Prolonged maturation of prefrontal white matter in chimpanzees

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Delayed maturation in the prefrontal cortex, a brain region associated with complex cognitive processing, has been proposed to be specific to humans. However, we found, using a longitudinal design, that prefrontal white matter volume in chimpanzees increased gradually with age, and the increase appears to continue beyond the onset of puberty, as in humans. This provides the first evidence for a prolonged period of prefrontal connection elaboration in great apes.

One of the most marked evolutionary changes underlying human-specific cognitive traits is a greatly enlarged prefrontal cortex[1-2]. This area has been found to mediate evolutionarily unique functions such as working memory, temporal integration, motivation, decision-making, self-awareness, creativity, language, and social interaction[1]. Intriguingly, the executive role played by the prefrontal cortex depends critically on its reciprocal connections to the posterior processing area[1]. Thus, focusing on the augmentation of white matter (WM) volume underlying the prefrontal cortex, which is thought to be attributable to the myelination of the cortico-cortical axons, is a key to understanding human brain evolution[3-4].

Comparative imaging studies suggested that prefrontal WM volume is disproportionately larger in humans than in other primates[4]. The prefrontal region is a relatively recently evolved brain region and exhibits relatively late maturation[1, 3]. The prefrontal WM volume of humans continues to increase gradually beyond puberty until young adulthood[3, 5-6], whereas that of macaques first increases and then decreases soon after the onset of puberty[7].

These findings suggested that a large disparity of central neural development has arisen between humans and monkeys since the last common ancestor 25-30 million years ago[8-9]. Given this deep branching history, comparisons of brain development between humans and chimpanzees, the closest living nonhuman primate, whose lineage diverged from humans 6-7 million years ago, are essential for understanding human brain evolution.

To this end, we obtained longitudinal T1-weighted magnetic resonance imaging (MRI) scans from three growing chimpanzees at scheduled intervals from six months to six years of age (= infant and the age of juvenile stages based on dental development[10]) (**Supplementary Methods**). For comparison, adult data were obtained from three chimpanzees. All subjects lived within a social group of 14 individuals in an enriched environment at the Primate Research Institute, Kyoto University (KUPRI) [11-12]. Our three study chimpanzees were born in 2000, and were raised by their biological mothers. They had not yet reached puberty by seven years of age. All protocols were approved by the Committee for the Care and Use of Laboratory Primates of KUPRI.

We defined the prefrontal portion as all coronal slices anterior to the corpus callosum of the cerebrum in accord with previous studies[4, 11]. The non-prefrontal portion is the remainder of the cerebrum. Through comparison with the findings of previous studies in humans, we sought to determine whether the human prefrontal white matter develops significantly more slowly than that of chimpanzees during infancy and the juvenile period.

The results of tissue segmentation revealed noteworthy developmental changes from six months to six years of age, and differences between juveniles and adults (**Fig.1** and **Supplementary Fig. 1-3**). Gray matter (GM) and WM volumes in the cerebrum, the prefrontal and non-prefrontal portions were calculated, based on a segmentation map generated with FSL software[13] (**Supplementary Methods** and **Supplementary Table 1**). The total volumes of each portion were the sum of GM and WM volume of that portion. We used linear polynomial regression analysis to assess the growth patterns of total and WM volume changes in each portion during this age period (**Supplementary Methods**).

The total volume of each of the cerebrum, prefrontal and non-prefrontal portions increased significantly during the period from six months to six years of age ($F = 3.72$; cubic effect, $P < 0.05$; **Fig. 2a**). The WM volume of the cerebrum, prefrontal and non-prefrontal portions increased non-linearly across this age period ($F = 74.49$; cubic effect, $P < 0.0001$, $F = 13.44$; cubic effect, $P < 0.0001$, $F = 83.57$; cubic effect, $P < 0.0001$; **Fig. 2a**).

The relative WM volume of the prefrontal plus non-prefrontal portions (the percentage of the total volume normalized by the adult percentage) increased non-linearly

(F = 22.25; cubic effect, P < 0.05; F = 49.18; quadratic effect, P < 0.005; **Fig. 2b**) (**Supplementary Methods**). However, the relative increase of WM volume in the prefrontal portion was significantly smaller than that in the non-prefrontal portion (ANCOVA, F = 54.62; P < 0.001; **Fig. 2b**) (**Supplementary Results**). At six years of age (the prepubertal stage), the relative WM volume in the prefrontal portion was 56.5% of the adult value, whereas the relative WM volume in the non-prefrontal portion was 77.0%. The WM volume of the cerebrum, especially of the prefrontal portion, increased gradually with age, and appears to increase beyond the onset of puberty, which is analogous to the delayed growth pattern of the WM volume shown by humans, not macaques.

In conclusion, we performed the first longitudinal analysis of the brain growth patterns in three chimpanzees for six consecutive years. Although an absolute difference in brain size between humans and chimpanzees is evident, a prolonged period of prefrontal connection elaboration is probably a shared feature that was present in the last common ancestor of humans and chimpanzees.

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Note: Supplementary information is available on the Nature Neuroscience website.

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AUTHOR CONTRIBUTIONS
TS designed the study, carried out the analysis and interpretation of the data, and wrote the first draft of the manuscript. AM and TS acquired the MRI data. YH oversaw the data-analysis strategy. TMa and MN supervised the study. DH assisted with data analysis and HM assisted with figure preparation. JS, MTa, MTo, and TMi, assisted with the MRI scans. This paper constitutes part of the first author's PhD thesis.

COMPETING INTERESTS STATEMENT
The authors declare no competing financial interests.

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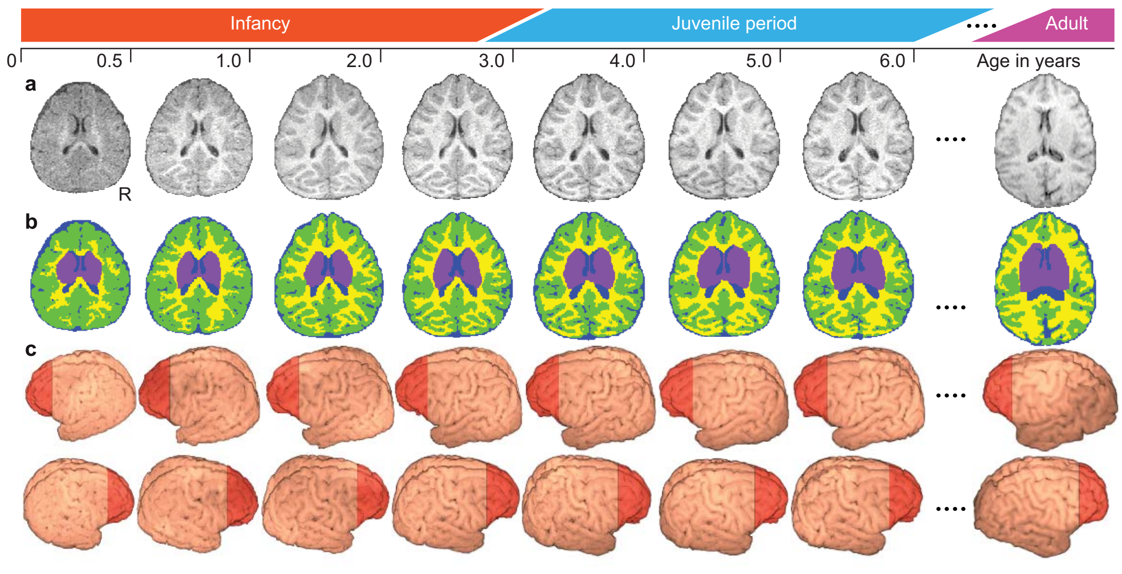
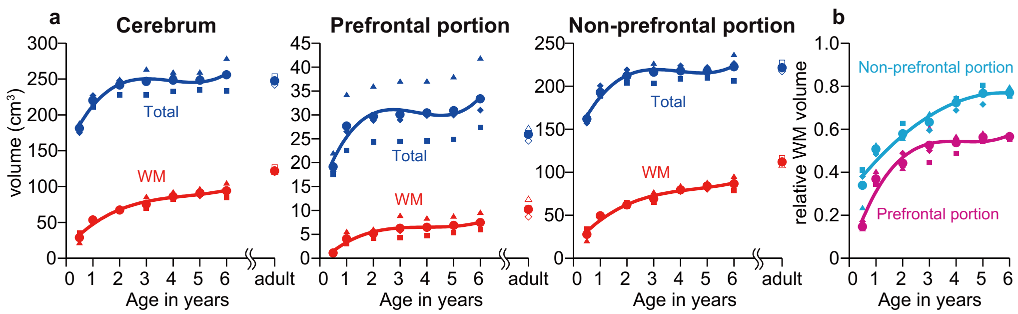
Figure 1 An ontogenetic series of the whole cerebrum and prefrontal portion of a chimpanzee during infancy and the juvenile period. MRI brain images aligned by age from a representative chimpanzee (Pal) and an adult (Reo) for comparison. **(a)** T1-weighted anatomical brain images. **(b)** Segmentation of the cerebrum: GM (green), WM (yellow), deep central gray matter (blue), and CSF (purple). **(c)** Three-dimensional renderings of the cerebrum from left and right lateral views, including the cortical portion designated as the prefrontal portion (red). The scale bar is 50 mm.

Figure 2 Quantification of volume changes during infancy and the juvenile period in chimpanzees. **(a)** Total (blue) and WM (red) volumes in the cerebrum (left), prefrontal portion (middle), and non-prefrontal portion (right). **(b)** Relative WM volume in the prefrontal portion (magenta) and non-prefrontal portion (cyan). Solid circles indicate the average volume of the three growing chimpanzees. Solid triangles, solid squares, solid diamonds, open triangles, open squares, and open diamonds indicate the volumes of Ayumu, Cleo, Pal, Reo, Puchi, and Popo, respectively.


Infancy
Juvenile period
Adult
0
0.5
1.0
2.0
3.0
4.0
5.0
6.0
Age in years
a
R
b
c



a
Cerebrum
Prefrontal portion
Non-prefrontal portion
b
volume (cm³)
Total
WM
adult
Age in years
relative WM volume
Non-prefrontal portion
Prefrontal portion