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

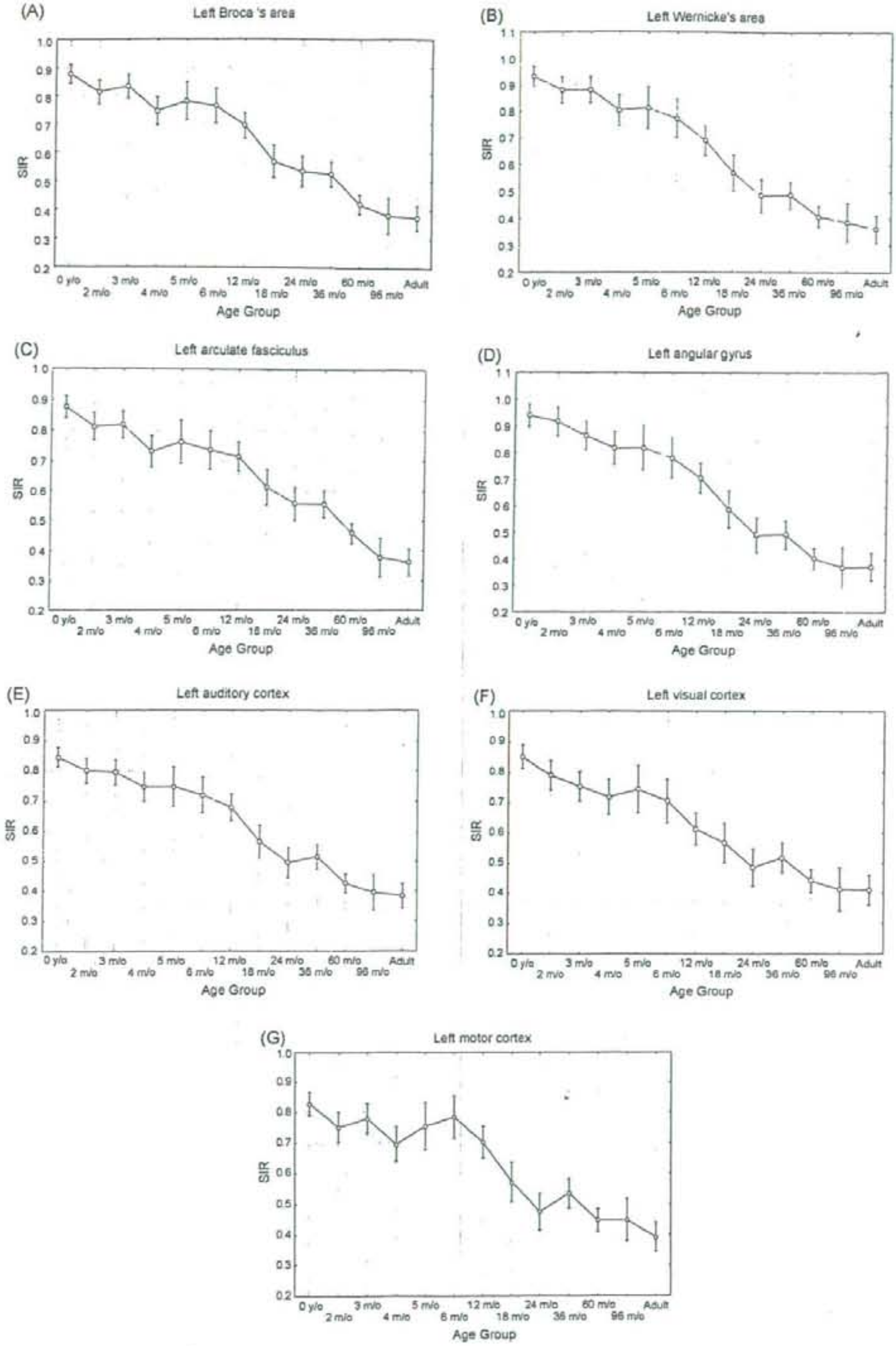

Fig. 7 The mean ± S.E.M. of the signal intensity ratio was obtained in different areas of the left hemisphere and tested by one-way ANOVA with the Tukey–Kramer test for multiple comparisons among different age groups. The mean ± S.E.M. of the signal intensity ratio was also obtained in the same areas 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.

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