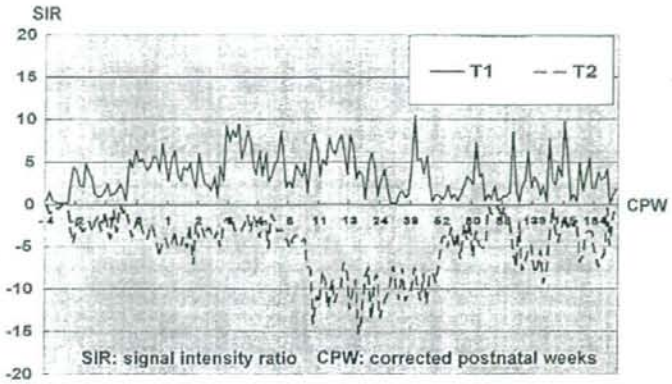

Fig. 3 SIR changes for the medial geniculate body (T1 and T2 weighted) SIR was calculated as follows: (ROI value of assessment site – the ROI value of surrounding tissue/ROI value of the assessment site) × 100. The SIR value of both sides was measured for each evaluation part, with the average value then computed. *X*-axis: corrected postnatal weeks (CPW), *Y*-axis: signal intensity ratio (SIR).

signal changes and determined that the medial geniculate body exhibited signal changes that were indicative of myelination at 28 fetal weeks (fw), which is much earlier than what we found in the current study. Nakagawa et al. [6] used 1.5 T MRI to examine the auditory radiation and splenium of the corpus callosum and found signal changes for both areas at 54–67 gestational weeks (both T1- and T2-weighted). After converting gestational weeks to weeks after birth (gestational weeks minus 40 weeks), their results were similar to our results. Bird et al. [16] examined the splenium of the corpus callosum and reported finding myelination at 10 months of age (40 weeks after birth). The difference between their results and the findings of our study most likely originate from methodological differences, as a visual evaluation by the researchers was used by Counsell et al. [28], Nakagawa et al. [6] and Bird et al. [16], while objective ROI measurements were employed in this study.

In our MRI study, the medial geniculate body, which contains the gray matter nuclei, started to show changes in the myelination signal at 10 CPW, with blurring occurring at 48 CPW on T2-weighted imaging. Even though the MRI can detect myelination signal intensity changes in the medial geniculate body, once blurring occurs, myelination signal intensity is no longer detectable. Blurring phenomenon which became difficult to distinguish central nucleus or pathway from the surrounding tissue on MRI is reported by Nakagawa et al. [6] as well as our study. A proposed theory for why this "blurring" phenomenon occurs can be explained from research of Moore et al. [5]. Moore's histological report compared material from adults and fetuses, they noted in adults, the myelinated axons fill the surrounding

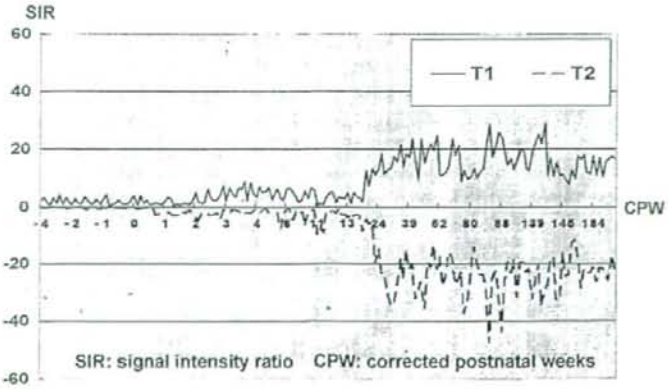

Fig. 4 SIR changes for the auditory radiation (T1 and T2 weighted). *X*-axis: corrected postnatal weeks (CPW), *Y*-axis: signal intensity ratio (SIR).

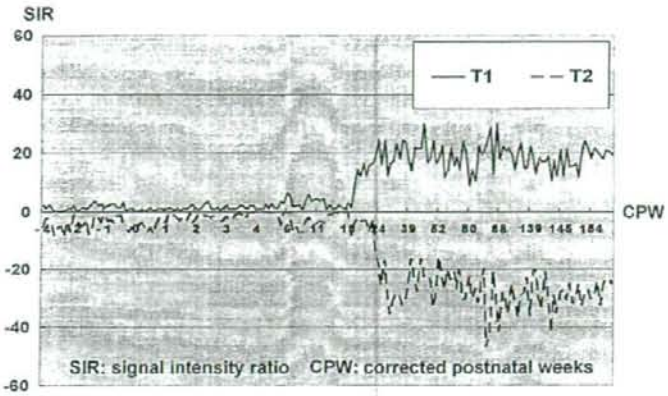

Fig. 5 SIR changes for the splenium of the corpus callosum (T1 and T2 weighted). *X*-axis: corrected postnatal weeks (CPW), *Y*-axis: signal intensity ratio (SIR).

tissue of central nervous nucleus (this means that MRI signal intensity of surrounding tissue changes as same as central nervous nucleus = blurring), so it become less prominent in adults as compared to that seen during the fetal period which shows contrast of central nervous nucleus and surrounding tissue. In our study we noted that the auditory radiation, which is a white matter tract, exhibited myelination-associated signal changes at 19 CPW at which point no blurring had occurred on the T1-weighted imaging. For the T2-weighted imaging, myelination- associated signal changes occurred at 24 CPW at which time there was also no blurring noted. The splenium of the corpus callosum, which is a white matter tract, showed myelination-associated signal changes at 16 and 24 CPW on the T1- and T2-weighted imaging, respectively. In both cases, no blurring was observed. Auditory radiation and the splenium of the corpus callosum are large structure of white matter tracts, it was considered that blurring phenomenon does not observed.

Flechsig's original results [2] documented that at 7 weeks the medial geniculate body exhibited myelination, while at 9 weeks, both the auditory radiation and the splenium of the corpus callosum exhibited myelination. Yakovlev and Lecours [3] reported that the auditory radiation first showed myelination at 0 weeks, with the splenium of the corpus callosum showing myelination at 16 weeks. The MRI results indicate that the signal intensity changes occur much later than what has been reported for the histological research studies. A proposed explanation for this difference might be that it takes a minimal concentration of myelin to have a significant effect on the signal intensities during MR imaging, i.e., there must be a major

Table 1 Comparisons of histological and MRI studies

	MGB	AR	SC
Histological study			
Flechsig	7 weeks	9 weeks	9 weeks
Yakovlev, Lecours	–	0 weeks	16 weeks
MRI study (T = Tesla)			
Counsell (1.0 T)	28 fw	–	–
Nakagawa (1.5 T)	–	14–27 weeks (T1T2)	14–27 weeks (T1T2)
Bird (1.5 T)	–	–	40 weeks (T1T2)~
Our results (1.5 T)	10 weeks (T2)	19 (T1), 24 (T2) weeks	16 (T1), 24 (T2) weeks

MGB: medial geniculate body, AR: auditory radiation, SC: splenium of corpus callosum, fw: fetal weeks.
Counsell et al examined myelination-associated T2-weighted signal changes and determined that the medial geniculate body exhibited signal changes that were indicative of myelination at 28 fetal weeks, which is much earlier than what we found in the current study. Nakagawa et al. examined the auditory radiation and splenium of the corpus callosum and found signal changes for both areas at 54–67 gestational weeks (both T1- and T2-weighted). After converting gestational weeks to weeks after birth (gestational weeks minus 40 weeks), their results were similar to our results. Bird et al. examined the splenium of the corpus callosum and reported finding myelination at 10 months of age (40 weeks after birth).

change in the myelin sheath makeup such as the loss of water and the gain of lipids.

Our study indicated that in the medial geniculate body, significant myelination- associated intensity changes were identified in the T2-weighted images, although the T1-weighted images did show a slight change of intensity at an early time than was seen for the T2-weighted imaging. It has been reported that the T2-weighted sequences are superior to the T1-weighted sequences with regard to demonstrating the contrast between the gray matter nucleus and the surrounding white matter, and thus, are more suitable when evaluating the gray matter nucleus [28]. T2-weighted sequences were superior to T1-weighted sequences in demonstrating the contrast between gray matter nucleus (medial geniculate body) and surrounding white matter, therefore more suitable for evaluating gray matter nucleus. This finding agrees with our last paper results [1].

The reason for this might be because the T1-relaxation times for the gray matter nucleus and the white matter are not large enough in a high-field strength system to be detected [28]. In the deep gray matter nuclei, the T2-weighted MRI was superior at showing myelin while the T1-weighted MRI was better at showing myelin in the white matter tracts. This could be due to the characteristics of the anatomical area, as has been suggested in other MRI brain region studies [28,29]. Overall, these results suggest that fine-tuning of the protocols for the specific area to be examined may be useful when assessing myelination in brain.

4.2. Myelination progress from other aspects

For the visual system the duration of functional maturation (spatiotemporal vision) correlates with the duration of the myelination of the optic radiation [30–32]. Moore et al. [5] has postulated that the time of myelination onset in central auditory pathway coincides with the onset of the acoustico-motor reflexes or the auditory startle reaction. Therefore evaluating the myelination degree of the central auditory pathway would be needed for the research of hearing development in infants. However, as in this study we clarify the time lag between the histological study and MRI evaluation about normal myelination period, so comparing with histological work directly is not correct when evaluate the maturation of central auditory pathway using MRI. New milestone of central auditory pathway development using MRI is needed and we suggest this study results as new milestones. The current results which correlate with the auditory function would be useful for research of hearing development in infants using MRI.

5. Conclusion

Use of 1.5 T MRI to examine the central auditory nuclei and pathway of the higher brain revealed signal intensity changes associated with myelination that were approximately 3, 7–24, and 7–15 weeks after that reported in histological literature for the medial geniculate body, auditory radiation and splenium of the corpus callosum, respectively. The reason for the delay is considered to be related to the fact that myelination does not take place suddenly but rather, happens gradually over time. Thus, substantial changes of the myelin sheath makeup, a loss of water and the gain of lipids are required in order for the myelination to be detectable by MRI. This study also shows that MRI can be used to follow the myelination progress pattern in the central auditory pathway of the higher brain. In conjunction with our previous study on the auditory brainstem pathway, [1] these results indicate that MRI can be used to assess the maturation of the auditory system of infants.

Acknowledgements

This study was supported by a Grant-Aid for Young Scientists (B) from The Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japan.

References

[1] M. Sano, K. Kaga, C.C. Kuan, K. Ino, K. Mima, Early myelination patterns in the brainstem auditory nuclei and pathway: MRI evaluation study, Int. J. Pediatr. Otorhinolaryngol. 71 (2007) 1105–1115.
[2] P. Flechsig, Anatomie des Menschichen Gehirn und Rueckenmarks auf Myelogenetischer Grundlage, Thime, Leipzig, 1920.
[3] P.I. Yakolvlev, A. Lecours, The myelogenetic cycles of regional maturation of the brain, in: A. Minkowski (Ed.), Regional Development of the Brain in Early Life, Blackwell Scientific Publication, Oxford, 1967, pp. 3–70.
[4] L.B. Rorke, H.E. Riggs, Myelination of the Brain in the Newborn, Lippincott Company, Philadelphia, 1969.
[5] J.K. Moore, L.M. Perazzo, A. Braun, Time course of axonal myelination in the human brainstem auditory pathway, Hear. Res. 87 (1/2) (1995) 21–31.
[6] H. Nakagawa, S. Iwasaki, K. Kichikawa, A. Fukusumi, T. Taoka, H. Ohishi, et al., Normal myelination of anatomic nerve fiber bundles: MR analysis, Am. J. Neuroradiol. 19 (1998) 1129–1136.

[7] M.A. Johnson, J.M. Pennock, G.M. Bydder, Clinical NMR imaging of the brain in children: normal and neurologic disease, AJR Am. J. Roentgenol. 141 (1983) 1005–1018.
[8] B.A. Holland, D.K. Haas, D. Norman, M. Brant-Zwadzki, T.H. Newton, MRI normal brain maturation, AJNR Am. J. Neuroradiol. 7 (1986) 201–208.
[9] R.B. Dietrich, W.G. Bradley Jr., MR evaluation of early myelination patterns in normal and developmentally delayed infants, AJNR 9 (1998) 69–76.
[10] C.B. McArdle, C.J. Richardson, D.A. Nicholas, M. Mirfakhraee, C.K. Hayden, E.G. Amparo, Developmental features of the neonatal brain: MR imaging, gray-white matter differentiation and myelination, Radiology 162 (1987) 223–229.
[11] M.S. van der Knaap, J. Valk, MR imaging of the various stage of normal myelination during the first year of life, Neuroradiology 31 (1990) 459–470.
[12] K. Hayakawa, Y. Konishi, M. Kuriyama, K. Konishi, T. Matsuda, Normal brain maturation in MRI, Eur. J. Radiol. 12 (1990) 208–215.
[13] E. Martin, R. Kikinis, M. Zuerrer, C. Boesch, J. Briner, G. Kewitz, et al., Development stages of human brain: an MR study, J. Comput. Assist. Tomogr. 12 (1988) 917–922.
[14] E. Martin, S. Krassnitzer, P. Kaelin, MR imaging of the brainstem: normal postnatal development, Neuroradiology 33 (1991) 391–395.
[15] A.J. Barkovich, B.O. Kjos, D.E. Jackson Jr., D. Norman, Normal maturation of the neonatal and infant brain: MR imaging at 1.5 T, Radiology 166 (1988) 173–180.
[16] C.R. Bird, M. Hedberg, B.P. Drayer, P.J. Keller, R.A. Flom, J.A. Hodak, MR assessment of myelination in infants and children: usefulness of marker sites, AJNR Am. J. Neuroradiol. 10 (1989) 731–740.
[17] J.A. Stone, D.W. Chakeres, P. Schmalbrock, High-resolution MR imaging of the auditory pathway, Magn. Reson. Imaging Clin. N. Am. 6 (1) (1998) 195–217.
[18] M.S. van der Knaap, J. Valk, MR imaging of the various stages of normal myelination during the first year of life, Neuroradiology 31 (1990) 459–470.
[19] D. Bergerbest, D.G. Ghahremani, D.E. Gabrieli, Neural correlates of auditory repetition priming: reduced fMRI activation in the auditory cortex, J. Cogn. Neurosci. 16 (2004) 966–977.
[20] K. Hittmair, D. Wimberger, T. Rand, L. Prayer, G. Bernert, J. Kramer, et al., MR assessment of brain maturation: comparison of sequences, AJNR 15 (1994) 425–433.
[21] B.D. Flannigan, W.G. Bradley Jr., J.C. Mazziotta, W. Rauschning, J.R. Bentson, R.B. Lufkin, et al., Magnetic resonance imaging of the brainstem: normal structure and basic functional anatomy, Radiology 154 (February (2)) (1985) 375–383.
[22] J.T. Curnes, P.C. Burger, W.T. Djang, O.B. Boyko, MR imaging of compact white matter pathways, AJNR Am. J. Neuroradiol. 9 (6) (1988) 1061–1068.
[23] A. Fee-Higins, J.C. Larroche, Development of the Human Foetal Brain, INSERM Masson, Paris, 1987.
[24] Gaining and growing: Calculating corrected age, University of Washington's homepage, http://depts.washington.edu/growing/Assess/Grca.htm.
[25] T. Stricker, E. Martin, C. Boesch, Development of the human cerebellum observed with high-field-strength MR imaging, Radiology 177 (2) (1990) 431–435.
[26] W. Grodd, Normal and abnormal patterns of myelin development of the fetal and infantile human brain using magnetic resonance imaging, Curr. Opin. Neurol. Neurosurg. 6 (3) (1993) 393–397.
[27] M. Staudt, I. Krageloh-Mann, W. Grodd, Normal myelination in childhood brains using MRI—a meta analysis, Rofo 172 (10) (2000) 802–811.
[28] S.J. Counsell, E.F. Maalouf, A.M. Fletcher, P. Duggan, M. Battin, H.J. Lewis, et al., MR imaging assessment of myelination in the very preterm brain, AJNR Am. J. Neuroradiol. 23 (5) (May 2002) 872–881.
[29] A.J. Barkovich, Magnetic resonance techniques in the assessment of myelin and myelination, J. Inherit. Metab. Dis. 28 (3) (2005) 311–343.
[30] B.A. Brody, H.C. Kinny, A.S. Kloman, F.H. Gilles, Sequence of central nervous system myelination in human infancy, an autopsy study of myelination, J. Neuropathol. Exp. Neurol. 46 (1987) 283–301.
[31] H.C. Kinney, B.A. Brody, A.S. Kloman, F.H. Gilles, Sequence of central nervous system myelination in human infancy, patterns of myelination in autopsied infants, J. Neuropathol. Exp. Neurol. 47 (1988) 217–234.
[32] H.R. Wilson, Development of spatiotemporal mechanisms in infant vision, Vis. Res. 28 (1988) 611–628.

International Journal of Pediatric Otorhinolaryngology (2008) 72, 1751–1763

ELSEVIER

International Journal of Pediatric Otorhinolaryngology

www.elsevier.com/locate/ijporl

Myelination progression in language-correlated regions in brain of normal children determined by quantitative MRI assessment

Peijen Su [a], Chen-Chieh Kuan [a,*], Kimitaka Kaga [a], Masaki Sano [a], Kazuo Mima [b]

[a] *Department of Otorhinolaryngology and Head and Neck Surgery, Graduate School of Medicine and Faculty of Medicine, University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan*
[b] *Division of Radiology, University of Tokyo Hospital, Tokyo, Japan*

Received 31 January 2008; received in revised form 14 May 2008; accepted 15 May 2008
Available online 11 October 2008

KEYWORDS
Myelination;
MRI study;
Language-correlated region;
Broca's area;
Wernicke's area;
Arcuate fasciculus;
Developing brain

Summary

Objective: To investigate the myelination progression course in language-correlated regions of children with normal brain development by quantitative magnetic resonance imaging (MRI) analysis compared with histological studies.
Methods: The subjects were 241 neurologically intact neonates, infants and young children (128 boys and 113 girls) who underwent MRI between 2001 and 2007 at the University of Tokyo Hospital, ranging in age from 0 to 429 weeks corrected by postnatal age. To compare their data with adult values, 25 adolescents and adults (14 men and 11 women, aged from 14 to 83 years) were examined as controls. Axial T2-weighted images were obtained using spin-echo sequences at 1.5 T. Subjects with a history of prematurity, birth asphyxia, low Apgar score, seizures, active systemic disease, congenital anomaly, delayed development, infarcts, hemorrhages, brain lesions, or central nervous system malformation were excluded from the analysis. Seven regions of interest in language-correlated areas, namely Broca's area, Wernicke's area, the arcuate fasciculus, and the angular gyrus, as well as their right hemisphere homologous regions, and the auditory cortex, the motor cortex, and the visual cortex were examined. Signal intensity obtained by a region-of-interest methodology progresses from hyper- to hypointensity during myelination. We chose the inferior cerebellar peduncle as the internal standard of maturation.
Results: Myelination in all these seven language-correlated regions examined in this study shared the same curve pattern: no myelination was observed at birth, it reached maturation at about 1.5 years of age, and it continued to progress slowly thereafter into adult life. On the basis of scatter plot results, we put these areas into three

* Corresponding author. Tel.: +81 3 5800 8665; fax: +81 3 3814 9486.
E-mail address: peijensu-tky@umin.ac.jp (C.-C. Kuan).

0165-5876/$ – see front matter
doi:10.1016/j.ijporl.2008.05.017

groups: Group A, which included the motor cortex, the auditory cortex, and the visual cortex, myelinated faster than Group B, which included Broca's area, Wernicke's area, and the angular gyrus before 1.5 years old; Group C, consisting of the arcuate fasciculus, has similar degree of myelination as Group B before 1.5 years but then myelinated more slowly after 3 years of age. No gender or left-right differences between homologous regions were found.

Conclusions: In this study, we determined the sequence of myelination of language-correlated regions in infants and children by quantitative MRI assessment. The higher cortical areas matured later than the primary cortical areas, and the arcuate fasciculus matured last. The observation that myelination reaches maturity after 18 months suggests that myelination may be a reason for the acceleration in vocabulary acquisition observed in children from that age. The slow pace of myelination also suggested the possibility of language development's continuation into early adult life. Myelination assessed by MRI was at least 1 month behind that assessed by histological staining. No gender or left-right hemisphere differences in myelination were noted.

1. Introduction

Language is a uniquely complex cognitive ability. Linguistic competence, which develops rapidly during early childhood, requires the cooperation among several areas of the cortex. An auditory signal received by the auditory cortex is understood after being processed in Wernicke's area, and then transmitted from Wernicke's area through the arcuate fasciculus to Broca's area. Broca's area, which performs the operation of verbalizing a message, then supplies it to the motor cortex, which drives the muscles used for speaking. When the subject is reading, the signal is received by the primary visual cortex and is delivered to the angular gyrus, which links the visual form of the written word with the corresponding auditory pattern in Wernicke's area. Speaking involves the same systems, but in a different order of operations.

It is well known that speech function is usually lateralized in the left hemisphere and hemispheric anatomical asymmetry is present at birth [1]. Maturation of the developing brain progresses rapidly in the early years and involves many changes in neuronal elements, including myelination [2] and synaptic pruning [3].

Myelination is an important process for brain development because it enhances the speed of neural communication and represents progression in functional brain maturation [4–7]. The maturation of myelination is virtually complete at the end of the first 2 years of life [7–9]. Nonetheless, myelination continues through childhood and into adulthood [10–12].

Before the development of magnetic resonance imaging (MRI), myelination was conventionally evaluated by histological staining methods [4,5,13,14]. Myelin is hydrophobic, and myelin formation is associated with a decrease in water content, which can be detected by MRI. The use of MRI to evaluate myelination visually and quantitative assessment of myelination-associated changes in the signal intensity of regions of interest (ROI) in the brain for detecting subtler changes has been reported [15–29]. However, a time lag has been noted between the determination of myelination by histological staining and its determination by MRI [7,15,21,29–31].

To date, there have been no studies specifically assessing the course of myelination in language-correlated regions of normal children by quantitative MRI assessment. The purpose of this study is to establish the progression of myelination in Broca's area, Wernicke's area, the arcuate fasciculus, and the angular gyrus, as well as their right hemisphere homologous regions, and the auditory cortex, the motor cortex, and the visual cortex in a normal developing brain.

1.1. Subjects

The subjects were 241 neurologically intact neonates, infants and young children (128 boys and 113 girls) who underwent MRI between 2001 and 2007 at the University of Tokyo Hospital, ranging in age from 0 to 429 weeks (8 years 3 months) by corrected postnatal age. For comparison with adult values, 25 adolescents and adults (14 men and 11 women, aged from 14 to 83 years) were examined as the control. These patients underwent MRI because a brain disorder was suspected: subjects with a history of prematurity, birth asphyxia, low Apgar score, seizures, active systemic disease, congenital anomaly, delayed development, infarcts, hemorrhages, brain lesions, or central nervous system malformation were excluded from analysis. The study protocol

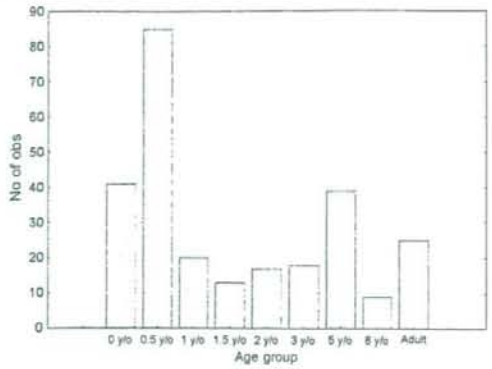

Fig. 1 Age distribution of the study population.

was approved by the Ethics Committee of the University of Tokyo. The corrected postnatal week (CPW) was calculated in accordance with the definition established by the World Health Organization, that is, by subtracting the number of weeks a child was born prematurely from the current age in weeks [32]. The age distribution of subjects is shown in Fig. 1.

1.2. Imaging methods

Axial T2-weighted magnetic resonance (MR) images were obtained using spin-echo sequences at 1.5 T (MagnetomVision 1.5 T, Siemens, Germany, Signa Excite HD 1.5 T, GE, USA). Sections were perpendicular to the long axis of the brain and 5–7 mm thick. Repetition time (TR) and echo time (TE) in T2-weighted images were 3000 ms and 70–100 ms, respectively. On the basis of previous studies, T2-weighted images were used because they correlate well with myelin-containing macroslices of age-matched postmortem brains and, they yield better gray and white matter contrasts than T1-sequences, and are therefore more suitable for evaluating maturation [23,24]. On T2-weighted MR images, signal intensity obtained by a region-of-interest method progresses from hyper- to hypointensity during myelination.

1.3. Depiction of regions of interest

For quantitative analysis, signal intensity was measured by the region-of-interest (ROI) method. Values for each ROI were determined using Centricity Web-J software (GE Yokogawa Medical Systems, Inc., Tachikawa, Japan). Seven regions of interest (ROIs) in language-correlated regions, namely Broca's area, Wernicke's area, the arcuate fasciculus, the angular gyrus, and their homologous regions in the right hemisphere as well as the auditory cortex,

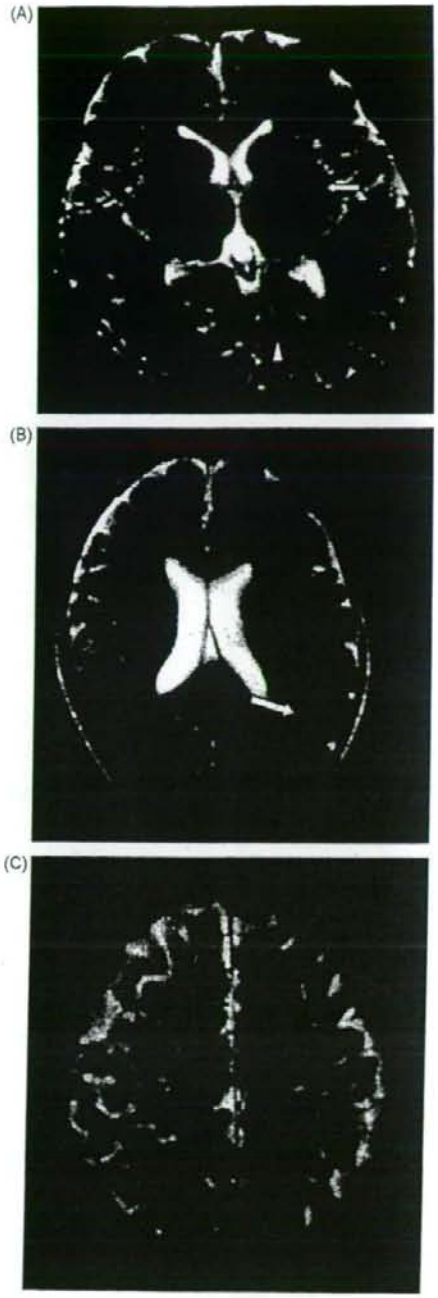

Fig. 2 (A) Depiction of regions of interest (T2-weighted images). Black arrow indicates Broca's area; white arrow indicates arcuate fasciculus; black arrowhead indicates auditory cortex; white arrowhead indicates visual cortex. (B) Black arrow indicates Wernicke's area; white arrow indicates angular gyrus. (C) Arrow indicates motor cortex.

the motor cortex, and the visual cortex were evaluated. We measured the subcortical white matter of Broca's area, Wernicke's area, the angular gyrus, the auditory cortex, the motor cortex, and the visual cortex. The boundaries and locations of these ROIs were typically as demonstrated in Fig. 2. Each ROI is about 8 pixels (0.22 cm^2) sampled about 1 mm just below the crest of the gyri cortex. In this study, we chose the inferior cerebellar peduncle as the internal standard of maturation.

1.4. Location of ROI

1. Wernicke's area (sensory, Brodmann area 22) is located in the posterior part of the superior temporal gyrus and lies between the primary auditory cortex and the angular gyrus (Brodmann area 39).
2. An important part of Wernicke's area projects into the motor speech area, Broca's area, via a corticocortical association pathway called the arcuate fasciculus. The arcuate fasciculus runs between the temporal, parietal and frontal lobes, and conjoins Wernicke's area, the visual-auditory conversion language area, and Broca's area.
3. Broca's area (motor speech, Brodmann area 44) lies in the frontal lobe, anterior to the primary motor and premotor cortex, corresponding to cytoarchitectonic areas 44 and 45 of the inferior frontal gyrus.
4. The primary motor cortex (Brodmann area 4) is located in the dorsal part of the precentral gyrus and the anterior bank of the central sulcus.
5. The primary visual cortex can be recognized by Gennari's band located in the occipital lobe in the upper and lower lips of the calcarine sulcus.
6. The primary auditory cortex (Brodmann area 41) is located in the anterior transverse temporal gyrus (of Heschl) on the floor of the lateral sulcus and is surrounded by higher-order auditory cortical areas (cytoarchitectonic areas 42 and 22), located on both the superior and lateral surfaces of the temporal lobe in the superior temporal gyrus.
7. The visual-auditory conversion language area is located in the angular gyrus.

1.5. ROI-based analysis

Counts for each ROI were measured using Centricity Web-J software (GE Yokogawa Medical Systems, Inc., Tachikawa, Japan). The ROIs were carefully chosen to minimize the effect of partial volume averaging. The number of pixels within each ROI was recorded, with a minimum of five pixels for each ROI. The signal intensity ratio (SIR) was calculated using the ratio of the signal intensity of each of the designated areas of the brain to that of its ipsilateral vitreous body, which is in accordance with the method reported by McArdle [25], and also used by Abe [15].

$$SIR = \frac{S_{region}}{S_{eyeball}}$$

The vitreous body was chosen as the reference because its chemical composition and gel state remain constant during youth and young adulthood (perinatal to 30 years of age) [33–35].

1.6. Statistical analysis

In this study, statistical analysis was performed using SPSS software, Ver. 14.0 for Windows. The changes in the signal intensity ratio (SIR) in these ROIs were compared to the corrected postnatal week [32]. We analyzed the correlation between the signal intensity ratio (SIR) of each region and the subject's age. Multiple scatter plots and best-fit regression analyses were used to compare the myelination curves among the different regions in relation to the subject's age. One-way ANOVA with the Tukey–Kramer test was used for multiple comparisons among different age groups and for multiple SIR comparisons among different ROIs. We used the *t*-test with a box-and-whisker plot to compare, separately, ROIs in Group A (the motor cortex, visual cortex, and auditory cortex) with the ROIs in group B (Wernicke's area, Broca's area, and the angular gyrus) before 1.5 years of age, and to compare each ROI of group B with group C (the arcuate fasciculus) in the group from 3 to 8 years of age. We also used the *t*-test with a box-and-whisker plot to compare left-right hemisphere ROIs among different age groups and male and female ROIs in the same region. A *P*-value less than 0.05 denoted the presence of a significant difference.

2. Results

Age-related myelination progression was best-fitted with an exponential curve showing the variations in myelination velocity throughout the studied period.

1. The SIR of the inferior cerebellar peduncle was between 0.5 and 0.4 at birth and varied subtly with corrected age (Fig. 3H).
2. From one-way ANOVA, we found that in nearly all language-correlated regions, myelination had reached quasi-maturity by the 18th month and then slowed down after that, but continuing into

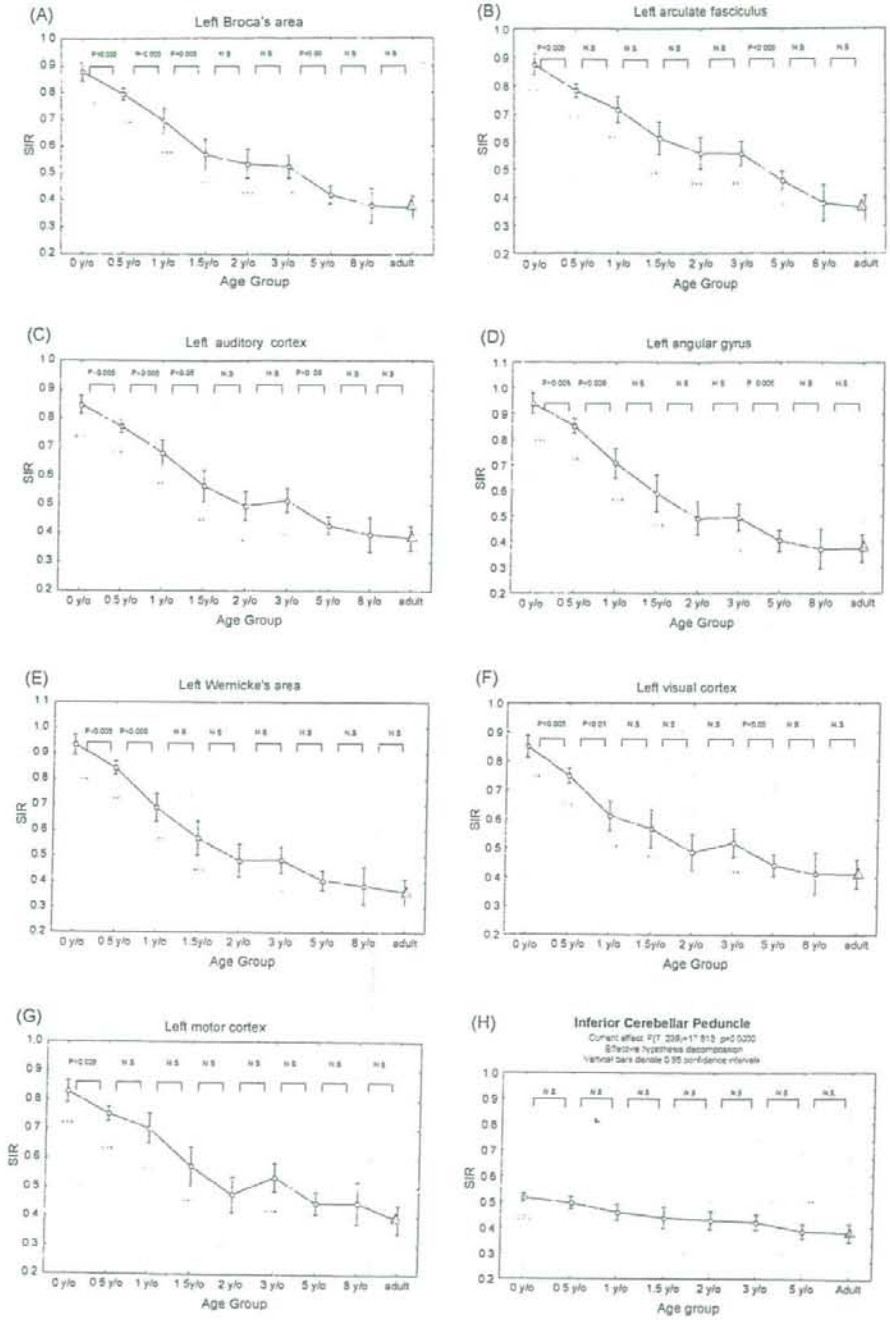

Fig. 3 The mean ± S.E.M. of the signal intensity ratio was obtained in different areas of the left hemisphere in each age group. N.S. not significant, $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.005$. One-way ANOVA with the Tukey–Kramer test was used for multiple comparisons among different age groups. Red asterisks show the Tukey–Kramer multiple-comparison test with adult control group, marked by a red triangle. Vertical bars denote 0.95 confidence intervals. (The mean ± S.E.M. of the signal intensity ratio was also obtained in the same regions of the right hemisphere, which are not shown in this article.)

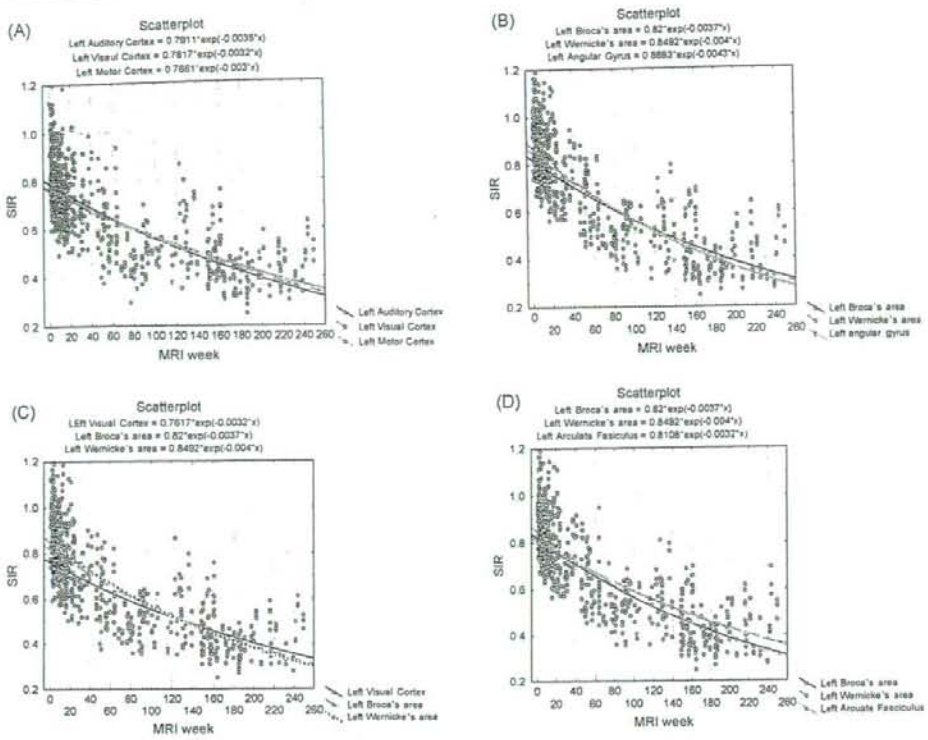

Fig. 4 Scatter plot graphs showing changes in the signal intensity ratio (SIR = S region/S eyeball) related to age. Each small circle is the SIR value in a given region for one subject at the time of measurement. The lines represent separate best-fit regression curves for each region. (A) Group A: Subjects' SIRs and best-fit regression curves for the left auditory cortex, the left visual cortex, and the left motor cortex. (B) Group B: Subjects' SIRs and best-fit regression curves for Wernicke's area, Broca's area, and angular gyrus. (C) Comparison between Group A and Group B. (C) Comparison between Group B and arcuate fasciculus.

adult life (Fig. 3A–G). Myelination shows similar patterns in these graphs. In the period from 0 to 1.5 years of age, the SIR changed from 0.88 to 0.5. In all regions, myelination continued progressively but slowly, the SIR reaching nearly 0.4 in the adult group. We further divided subjects aged younger than 6 months old into six groups at intervals of 1 month and carried out one-way ANOVA analysis. From the Tukey–Honestly Significant Differences (HSD) test, in Broca's area, Wernicke's area, the left arcuate fasciculus, the left visual cortex, the left motor cortex, and the left auditory cortex, the SIR showed a significant change from 4 months ($P < 0.05$), and in the left angular gyrus from 6 months ($P < 0.05$) (Fig. 7).

3. Based on the results of multiple scatter plots, we divided the regions under consideration into three groups. The motor cortex, auditory cortex, and visual cortex, which carry out primary functions, were classified into group A (Fig. 4A); Broca's area, Wernicke's area, and the angular gyrus, which are higher-order association areas, were classified into group B (Fig. 4B); and the arcuate fasciculus alone was classified into group C. From the *t*-test with a box-and-whisker plot, we found that myelination proceeded markedly faster in group A than in group B until 1.5 years of age ($P < 0.05$) (Fig. 4C); myelination of the arcuate fasciculus was similar to the pace of myelination in group B at the beginning of childhood but slower after 3 years of age (Fig. 4D).
4. When we analyzed the data using the *t*-test with a box-and-whisker plot, we found no gender difference (Fig. 5).
5. Likewise, we observed no left-right hemisphere differences between homologous regions (Fig. 6).

3. Discussion

No previous study has, to our knowledge, evaluated myelination specifically in language-correlated

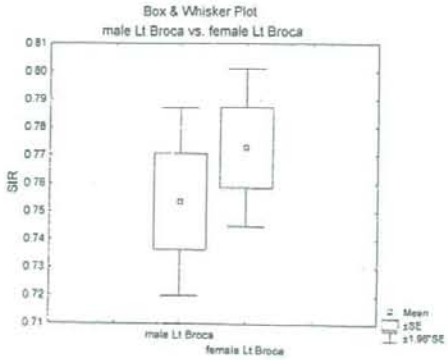

Fig. 5 Results of the *t*-test with a box and whisker plot comparing signal intensity ratio (SIR) differences (long axis) in Broca's area between male and female subjects in the age 0 group (shown in this figure) were not significant ($P = 0.384$). Other comparisons, which similarly failed to detect statistically significant sex differences in other ROIs, are not shown in this study.

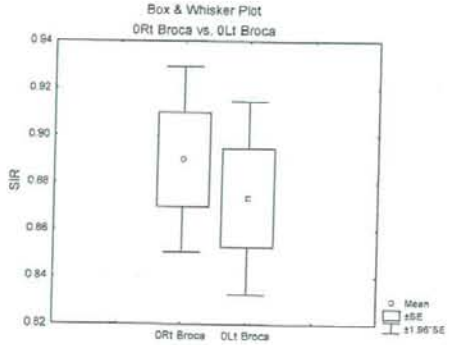

Fig. 6 Results of the *t*-test with a box and whisker plot comparing differences between Broca's area and the right hemisphere homolog of Broca's area in the age 0 group (shown in this figure) were not significant ($P = 0.57$). Other comparisons, which similarly failed to detect statistically significant hemisphere asymmetry in other age groups and in other ROIs, are not shown in this study.

regions of normal children. We therefore believe this to be the first study to have established the progression of myelination in Broca's area, Wernicke's area, and the arcuate fasciculus, the angular gyrus, the auditory cortex, the visual cortex, and the motor cortex in a normal developing brain by quantitative MRI assessment and to have compared the MRI with histological findings. This method is applicable clinically for the diagnosis of delayed myelination or demyelination. We compare our results with previous MRI studies and then with histological studies at the end of this paper.

3.1. Language processing

Language is an extremely complicated ability, involving several distinct areas of the cortex in order to complete linguistic processing. Linguistic competence requires coordination among these different areas of the cortex. Once an auditory signal has been detected, it is received by the auditory cortex, but it cannot be understood as a word until it has been processed in Wernicke's area. If a spoken word is heard, some representation is transmitted from Wernicke's area to Broca's area through a white fibrous tract called the arcuate fasciculus. Similar to a computer, Broca's area is responsible for the programming that verbalizes a message, which is then supplied to the face area of the motor cortex. The motor cortex then drives the muscles of the lips, the tongue, the larynx, etc., which are responsible for respiration, phonation, resonation, and articulation. When a written word is read, it is received by the primary visual cortex, then delivered to the angular gyrus, which joins the visual form of the word with the corresponding auditory pattern in Wernicke's area. Speaking the word involves the same neuronal systems mentioned above.

Generally speaking, Broca's area and Wernicke's area are the areas specifically responsible for the production and comprehension of language. The angular gyrus mediates between the visual and auditory forms of information, called the visual-auditory conversion language area. These specializations have only been detected on the left side. The corresponding areas on the contralateral side do not have the same linguistic ability.

The auditory sector of the language system, which comprises the pathway from the inner ear over the inferior colliculus to the auditory cortex, is functional prenatally from 20 to 24 gestational weeks (GW) of age [2]. The speech function is lateralized in the left hemisphere, and hemispheric anatomical asymmetry is present at birth. The language-mediating area of the superior surface of the temporal lobe (planum teporale), which is a part of the classical area of Wernicke, has been found to be statistically significantly larger on the left side both in neonates and adults [1,36]. Morphological asymmetry of the frontal operculum and temporal planum becomes measurable at the 29th GW [37].

3.2. Myelination examination by MRI

Language development during childhood is rapid, and maturation of the developing brain also progresses rapidly in the early years and involves many changes in neuronal elements, including

myelination [2], synaptic pruning [3], synaptogenesis, and dendritric and axonal arborization [6].

Myelination is the development of a protective myelin sheath around cranial nerves that facilitates neural functioning. It has been proven to be an important factor for brain maturation because it increases the propagation of neural impulses through the nerve system. The speed of neural transmission depends on not only on the synapses, but also structures of connecting fibers, which include axonal diameter and myelin sheath thickness. Myelination is associated with changes in water content owing to the expression of proteins and phospholipids. Because myelin is hydrophobic, composed of a bilayer of lipids with several large proteins, myelin formation is associated with a decrease in water content [8]. Myelination begins in the brain stem during the intrauterine stage, that is, 29 weeks [33], changes most rapidly during the first 2 years of life, and then continues throughout life.

Myelination proceeds from the inferior to superior, posterior to anterior, at different rates in different neuronal systems and in different tracts of the same neuronal systems [38]. Proximal pathways tend to myelinate before distal pathways, sensory areas before motor areas, and projection fibers before association fibers.

Histological studies of myelination have been reported previously [4,5,13,14]. However, it is difficult to evaluate the progression course of myelination owing to the scarcity of brain specimens. Therefore, the unique sensitivity of MRI to detect changes in water content offers opportunities to investigate the developmental process in vivo. However, a minimal threshold concentration of myelin build-up is necessary to change the signal intensity on MRI; thus, the MRI lags several weeks behind the histological timetable [7,15,21,29–31].

In previous studies, myelination was examined by using MRI qualitative or semiquantitative ratings in normal infants and children [8,15,16,18,20,22,27–30,36,38,39]. As many studies have shown that delayed myelination in children is related to developmental delay [13,14,16,31,40], it is important to establish the pace of myelination in normal children.

3.3. Previous MRI studies of myelination

Myelination during subcortical white matter maturation has been previously studied by T2-weighted MRI. Baierl et al. [16] mentioned that the subcortical white matter underwent a slow myelination. The contrast between gray and white matter continues to increase up to age 10 years whereas a rapid myelination of the internal capsule has been observed only in the first 2 years of life.

Holland et al. [21] reported that the subcortical white matter can be distinguished from the cortical gray matter at about 4–6 months by MRI assessment. Myelination begins around 9 months. The subcortical occipital white matter at 3 years shows a similar myelination level to that of adults, whereas the subcortical frontal white matter matures at 5 years. Owing to further minor refinements, the cortical white matter does not reach maturity until early adolescence.

The results of Girard et al. [41] differ from ours, and the results of Holland et al., Baierl et al., and Girard et al. mentioned that cortical myelination was visible in the occipital and ascending frontal regions as early as the 15th day of life, temporal region myelination had occurred at the age of 3 months, and cortical frontal myelination occurred last. Cortical myelination progressed in a rostral direction gradually and from place to place, developed earlier than that of the corresponding tracts, and was not continuous with it. Cortical myelination was completed at 26 months old, whereas our results showed myelination continuing later into adult life. Dietrich et al. [20] mentioned that myelination occurred in the optic radiations (3 months), the anterior limb of the internal capsule extending to the precentral gyrus (6 months), the parietal and frontal white matter (8 months), and the white matter of the temporal lobes (1 year), and later in the subcortical fibers. Dietrich [19] also reported that myelination progressed in the parietal and frontal white matter (8 months) and then in the white matter of the temporal lobe (1 year). After 1 year, myelination extended more peripherally and further myelinated subcortical fibers were noted at 2 years of age. Bird et al. [39] mentioned that the superficial or subarcuate white matter in the cerebral lobes showed similar patterns to the deep white matter, that is, it showed a slow progression of myelination and reached the same level of maturity as the internal capsule at about 2 years of age. This time course corresponds closely to our observation. Barkovich [17] found that the subcortical white matter (excluding the calcarine and rolandic areas) mature last; myelination begins at 9–12 months of age in the occipital lobe, at 11–14 months in the frontal lobe and then in the temporal lobe. He defined the peritrigonal region as the terminal zone, owing to its persistent hypersensitivity observed in T2-weighted images, and described it as the last associative area to mature. With the exception of the terminal zone, the entire white matter should mature by the 2nd year of life. However, Parazzini et al. [26] redefined the terminal zones of myelina-

tion as the subcortical areas rather then the peritrigonal region [17]. Parazzini found that the subcortical frontal, temporal, and parietal areas should be regarded as the terminal zones, because these areas complete their myelination at 36–40 months.

3.4. Comparison with histological studies of myelination

According to previous reports, changes in white matter maturation are best determined on T1-weighted images during the first 6–8 months, while after 6 months, T2-weighted images are more useful for evaluation of normal brain maturation [8,21,39,42]. T2-weighted sequences enable detection of true myelination, whereas T1-weighted sequences enable detection only of "myelination gliosis" [41]. We chose T2-weighted images because they correlate better with myelin-stained macroslices of age-matched postmortem brains, thus providing a better gray-white matter contrast [24]. We calculated SIRs using the ratio of the signal intensity of each of the designated areas of the brain to that of its ipsilateral vitreous body. The vitreous body was chosen as the reference because its chemical composition and gel state remain constant during youth and young adulthood (perinatal to 30 years of age) [33–35], and it is frequently used in MRI image studies to standardize different T2-weighted pulses.

In this study, we chose the inferior cerebellar peduncle as the internal standard of maturation because myelination there has been detected at 25 weeks of gestation [43] and has reached maturity at birth [23]. Thus, the value of the SIR at maturation in our study was defined to be about 0.5. The posterior limb of the internal capsule was taken as the mature standard in the myelination evaluation in histological specimens [4] and MRI images [39]; myelination of the posterior limb of the internal capsule has been discerned by 37–38 weeks using T2-weighted sequences [43].

We divided the samples according to age for more detailed analyses of SIR changes. Considerable changes occurred within age intervals and showed similar patterns in these seven language-correlated regions. The SIR decreased from 0.88 to 0.5 in the 0-year-old group and the 1.5-year-old group, and then slowly decreased to 0.4 in the adult group (Fig. 3). On the basis of the SIR, we observed that myelination changed significantly after 4 months and approached near-maturity by the 18th month, continually extending slowly into adult life, which agreed with the findings by Yakovlev and Lecour [5] and Flechsig [13]. The progression matched the development of "language explosion." Around the end of the 2nd year, an explosion in the number of words a child understands and produces is noted: it increases fourfold, and word comprehension always develops before word production [44].

In Yakovlev and Lecour's study [5], the cerebral wall was divided into three respective myeloarchitectonic zones: the median, paramedian, and the supralimbic zones. These zones myelinate as tecogenetic and myeloarchitectonic units, and each exhibits a different cycle of myelination. The ROIs of our study are all located in the supralimbic zone. Yakovlev and Lecour observed that in the white matter of the supralimbic zone, the long association and commissural fiber systems began myelination from 3 months and continued into at least the second half of the first decade of life, continuing myelination at 7 years of age and later. Flechsig reported that within the supralimbic zone, the association areas of the convexity of the frontal, parietal and temporal lobes contain the highest numbers in the orders of myelogenesis according to him (explained below), which he termed the terminal areas. They began myelination from 3 months and, according to Yakovlev and Lecour, maintain myelination the longest, that is, longer than other regions. The above areas of the supralimbic division of the hemisphere all exhibit an exponential "cycle" of myelination, beginning during the first 3 postnatal months and ending at a time that cannot be determined.

To define in more detail the differences, we further divided the subjects younger than 6 months of age into 6 groups at intervals of 1 month and carried out one-way ANOVA. From the Tukey–Kramer test, SIRs in Broca's area, Wernicke's area, the left arcuate fasciculus, the left visual cortex, the left motor cortex, and the left auditory cortex significantly changed from 4 months ($P < 0.05$), the left angular gyrus from 6 months ($P < 0.05$). Our results showed at least a 1-month lag compared with histological findings (Fig. 7).

As described previously in Section 2, we assigned these regions to three groups based on the results of multiple scatter plots. The motor cortex, auditory cortex, and visual cortex were classified into group A (Fig. 4A); Broca's area, Wernicke's area, and the angular gyrus were classified into group B (Fig. 4B); and the arcuate fasciculus alone was classified into group C. Our results showed that myelination appeared more rapidly in group A (primary cortical area) than in group B (higher cortical area) before the 18th month (Fig. 4C). Maturation was not observed earlier in Wernicke's area than in Broca's area, which might explain, or be explained by, the earlier acquisition of speech comprehension than speech production [45]. The arcuate fasciculus myelinates later than the motor cortex, the visual

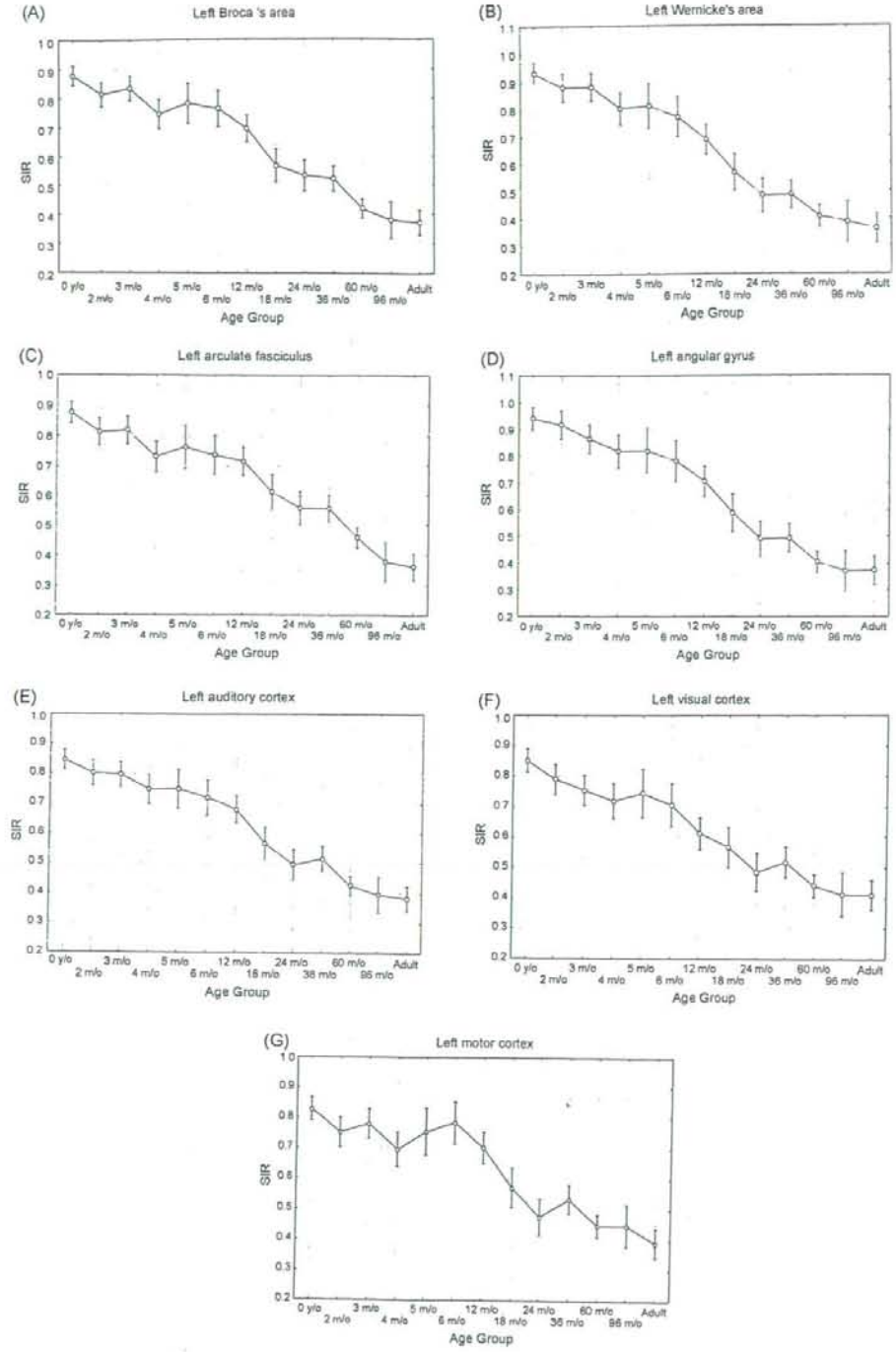

Fig. 7 The mean ± S.E.M. of the signal intensity ratio was obtained in different areas of the left hemisphere and tested by one-way ANOVA with the Tukey–Kramer test for multiple comparisons among different age groups. The mean ± S.E.M. of the signal intensity ratio was also obtained in the same areas of the right hemisphere (not shown in this article). Vertical bars denote 0.95 confidence intervals.

cortex, and the auditory cortex (group A); to be more specific, it myelinates later than Broca's area and Wernicke's area (group B), after 3 years of age (Fig. 4D). These results agreed well with those of Flechsig [13], Kinney et al. [4], and van der Knaap and Valk [7].

Flechsig was the first to report that the degree of myelination of the central nervous system may correlate with functional capacity [13]. In Flechsig's map, he classified the cortical areas into (1) "primary" myelogenetic areas, to which are assigned the lowest numbers in the order of their myelination (1–10) and include the motor cortex, the visual cortex, and the auditory cortex in our study. (2) He termed the opercular and paralimbic areas surrounding these primary areas "intermediate" areas and "terminal zones," which were numerically designated from 11 to 36 and include Broca's area, Wernicke's area, the angular gyrus, and the arcuate fasciculus in our study. He also stated that myelination started in projection pathways before association pathways, in peripheral nerves before central pathways, and in sensory areas before motor areas. He maintained that fibers myelinated in the same order: first the afferent (sensory), then the efferent (motor), and then the association fibers.

In our MRI study, group A myelinated earlier than group B (Fig. 4C), which also agreed well with the classification of myelination in autopsied infants by Kinney et al. [4]. Their study showed that subcortical association fibers of the visual cortex and Heschl's gyrus belong to the same group, whose myelination began earlier and also reached maturity earlier than the group of subcortical fibers in all sites except the calcarine cortex (visual cortex). All these areas were found by microscopy not to contain myelin at birth, which is consistent with our finding: we also found that these areas were not myelinated at birth. In their study, in 50% of infants, the subcortical association fibers of the visual cortex reached maturity in myelination of degree 3 (myelin mature but not as completely mature as adult myelin) at 72 postconceptional weeks (32 corrected postnatal weeks), and Heschl's gyrus at 88 weeks (48 corrected postnatal weeks).

Van der Knaap and Valk [7] mentioned that myelination of the nervous system follows a pattern of ordered sequences of myelinating systems, which they described as "rules." The first rule is that tracts in the nervous system become myelinated at the time they become functional. Myelination occurs in the peripheral before it occurs in the central nervous system, in central sensory areas earlier than in central motor areas, and in areas of primary function earlier than in association areas; most tracts become myelinated in the direction of the impulse conduction, progress from caudal (spinal cord) to rostral parts (brain) and from central to peripheral parts of the brain, although there are exceptions. Our scatter plots are compatible with these rules.

Gender differences in language function have been well known for decades and are reported in the literature on psychology, whereas there has been little systematic research into the effect of gender on structural differences in the brain related to language [38]. Our results revealed no gender difference in myelination (Fig. 5), nor did we find any difference between myelination in these regions and myelination in their right hemisphere homologs (Fig. 6).

4. Conclusion

Our results showed that in a normal developing brain the progression of myelination in the language-correlated regions could be assessed by MRI. During the brain's development, higher cortical areas matured later than primary cortical areas; the arcuate fasciculus matured last. No gender or left-right hemisphere differences in myelination were found.

The slow pace of progressive myelination also disclosed the possibility of continuation of language development into early adult life. A mature myelination phase was attained in the language-correlated regions in the brain after 18 months, when children begin showing accelerated vocabulary acquisition. Thus our results point to a relationship between myelin deposition in the language domains and acceleration of vocabulary acquisition in children, although myelination itself may not be the only cause, because other variables related to myelination, such as synaptic efficiency, may also be important, or more important, in vocabulary growth.

4.1. Limitations of the study

We did not investigate whether our subjects were right-handed or left-handed, although handedness has been proven to affect development in language-correlated regions by a previous study [36]. The decreased T2 signal intensity in the adult group may be due to the effect of aging: it has been reported that iron content in the cerebral cortices increases with age; thus T2 shortening is frequently observed in the cerebral cortices in neurologically normal older people [46]. The effect of iron on local fields causes the subcortical white matter to appear more myelinated than the deep white matter [39], while the reverse is true in histological staining [47].

Finally, we were unable, by this method, to define the differences among the motor cortex, the visual cortex, and the auditory cortex in this study, although we were able to establish a trend. Further research may be required to clarify.

Acknowledgments

We would like to express gratitude to Dr. Kondo for his help, and also gave thanks to Dr. Holmes for his English advising and contribution to this article.

References

[1] S.F. Witelson, W. Pallie, Left hemisphere specialization for language in the newborn. Neuroanatomical evidence of asymmetry, Brain 96 (3) (1973) 641–646.
[2] N. Herschkowitz, J. Kagan, K. Zilles, Neurobiological bases of behavioral development in the second year, Neuropediatrics 30 (1999) 221–230.
[3] P.R. Huttenlocher, C. de Courten, The development of synapses in striate cortex of man, Hum. Neurobiol. 6 (1987) 1–9.
[4] H.C. Kinney, B.A. Brody, A.S. Kloman, F.H. Gilles, Sequence of central nervous system myelination in human infancy. II. Patterns of myelination in autopsied infants, J. Neuropathol. Exp. Neurol. 47 (3) (1988) 217–234.
[5] P.I. Yakovlev, A. Lecour, The myelogenetic cycles of regional maturation of the brain, in: Minkowski (Ed.), Regional Development of the Brain in Early Life, Blackwell Scientific Publication, Oxford, 1967, pp. 3–70.
[6] R.K. Lenroot, J.N. Giedd, Brain development in children and adolescents: insights from anatomical magnetic resonance imaging, Neurosci. Biobehav. Rev. 30 (6) (2006) 718–729.
[7] M.S. van der Knaap, J. Valk, Magnetic Resonance of Myelin, Myelination, and Myelin Disorders, 2nd ed., Springer, Berlin, Heidelberg, New York, 1995.
[8] A.J. Bakovich, B.O. Kjos, D.F. Jackson Jr., et al., Normal maturation of the neonatal and infant brain: MR imaging at 1.5 T, Radiology 166 (1988) 173–180.
[9] C. Christophe, M.F. Muller, D. Baleriaux, et al., Mapping of normal brain maturation in infants on phase-sensitive inversion-recovery MR images, Neuroradiology 32 (1990) 173–178.
[10] L. Svennerholm, M.T. Vanier, Lipid and fatty acid composition of human cerebral myelin during development, Adv. Exp. Med. Biol. 100 (1978) 27–41.
[11] K. Hayakawa, Y. Konishi, M. Kuriyama, et al., Normal brain maturation in MRI, Eur. J. Radiol. 12 (1991) 208–215.
[12] A. Pfefferbaum, D.H. Mathalon, E.V. Sullivan, et al., A quantitative magnetic resonance imaging study of changes in brain morphology from infancy to late adulthood, Arch. Neurol. 51 (1994) 349–358.
[13] P. Flechsig, Anatomie des menschlichen Gehirns und Rückenmarks auf myelogenetischer Grundlage, Thieme, Leipzig, 1920.
[14] L.B. Rorke, H.E. Riggs, Myelination of the Brain in the Newborn, Lippincott Company, Philadelphia, 1969.
[15] S. Abe, K. Takagi, T. Yamamoto, Y. Okuhata, T. Kato, Semiquantitative assessment of myelination using magnetic resonance imaging in normal fetal brains, Prenat. Diagn. 24 (5) (2004) 352–357.
[16] P. Baierl, C. Förster, H. Fendel, M. Naegele, U. Fink, W. Kenn, Magnetic resonance imaging of normal and pathological white matter maturation, Pediatr. Radiol. 18 (3) (1988) 183–189.
[17] A.J. Barkovich, Normal development of the neonatal and infant brain, skull, and spine, in: Pediatric Neuroimaging, 3rd ed., Lippincott Williams & Wilkins, Philadelphia, 2000, pp. 13–69.
[18] S.J. Counsell, E.F. Maalouf, A.M. Fletcher, P. Duggan, M. Battin, H.J. Lewis, A.H. Herlihy, A.D. Edwards, G.M. Bydder, M.A. Rutherford, MR imaging assessment of myelination in the very preterm brain, Am. J. Neuroradiol. 23 (5) (2002) 872–881.
[19] R.B. Dietrich, Magnetic resonance imaging of normal brain maturation, Semin. Perinatol. 14 (3) (1990) 201–211.
[20] R.B. Dietrich, W.G. Bradley, I.V. Zaragoza, et al., MR evaluation of early myelination patterns in normal and developmentally delayed infants, Am. J. Roentgenol. 150 (1988) 889–896.
[21] B.A. Holland, D.K. Haas, D. Norman, M. Brant-Zawadzki, T.H. Newton, MRI of normal brain maturation, Am. J. Neuroradiol. 7 (2) (1986) 201–208.
[22] M. Maezawa, Magnetic resonance signal intensity ratio of gray/white matter in children, Brain Dev. 15 (1993) 198–204.
[23] E. Martin, C. Boesch, M. Zuerrer, R. Kikinis, L. Molinari, P. Kaelin, et al., MR imaging of brain maturation in normal and developmentally handicapped children, J. Comput. Assist. Tomogr. 14 (5) (1990) 685–692.
[24] E. Martin, R. Kikinis, M. Zuerrer, C. Boesch, J. Briner, G. Kewitz, et al., Developmental stages of human brain: an MR study, J. Comput. Assist. Tomogr. 12 (6) (1988) 917–922.
[25] C.B. McArdle, C.J. Richardson, D.A. Nicholas, M. Mirfakhraee, C.K. Hayden, E.G. Amparo, Development features of the neonatal brain: MR imaging. Part I. Gray-white matter differentiation and myelination, Radiology 162 (1987) 223–229.
[26] C. Parazzini, C. Baldoli, G. Scotti, F. Triulzi, Terminal zones of myelination: MR evaluation of children aged 20–40 months, Am. J. Neuroradiol. 23 (10) (2002) 1669–1673.
[27] M. Sano, K. Kaga, C.C. Kuan, K. Ino, K. Mima, Early myelination patterns in the brainstem auditory nuclei and pathway: MRI evaluation study, Int. J. Pediatr. Otorhinolaryngol. 71 (7) (2007) 1105–1115.
[28] M. Staudt, C. Schropp, F. Staudt, N. Obletter, K. Bise, A. Breit, H.M. Weinmann, MRI assessment of myelination: an age standardization, Pediatr. Radiol. 24 (2) (1994) 122–127.
[29] M.S. van der Knaap, J. Valk, MR imaging of the various stages of normal myelination during the first year of life, Neuroradiology 31 (6) (1990) 459–470.
[30] T.E. Inder, P.S. Huppi, In vivo studies of brain development by magnetic resonance techniques, Ment. Retard. Dev. Disabil. Res. Rev. 6 (1) (2000) 59–67.
[31] B.O. Kjos, R. Umansky, A.J. Barkovich, Brain MR imaging in children with developmental retardation of unknown cause: results in 76 cases, Am. J. Neuroradiol. 11 (5) (1990) 1035–1040.
[32] Growing Ga. Calculating corrected age. University of Washington's homepage, http://depts.washington.edu/growing/Assess/Grca.htm.
[33] E.A. Balazs, J.L. Denlinger, The vitreous, in: H. Davson (Ed.), 3rd ed., The Eye, vol. 1a, Academic Press, London, 1984, pp. 560–564.
[34] J. Sebag, Age-related changes in human vitreous structure, Graefes Arch. Clin. Exp. Ophthalmol. 225 (2) (1987) 89–93.

[35] J. Sebag, Structure, function, and age-related changes of the human vitreous, Bull. Soc. Belge. Ophtalmol. 223 (1987) 37–57.
[36] J. Shapleske, S.L. Rossell, P.W. Woodruff, A.S. David, The planum temporale: a systematic, quantitative review of its structural, functional and clinical significance, Brain Res. Brain Res. Rev. 29 (1) (1999) 26–49.
[37] J.A. Wada, R. Clarke, A. Hamm, Cerebral hemispheric asymmetry in humans. Cortical speech zones in 100 adults and 100 infant brains, Arch. Neurol. 32 (4) (1975) 239–246.
[38] R.B. Dietrich, W.G. Bradley Jr., Normal and abnormal white matter maturation, Semin. Ultrasound CT MR 9 (3) (1988) 192–200.
[39] C.R. Bird, M. Hedberg, B.P. Drayer, P.J. Keller, R.A. Flom, J.A. Hodak, MR assessment of myelination in infants and children: usefulness of marker sites, Am. J. Neuroradiol. 10 (1989) 731–740.
[40] L.A. Squires, K.S. Krishnamoorthy, M.R. Natowicz, Delayed myelination in infants and young children: radiographic and clinical correlates, J. Child Neurol. 10 (2) (1995) 100–104.
[41] N. Girard, C. Raybaud, P. du Lac, MRI study of brain myelination, J. Neuroradiol. 18 (4) (1991) 291–307 (English, French).
[42] A.J. Barkovich, Magnetic resonance techniques in the assessment of myelin and myelination, J. Inherit. Metab. Dis. 28 (3) (2005) 311–343.
[43] L.T. Sie, M.S. van der Knaap, G. van Wezel-Meijler, J. Valk, MRI assessment of myelination of motor and sensory pathways in the brain of preterm and term-born infants, Neuropediatrics 28 (2) (1997) 97–105.
[44] N. Herschkowitz, Neurological bases of behavioral development in infancy, Brain 22 (7) (2000) 411–416 (Review).
[45] L.E. Berk, Language development, in: L.E. Berk (Ed.), Child Development, 6th ed., Allyn & Bacon, Boston, 2003, pp. 352–391.
[46] Y. Korogi, T. Hirai, Y. Komohara, T. Okuda, I. Ikushima, M. Kitajima, Y. Shigematu, T. Sugahara, M. Takahashi, T2 shortening in the visual cortex: effect of aging and cerebrovascular disease, Am. J. Neuroradiol. 18 (4) (1997) 711–714.
[47] B.A. Brody, H.C. Kinney, A.S. Kloman, F.H. Gilles, Sequence of central nervous system myelination in human infancy, an autopsy study of myelination, J. Neuropathol. Exp. Neurol. 46 (1987) 283–330.