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Diffusional Anisotropy of the Human Brain Assessed with Diffusion-Weighted MR: Relation with Normal Brain Development and Aging

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PURPOSE: To analyze diffusional anisotropy in frontal and occipital white matter of human brain quantitatively as a function of age by using diffusion-weighted MR imaging. **METHODS:** Ten neonates (<1 month), 13 infants (1–10 months), 9 children (1–11 years), and 16 adults (20–79 years) were examined. After taking axial spin-echo images of the brain, diffusion-sensitive gradients were added parallel or perpendicular to the orientation of nerve fibers. The apparent diffusion coefficient parallel to the nerve fibers (0) and that perpendicular to the fibers (90) were computed. The anisotropic ratio (90/0) was calculated as a function of age. **RESULTS**: Anisotropic ratios of frontal white matter were significantly larger in neonates as compared with infants, children, or adults. The ratios showed rapid decrease until 6 months and thereafter were identical in all subjects. In the occipital lobe, the ratios were also greater in neonates, but the differences from other age groups were not so prominent as in the frontal lobe. Comparing anisotropic ratios between frontal and occipital lobes, a significant difference was observed only in neonates. **CONCLUSIONS**: Diffusion-weighted images demonstrated that the myelination process starts earlier in the occipital lobe than in the frontal lobe. The changes of diffusional anisotropy in white matter are completed within 6 months after birth. Diffusion-weighted imaging provides earlier detection of brain myelination compared with the conventional T1- and T2-weighted images.

Index terms: Brain, growth and development; Brain, magnetic resonance; Magnetic resonance, diffusion-weighted scanning; Myelin

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Intravoxel incoherent motion imaging enables quantitative assessment of water diffusion in the tissue by measuring the apparent diffusion coefficient, which reflects the mobility of water molecules in the tissue (1–3). Moseley et al (4) investigated anisotropic water diffusion in white matter of the cat brain with a 2.0-T experimental magnetic resonance (MR) magnet. They demonstrated that signal attenuation depends on the relationship between the orientation of nerve fibers and the direction of the diffusion-sensitive gradients. Greater signal attenuation (faster diffusion) was observed when their direction was parallel, compared with that obtained with perpendicular alignment. Chenevert et al (5) estimated an apparent diffusion coefficient of the human adult brain with a 10×10-mm column location technique and demonstrated the diffusional anisotropy in the white matter quantitatively. In our previous paper (6), we reported that the diffusional anisotropy in white matter of neonatal brain was quite weak compared with that of infants or adults. These data suggested that the diffusional anisotropy is related to the development of myelination. In this study we tried to evaluate diffusional anisotropy in white matter of the brain in a large number of subjects without neurologic abnormalities from newborns to an elderly adults. The purpose of this paper is to investigate the relation between the changes of diffusional anisotropy in the white matter as a function of normal brain development and aging.

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Materials and Methods

The work was done between October 1989 and November 1991. We studied 48 subjects including 10 neonates

(less than 4 weeks of age), 13 infants (1 month to 1 year of age), 9 children (ages 1–11 years), and 16 adults (ages 20–79 years). No subjects showed neurologic abnormalities or growth retardation. Some neonates, infants, and children were sedated when necessary. A 1.5-T Signa system (GE Medical Systems, Milwaukee, Wis) equipped with self-shielded gradient coils was used in this study. The data were obtained using a standard quadrature head coil with peripheral optical gating. To obtain diffusion-weighted images, we modified a standard spin-echo sequence as reported previously (6). First, axial 10-mm-thick single-section spin-echo images were obtained as non-diffusion–weighted standard images (repetition time of two cardiac cycles in children and adults and three in neonates and infants, echo time of 120 msec, 200 msec delay after cardiac trigger, phase-encoding steps of 128, 2 excitations). Then diffusion-sensitive gradient pulses (duration of 44 msec, gradient separation of 10.8 msec, amplitude of 0.9 G/cm) were added on either side of a 180° pulse in the sequence. The direction of diffusion-sensitive gradient pulses was changed between X (readout) and Y (phase-encoding) axes depending on the direction of diffusion to be detected. Diffusional anisotropy of frontal and occipital white matter was visually evaluated by comparing a reference spin-echo image and two diffusion-weighted images having orthogonal diffusion-sensitive gradients. In addition, at least four regions of interest were taken in frontal and occipital white matter, and the apparent diffusion coefficient in each region of interest was calculated (Fig 1). We calculated apparent diffusion coefficient (90), in which the diffusion-sensitive gradients were perpendicular to the nerve fibers, and apparent diffusion coefficient (0), in which the gradients were parallel, using the following equation:

$$\text{apparent diffusion coefficient} = -\ln(S1/S0)/b,$$

where S1 is signal intensity in the presence of diffusion-sensitive gradients, and S0 is signal intensity without diffusion-sensitive gradients (1). The gradient factor b was calculated from the equation:

$$b = \gamma^2(DG)^2(2/3D + I),$$

where γ is the gyromagnetic ratio, D and G are the duration and amplitude of diffusion sensitive gradient, and I is the interval of each diffusion-sensitive gradient. The gradient factor in the Y axis was 450 sec/mm^2. The gradient factor in the readout (X) axis was slightly higher (493 sec/mm^2) than in the Y axis, because of the cross-product effects between the diffusion-sensitive gradients and the readout gradients. For the quantitative assessment of diffusional anisotropy, the anisotropic ratio (apparent diffusion coefficient 90/0) was calculated.

The data are expressed as a mean ± SD. Significance of differences in ratios of diffusional anisotropy between age groups was assessed by the new multiple range test (Duncan method) (7). For the comparison between the frontal and occipital lobe in each age group, Student paired *t* test was used. A value of $P < .05$ was considered significant.

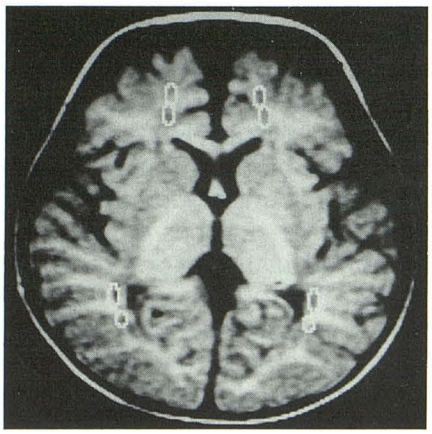


Fig. 1. Regions of interest are demonstrated on a diffusion-weighted image (*white circles*). At least two regions of interest were chosen in the frontal and occipital lobes in order to calculate the apparent diffusion coefficient.

Results

In all adults, diffusional anisotropy of frontal and occipital white matter was clearly seen. When the diffusion-sensitive gradients were perpendicular to the nerve fibers, the diffusion-induced reduction in signal intensity was small (Fig 2A). In contrast, when the gradients were parallel to the nerve fibers, a large signal reduction was observed, reflecting a rapid diffusion along the nerve fibers (Fig 2B). Diffusional anisotropy in children and infants more than 6 months of age was also as obvious in the adults (Figs 3A and 3B). In neonates, however, diffusion anisotropy was quite obscure in deep and cortical white matter compared with the adults or infants, although it was slightly more obvious in the occipital lobe than in the frontal lobe (Figs 4 and 4B).

The anisotropic ratios (apparent diffusion coefficient 90/0) in frontal and occipital white matter are plotted against the ages in all subjects (Fig 5). The ratios in the frontal lobe are about 0.8 at the neonatal period and then show rapid decrease until approximately 6 months of age. After 6 months the ratios do not differ significantly throughout infants, children, and adults. The ratios in the occipital lobe, by contrast, are higher in neonates and young infants under 6 months of age than other subjects, but their difference is not so striking compared with those in the frontal lobe. By comparison between frontal and occipital lobes, the ratios are higher in the frontal lobe than the occipital lobe just at the neonatal period. After 1 month they became similar.

The mean anisotropic ratios in frontal and occipital lobes in individual age groups are shown in Table 1. In frontal lobe the mean anisotropic

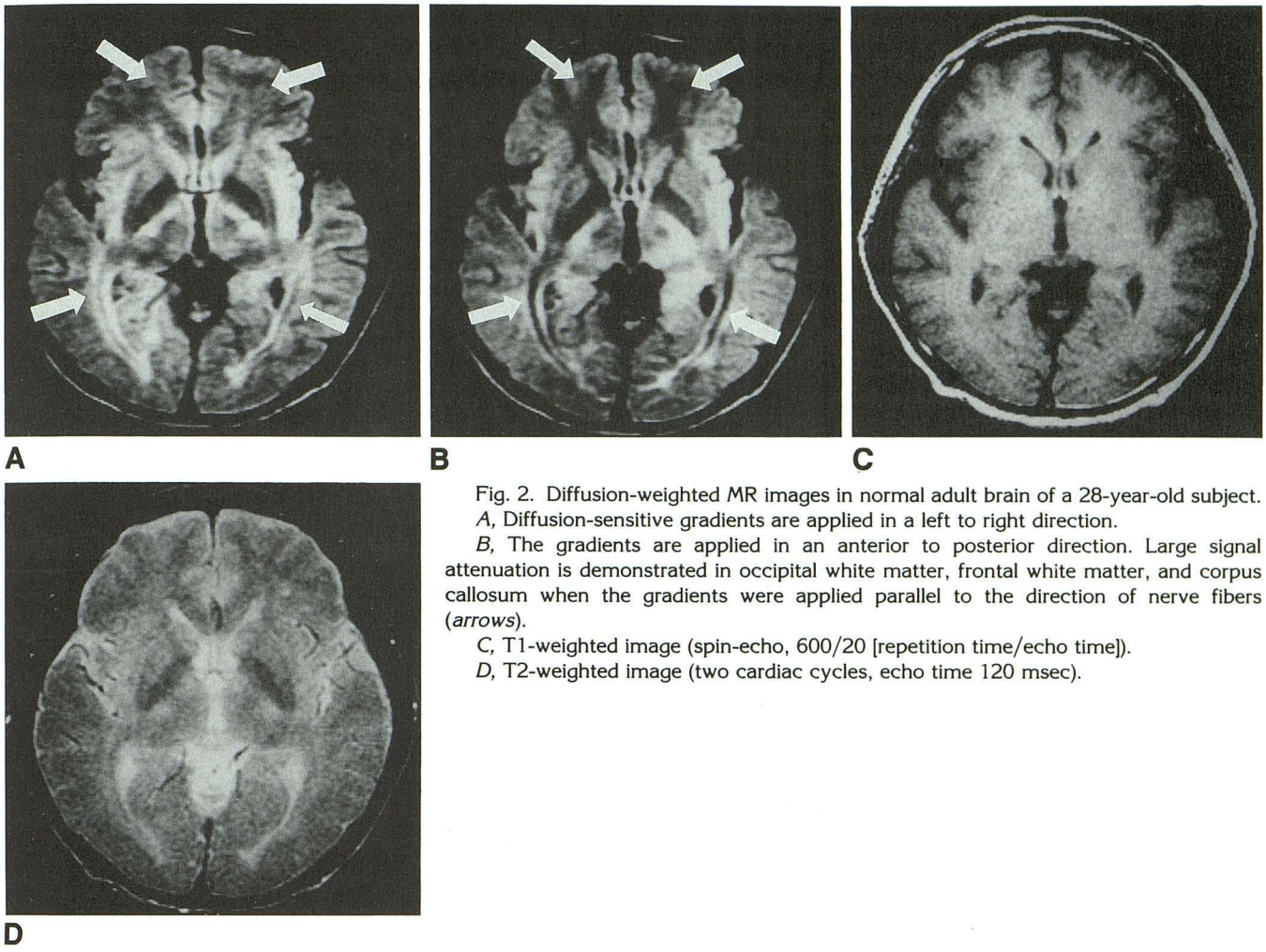


Fig. 2. Diffusion-weighted MR images in normal adult brain of a 28-year-old subject.
A, Diffusion-sensitive gradients are applied in a left to right direction.
B, The gradients are applied in an anterior to posterior direction. Large signal attenuation is demonstrated in occipital white matter, frontal white matter, and corpus callosum when the gradients were applied parallel to the direction of nerve fibers (*arrows*).
C, T1-weighted image (spin-echo, 600/20 [repetition time/echo time]).
D, T2-weighted image (two cardiac cycles, echo time 120 msec).

ratio is 0.79 ± 0.05 in neonates, being significantly higher than that in infants, children, or adults ($P < .01$, respectively). In occipital lobe the ratio is still higher in neonates than infants ($P < .05$) or adults ($P < .01$), but the difference was less marked compared with the frontal lobe. Comparing the ratios between occipital and frontal lobes in each age group, a significant difference was observed only in neonates ($P < .01$).

Absolute values of apparent diffusion coefficients (0) and (90) in frontal and occipital white matter are plotted against the ages in all subjects (Figs 6A and 6B). In the frontal lobe, apparent diffusion coefficient (0) does not differ significantly from neonates to elderly adults. By contrast, apparent diffusion coefficient (90) in neonates is higher than older subjects and shows rapid decrease until 6 months and then keeps fairly constant. In the occipital lobe, on the other hand, neither apparent diffusion coefficient (0) nor (90) differ significantly throughout all subjects.

Discussion

Since Moseley et al (4) obtained diffusion-weighted MR images in the cat brain using a 2-T CSI system, diffusion-weighted imaging has an increasing interest because of its potential to show diffusional anisotropy along the nerve fibers in the white matter. They speculated that the diffusional anisotropy reflects the degree of myelination in white matter. Recently, anisotropically restricted diffusion of water was demonstrated in the brains of neonates and infants by Bydder's group (8–10). They reported that restricted diffusion appeared within white matter, which appeared to be myelinated with T1-weighted sequence and within white matter where the presence of myelin was not demonstrated on T1-weighted images. However, the MR system they

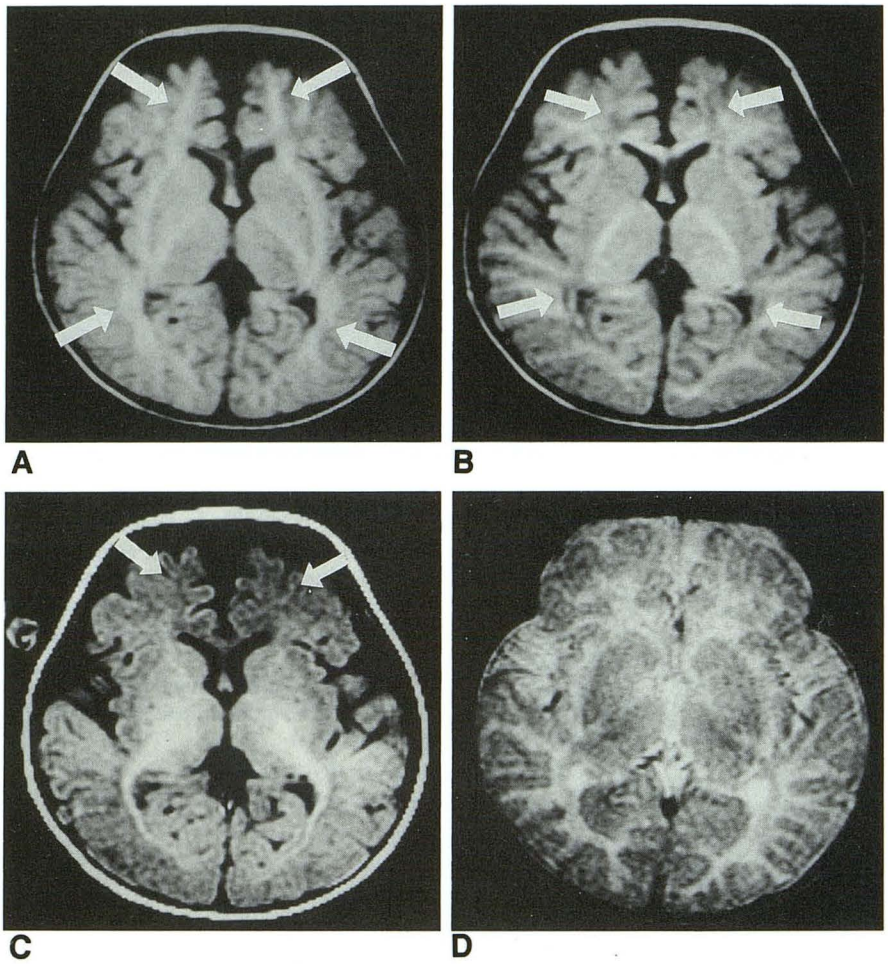


Fig. 3. Diffusion-weighted MR images in brain of a healthy 7-month-old infant.

A, Diffusion-sensitive gradients are applied in a left to right direction.

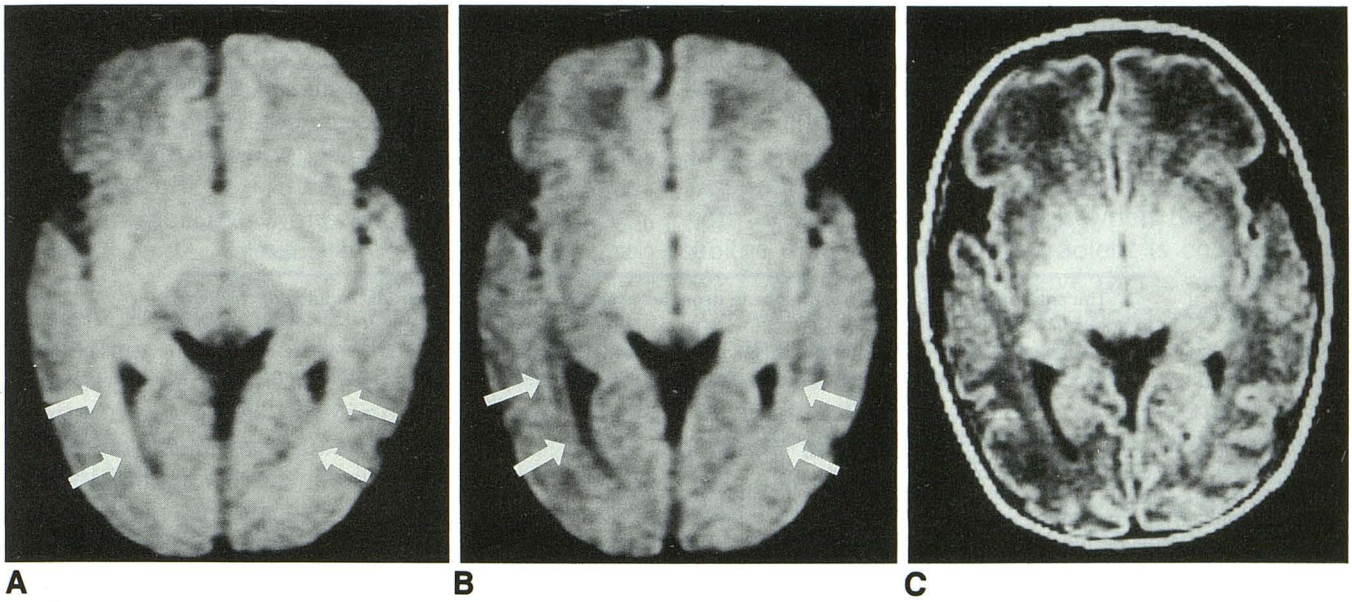
B, The gradients are applied in an anterior to posterior direction. Diffusional anisotropy is clearly seen in frontal white matter and in occipital white matter (*arrows*).

C, T1-weighted image (spin-echo, 600/20) shows increase in signal intensity in occipital white matter, whereas increased signal intensity is not prominent in frontal white matter (*arrows*).

D, On T2-weighted image (spin-echo, 2000/80), signal intensity in white matter is still high.

used had a low magnetic field (0.15 T), and their gradient system was not self-shielded. In this study, we obtained diffusion-weighted images and determined the apparent diffusion coefficient in the subjects ranging in age from neonates to more than 70 years old by using with high magnetic field and self-shielded gradient coils. We performed a quantitative analysis of diffusional anisotropy by calculating anisotropic ratio (apparent diffusion coefficient 90/0). The diffusional anisotropy in neonatal white matter was quite weak, especially in the frontal lobe. The anisotropic ratio in white matter was significantly higher in neonates than that in infants, children, or adults. The anisotropic ratio showed a rapid decrease until 6 months after birth and then reached the level quite close to that in adults. Figures 6A and 6B demonstrated that the rapid decrease of the anisotropic ratio was mainly caused by the decrease of apparent diffusion coefficient (90) measured with the perpendicular gradients to the nerve fibers. In contrast, the apparent diffusion coefficient (0) measured with the parallel gradient to the fibers showed only mild decrease after brain development.

The origin of diffusional anisotropy is still unclear. Rutherford et al (8) commented that because the permeability of water of myelin lipid bilayers is 10 to 50 times smaller than the permeability of axoplasmic membranes, the addition of just one layer of myelin would be expected to result in a significant reduction in the apparent diffusion coefficient of unmyelinated axons. As the membranous structure of the myelin sheath is matured after brain development, motion of water in a direction perpendicular to the fibers is severely prevented by myelin sheath. When diffusion measurements are made parallel to the fibers, water motion is relatively free. In this way, water will diffuse relative to the direction of nerve fibers. If the diameter of an axon is smaller than the distance that a water molecule travels by diffusion during the time of observation in bulk water, the diffusion coefficient may be reduced. Most of the myelinated fibers are 1 to 10 μm in diameter (9). Moseley et al (11) estimated in their paper that



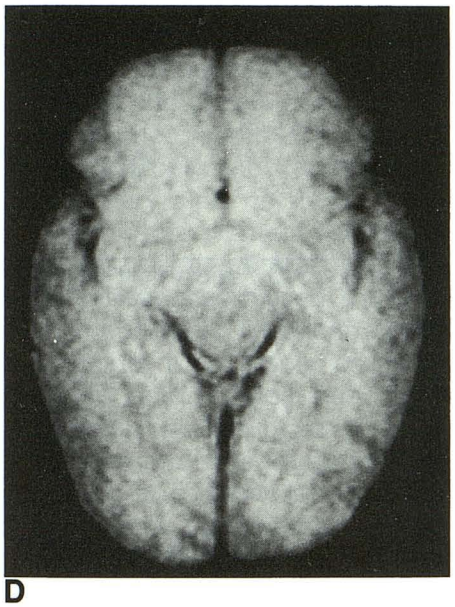


Fig. 4. Diffusion-weighted MR images in a neonate 35 weeks of age after conception.

A, Diffusion-sensitive gradients are applied in a left to right direction.

B, The gradients are applied in an anterior to posterior direction. Diffusional anisotropy is slightly observed in occipital white matter (*arrows*) but is not obvious compared with infant or adult brain. In frontal white matter, diffusional anisotropy is quite weak.

C, T1-weighted image (spin-echo, 600/20).

D, T2-weighted image (spin-echo, 2000/80). On both T1- and T2-weighted images, no myelination is observed in frontal and occipital white matter.

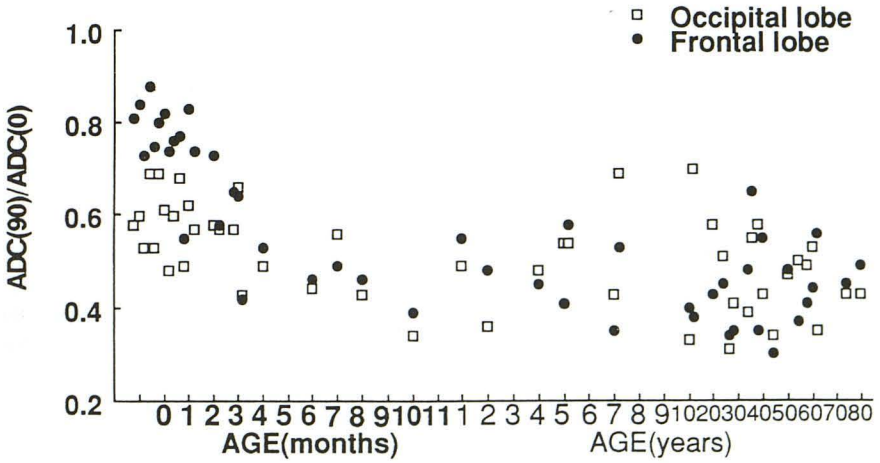


Fig. 5. Scatter plot shows relation between anisotropic ratio (apparent diffusion coefficients 90/0) and ages in all subjects. The *abscissa* represents ages of subjects with two different scales from 0 to 11 months (*left half*) and from 1 to 80 years (*right half*). In the frontal lobe the anisotropic ratios are considerably high at the neonatal period and followed by rapid decrease until 6 months. In the occipital lobe, the anisotropic ratios in neonates are also higher than in older subjects, but the difference is not distinct. After 6 months, the ratios are almost identical in both frontal and occipital lobes.

TABLE 1: Average of anisotropic ratios in frontal and occipital lobes among neonates, infants, children, and adults

	Apparent Diffusion Coefficient 90/0 (mean ± SD)			
	Neonates (n = 10)	Infants (n = 13)	Children (n = 9)	Adults (n = 16)
Frontal lobe	0.79 ± 0.05	0.57 ± 0.13[a]	0.45 ± 0.07[a]	0.44 ± 0.09[a]
Occipital lobe	0.60 ± 0.07[b]	0.52 ± 0.09[c]	0.52 ± 0.12	0.45 ± 0.08[d]

[a] The anisotropic ratio of the frontal lobe in neonates is significantly higher than that in infants, children, or adults ($P < .01$).

[b] The difference between frontal and occipital lobe in neonates is significant ($P < .01$).

[c,d] The ratio of the occipital lobe in neonates is higher than in infants ($P < .05$) or adults ($P < .01$).

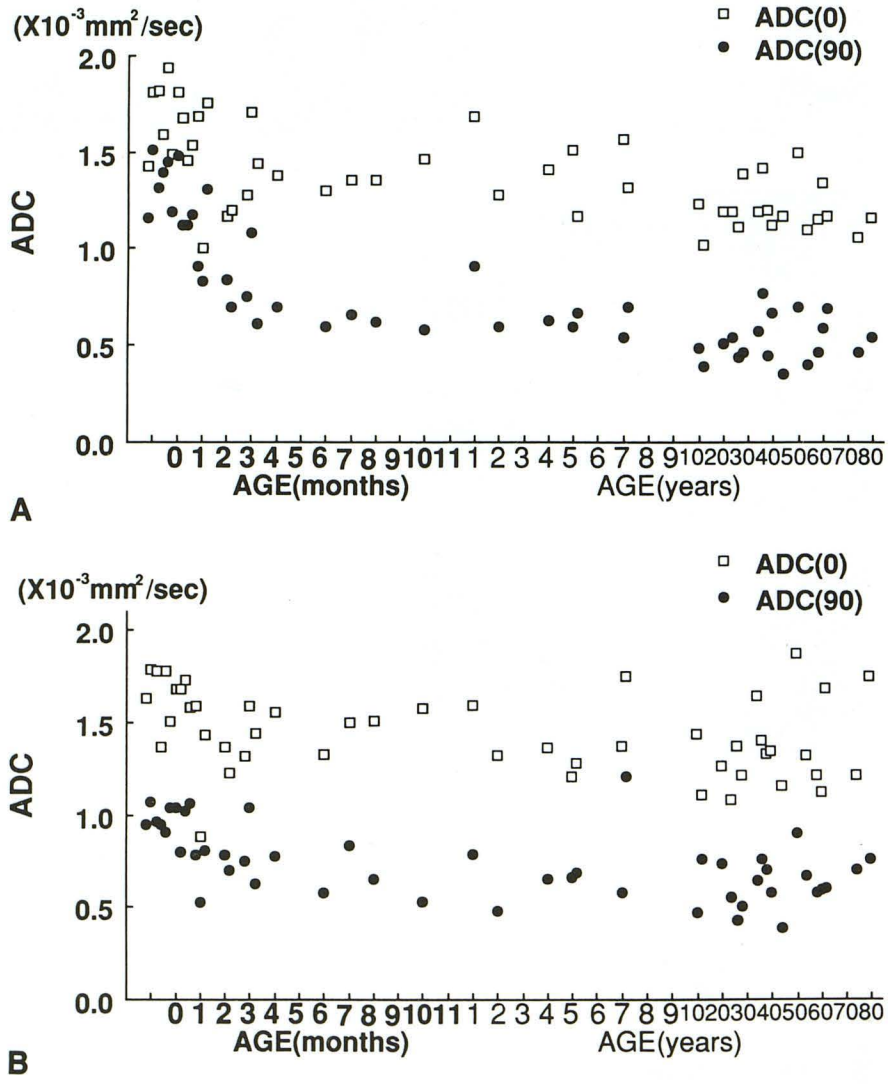


Fig. 6. Scatter plot shows relation between absolute values of apparent diffusion coefficient and ages in the frontal (*A*) and occipital lobe (*B*). In the frontal lobe, apparent diffusion coefficient (90) reveals a rapid decrease until 6 months, whereas the apparent diffusion coefficient (0) shows a slight fall. In the occipital lobe, both apparent diffusion coefficient (90) and apparent diffusion coefficient (0) remain fairly constant throughout the subjects.

restricted diffusion will occur if the range of scale length is less than 14 to 16 μm. However, the role of the myelin sheath on diffusional anisotropy is not fully understood. Le Bihan et al measured restricted diffusion in white matter using different diffusion times and demonstrated that no real restrictive diffusion pattern could be found in white matter (12). Thus, the reduced value of the diffusion coefficient across the myelin fibers may reflect only a decreased water mobility through lipid layers (13). Therefore, both the extent of myelination and the permeability of myelin

sheaths in the developing brain could influence the degree of restricted diffusion.

Water content of the brain is another important factor affecting diffusion coefficient in white matter. The brain is about 90% water at birth and decreases to 82% ~ 83% at 6 months (14). The ratio of intracellular water with restriction to extracellular water without restriction changes during these 6 months. As shown in our study, apparent diffusion coefficient (0) in neonatal brain was slightly higher than that in adults. Reduction of apparent diffusion coefficient (0) during first 6 months may reflect the change of tissue water content in the extracellular space. The decrease of extracellular water will enhance the diffusional anisotropy in white matter.

The anisotropic ratios in frontal white matter was significantly larger than those of occipital white matter at neonatal periods, but the difference between them became less significant in infancy, especially after 6 months. This fact suggests that the development of myelination starts earlier in the occipital lobe than the frontal lobe. The anisotropic ratio at 6 months after birth is already very close to that in adult in frontal and occipital white matter. X-ray computed tomography and conventional T1- and T2-weighted MR images have been used for the assessment of brain maturation. Quencer assessed myelination of neonatal brain using computed tomography numbers and pointed out that two phases of maturation are identified: a rapid phase (first 8–12 weeks) and a gradual phase (after 12 weeks) (15). T1- and T2-weighted images also reflect development of myelination and maturation of brain (16, 17). On T2-weighted images, the change of signal intensity in white matter continues after 6 months, and T2-weighted images are more useful in monitoring brain development in this period (18). The signal intensity changes mainly relate to slow decrease of water content in the brain after 6 to 8 months (14). On the other hand, T1-weighted images are useful in monitoring brain development in the first 6 months (18). As is shown in the figures in this study and in our previous paper (6), the changes in diffusional anisotropy precede the changes in the signal intensity on T1- and T2-weighted images. Thus, diffusion imaging is expected to be clinically important because it enables earlier assessment of not only neonatal brain development but also white matter demyelinating diseases compared with routine MR images or other diagnostic methods.

It has been believed that the diffusion-sensitive gradient applied on the phase-encoding axis or the section-selecting axis is likely to induce more severe eddy current problems than on the readout axis. As reported in our previous paper (6), the apparent diffusion coefficients of the water phantom are fairly constant even when the direction of the diffusion-sensitive gradient is changed on X, Y, and Z axes. We believe this is attributable to the use of active shielded gradient coils. Based on this result, the data of apparent diffusion coefficient in the present study were thought to be highly reliable. The artifacts caused by motion may be a problem in the clinical application of this technique; however, those artifacts caused by vascular pulsations can be reduced by cardiac or peripheral gating. Involuntary movement of the head, on the other hand, is occasionally difficult to suppress even with sedation or some head-holding devices. Echo-planar diffusion-weighted imaging will be the solution for the motion artifact problems.

In conclusion, diffusion-weighted images demonstrated that the myelination process starts earlier in the occipital lobe than in the frontal lobe. The changes of diffusional anisotropy in white matter are completed within 6 months after birth. Diffusion-weighted imaging provides an earlier detection of brain myelination than the conventional T1- and T2-weighted images.

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