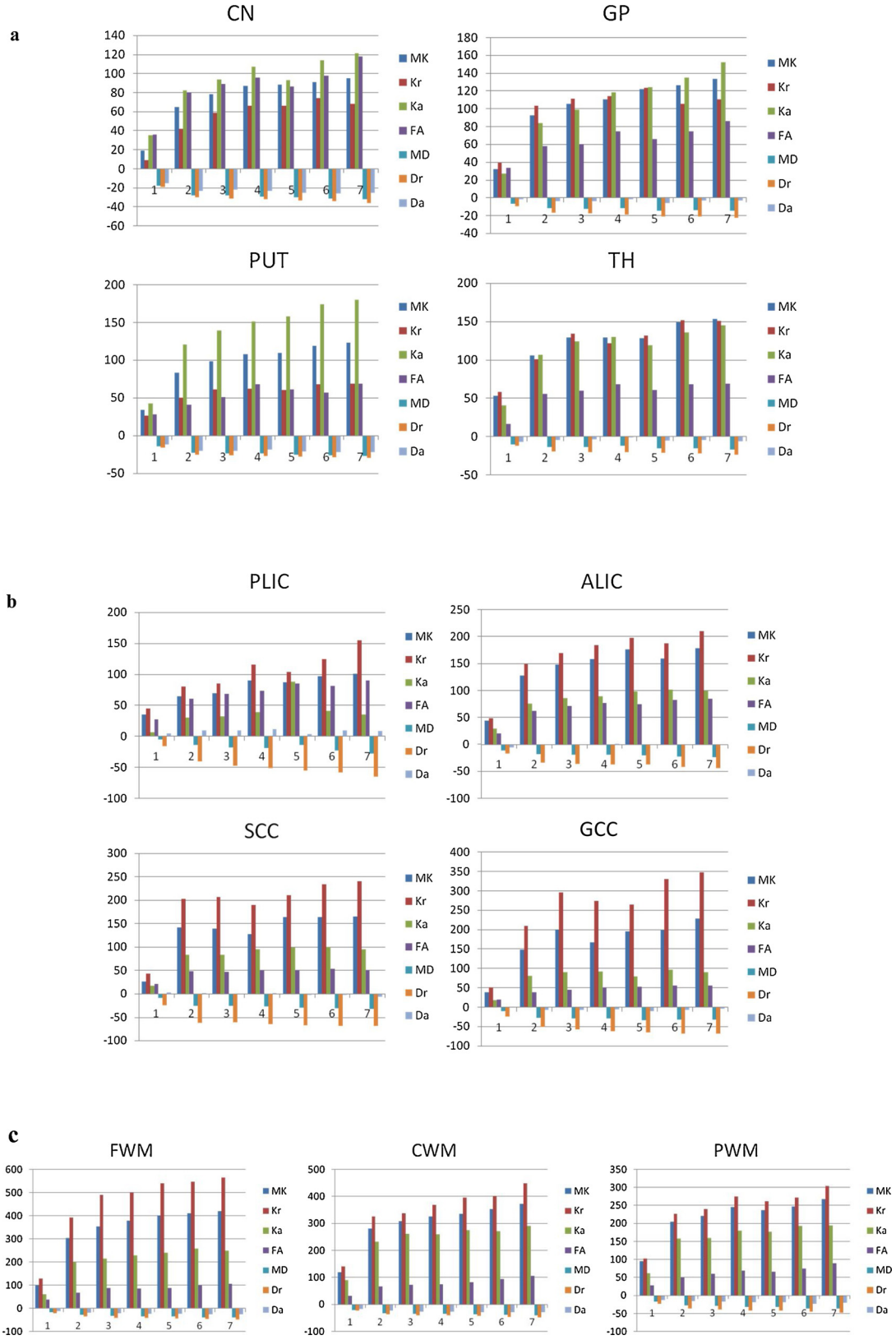

Fig. 4. a–c The histogram of kurtosis and diffusion values of different groups. The variation range of diffusion values was around 50% compare to the baseline value of neonatal, which was lower than the corresponding kurtosis values.

changed more rapidly than diffusion values in both white matter and gray matter, which demonstrates that kurtosis values have obvious advantages in the observation of children's brain development. Kr value increased more rapidly in the white matter while Ka changed more in the gray matter areas, which corresponds to the myelination processes and the neurites growth respectively. Intra- and extra-cellular matrix, axon and myelin sheath function restructuring existed in the late stage of brain development, caused the isotropic diffusion barrier, which

might be detected by DKI; Another reason might be that cross fiber bundles continued to mature, which had been confirmed by fiber bundle tracking maps [36]. DTI had its limitation to estimate cross fibers as diffusion tensor can only use each voxel to calculate the direction of single fiber bundles, while kurtosis can better define the multi-directional fibers [22,37,38]. Therefore, considering the more complex myelinated fibrous bundle model with a variety of diffusion limited factors and neuronal maturation of the gray matter, non-Gaussian DKI could provide a better insight to these later developmental changes.

Some limitations of our study should be mentioned. First, there is unavoidable subjectivity with a ROI method; however the intra-observer agreement in this study was good in the repeatability test. More detailed changes could be investigated using an appropriate brain atlas in our future studies. Second, the variability in Kr values is larger compared to that found in Dr values, which corresponds to previous studies [39]. As inter-subject differences contribute more than imaging noise to the total variability, we recruited a large number of subjects in our study and adjusted the ROI by each structure size to reduce this adverse effect. In addition, we will further increase scanning time to verify the present results [40]. Third, we had to use cross-sectional data in our study as obtaining longitudinal data in the same children is difficult.

In conclusion, DKI parameter values had good correlation with age, changed rapidly within the first 2 years of age and relatively slowly after 2 years; the change rate of kurtosis values in white matter and gray matter areas was larger than that of diffusion values. DKI parameters especially kurtosis values offer the potential to gain insight into the rapid brain development that occurs during childhood.

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Declaration of Competing Interest

The authors declared that they have no conflicts of interest to this work.

We declare that we do not have any commercial or associative interest that represents a conflict of interest in connection with the work submitted.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ejrad.2019.108690.

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