

# Differential Prefrontal White Matter Development in Chimpanzees and Humans

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## Summary

A comparison of developmental patterns of white matter (WM) within the prefrontal region between humans and non-human primates is key to understanding human brain evolution. WM mediates complex cognitive processes and has reciprocal connections with posterior processing regions [1, 2]. Although the developmental pattern of prefrontal WM in macaques differs markedly from that in humans [3], this has not been explored in our closest evolutionary relative, the chimpanzee. The present longitudinal study of magnetic resonance imaging scans demonstrated that the prefrontal WM volume in chimpanzees was immature and had not reached the adult value during prepuberty, as observed in humans but not in macaques. However, the rate of prefrontal WM volume increase during infancy was slower in chimpanzees than in humans. These results suggest that a less mature and more protracted elaboration of neuronal connections in the prefrontal portion of the developing brain existed in the last common ancestor of chimpanzees and humans, and that this served to enhance the impact of postnatal experiences on neuronal connectivity. Furthermore, the rapid development of the human prefrontal WM during infancy may help the development of complex social interactions, as well as the acquisition of experience-dependent knowledge and skills to shape neuronal connectivity.

## Results

We obtained longitudinal T1-weighted magnetic resonance imaging (MRI) scans at scheduled intervals from three growing chimpanzees (*Pan troglodytes*) between the ages of 6 months and 6 years (the middle of early infancy and the second half of the juvenile stage, respectively; 6 years is still considered the prepubertal stage in chimpanzees) (see Figure S1 available online). The prefrontal and nonprefrontal portions of the cerebrum were divided by the coronal slice anterior to the corpus callosum, as a proxy for the prefrontal volume on MRI data,

in accordance with previous neuroimaging studies [4–7]. The rationale for this definition is explained in the [Supplemental Discussion](#). Gray and white matter (GM and WM) volumes in the prefrontal and nonprefrontal portions were calculated based on a segmentation map generated with FSL software [8] (Table S1). The results were compared with those of humans (*Homo sapiens*) between the ages of 1 month and 10.5 years, corresponding to the near onset of early infancy and the second half of the juvenile stage, respectively; 10.5 years is still considered the prepubertal stage in humans based on sexual maturation (Figure S1) [9] (M.M., C. Tanaka, L. Niu, J. Matsuzawa, K. Noguchi, T. Miyawaki, W.B. Bilker, M. Wierzbicki, and R.C. Gur, unpublished data). The results were also compared with those of rhesus macaques (*Macaca mulatta*) between the ages of 10 months and 5.3 years, corresponding to the middle of late infancy and the near onset of the adult stage, respectively (Figure S1) [3]. A more detailed account of the materials and methods is available in [Supplemental Experimental Procedures](#) and [Supplemental Discussion](#).

## Total and Prefrontal Tissue Volumes

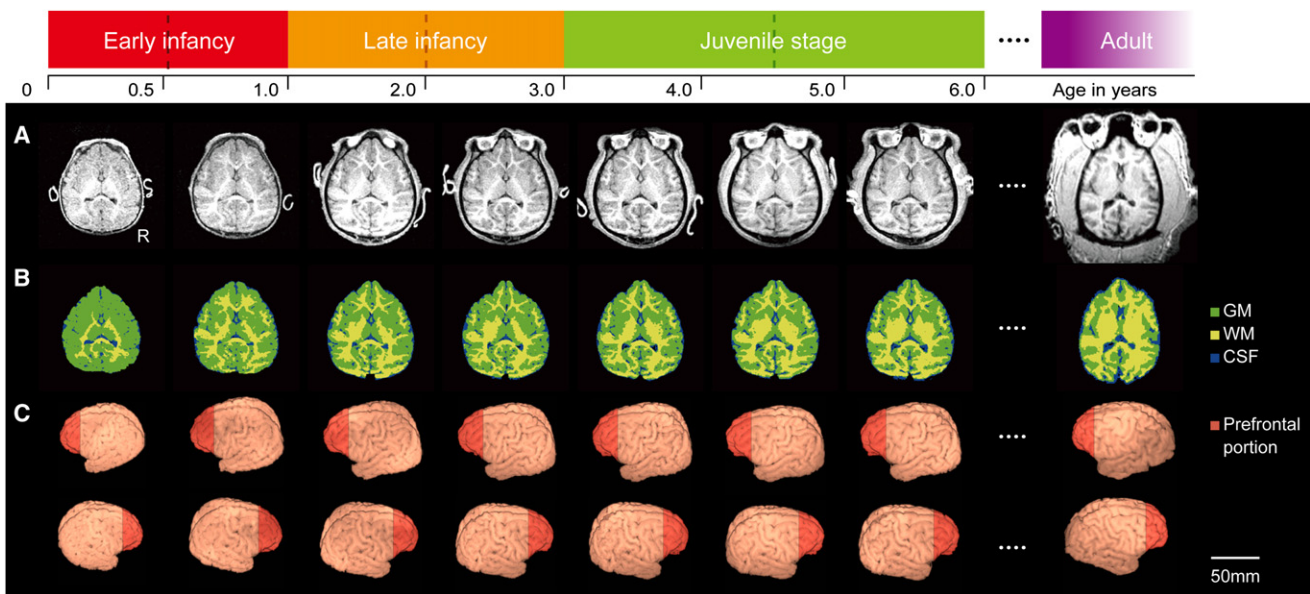
The results of tissue segmentation revealed noteworthy developmental changes in chimpanzees through the study period (Figure 1). The total (GM plus WM) volumes of each of the prefrontal and nonprefrontal portions increased nonlinearly ( $F = 7.11$ ; quadratic effect,  $p < 0.01$ ;  $F = 27.76$ ; cubic effect,  $p < 0.0001$ ) (Figure 2A). The nonprefrontal GM volume followed a nonlinear developmental trajectory with the maximum value at about 3 years (the end of late infancy) and decreased gradually thereafter ( $F = 8.73$ ; cubic effect,  $p < 0.001$ ), whereas the prefrontal GM volume continued to increase gradually with age ( $F = 4.31$ ; quadratic effect,  $p < 0.05$ ) (Figure 2C). The WM volumes in the prefrontal and nonprefrontal portions increased nonlinearly ( $F = 11.15$ ; cubic effect,  $p < 0.001$ ;  $F = 34.05$ ; cubic effect,  $p < 0.0001$ ) (Figure 2B).

Chimpanzees and humans differ from macaques in the delayed development of WM volume, especially of the prefrontal portion. The WM volumes of the prefrontal and nonprefrontal portions of the chimpanzee were 60.0% and 71.1%, respectively, of the adult volume (Supplemental Experimental Procedures) at the second half of the juvenile stage (6 years) (Figure 3A). In humans, the WM volumes of the prefrontal and nonprefrontal portions were 85.1% and 79.1% of the adult volume at almost the same developmental stage (10.5 years), respectively (Figure 3B).

By marked contrast, the corresponding WM volumes of macaques reached the adult volume at 1.9 and 2.9 years, respectively (Figure 3C). These ages are prepubertal stages and correspond to the first half of the juvenile stage and near the end of the juvenile stage, respectively. The prefrontal WM volume reached the developmental peak at 2.9 years and then decreased from puberty onward (Figure S3B).

However, the chimpanzee WM volumes of the prefrontal and nonprefrontal portions in the second half of the juvenile stage were lower than those of humans (Figures 3A and 3B). This difference can be attributed to differences in the rates of WM volume increases during infancy between the two species (Supplemental Discussion). The WM volumes of the prefrontal

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**Figure 1.** An Ontogenetic Series of the Whole Cerebrum and the Prefrontal Portion in a Chimpanzee Brain during Early Infancy and the Juvenile Stage  
MRI brain images were acquired from three young chimpanzees as they developed between the ages of 6 months and 6 years, and also from two adult chimpanzees. MRI brain images were aligned by age with the images from a representative young chimpanzee (Pal) and an adult (Reo) for comparison. (A) T1-weighted anatomical brain images. (B) Segmentation of the cerebrum: gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF). (C) Three-dimensional renderings of the cerebrum from left and right lateral views, including the cortical portion designated as the prefrontal portion. The color bar at top represents the developmental stages based on combined dental eruption and sexual maturation. The developmental stage in chimpanzees corresponds to early infancy (red), late infancy (orange), juvenile stage (green), and adult stage (purple). See also [Supplemental Experimental Procedures](#) for a more detailed account of the experimental procedures (subjects, image acquisition, and image processing), [Supplemental Discussion](#) for the demarcation of the prefrontal portion, and [Supplemental Experimental Procedures](#) and [Figure S1](#) for the definitions of the developmental stages in chimpanzees.

and nonprefrontal portions in chimpanzees increased 173.4% and 62.3%, respectively, across the developmental stage from the middle of early infancy to the end of late infancy (6 months to 3 years) ([Figure 2B](#)). By contrast, the WM volumes of the prefrontal and nonprefrontal portions in humans increased 185.2% and 79.7%, respectively, during nearly the same developmental stage (1 year to 6 years) ([Figure S2B](#)). On the other hand, the corresponding WM volumes in macaques increased by only 24.6% and 21.8% from the middle of late infancy to the end of the juvenile stage (10 months to 3.2 years).

### Proportional Growth of WM Volume

In chimpanzees, the developmental trajectories of the total volume in the prefrontal portion differed from those of the nonprefrontal portion, a finding not observed in either humans or macaques ([Figure 2A](#); [Figure S2A](#); [Figure S3A](#)). Differences in the prefrontal and nonprefrontal developmental patterns of WM volume appear to greatly influence the differences in the total volume of the adult prefrontal portion. Thus, to elucidate species-specific variations in chimpanzees, humans, and macaques, we evaluated the proportional growth of the WM volume relative to the total volume of the developing cerebrum and compared the result to the adult value. The proportional growth of WM volume was calculated by dividing WM volume expressed as a percentage of the total volume of GM plus WM in the prefrontal and nonprefrontal portions by the adult percentage.

The proportional growth of WM volume of the prefrontal and nonprefrontal portions in chimpanzees significantly increased,

following a cubic and quadratic curve, respectively ( $F = 36.54$ ; cubic effect,  $p < 0.0001$ ;  $F = 26.18$ ; quadratic effect,  $p < 0.0001$ ) ([Figure 4A](#)). The proportional increase in WM volume in the prefrontal portion was significantly smaller than that in the nonprefrontal portion (analysis of covariance;  $F = 74.60$ ;  $p < 0.0001$ ).

As observed in humans, the chimpanzee cerebral WM volume at an early developmental stage was immature compared to the adult volume, especially in the prefrontal portion. At the middle of early infancy (6 months), the proportional WM volume in the prefrontal and nonprefrontal portions was 25.5% and 50.9%, respectively ([Figure 4A](#)). The corresponding WM volumes in humans at approximately the same developmental stage (1 year) were 33.0% and 53.4%, respectively ([Figure 4B](#)).

Chimpanzees also share with humans a common protracted developmental trajectory of WM volume, especially in the prefrontal portion during infancy and the juvenile stage. In the second half of the juvenile stage (6 years), the proportional WM volume in the prefrontal and nonprefrontal portions was 55.7% and 73.6%, respectively, and had not yet attained the adult value ([Figure 4A](#)). The corresponding values in humans at approximately the same developmental stage (10.5 years) were 83.9% and 84.3% of the adult value, respectively, and had also not yet attained the adult value ([Figure 4B](#)). In contrast, the proportional WM volume in the prefrontal and nonprefrontal portions of macaques had already reached a plateau at an early developmental stage: the prefrontal and nonprefrontal proportional values were 91.7% and 90.8% of the adult value, respectively, at the end of late infancy (1.3 years) and

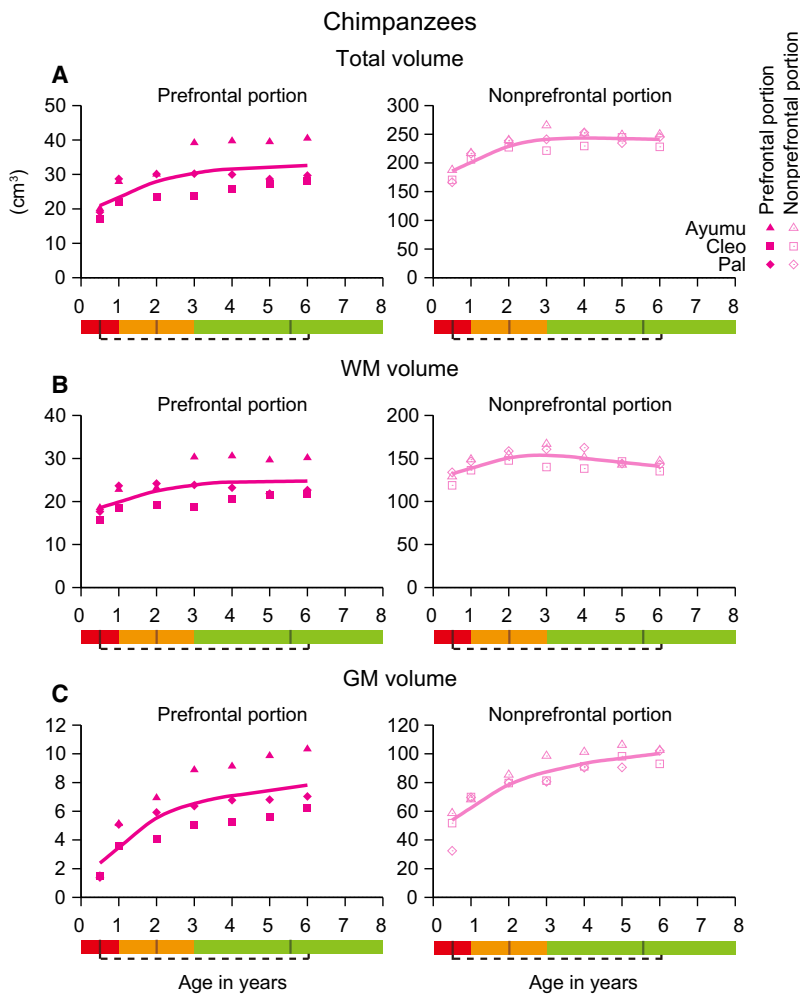


Figure 2. Volumetric Changes in the Prefrontal and Nonprefrontal Portions during Early Infancy and the Juvenile Stage in Chimpanzees

Age-related changes in the total volume (WM plus GM) (A), WM volume (B), and GM volume (C) in the prefrontal and nonprefrontal portions. The color bars below the graphs represent the developmental stages based on combined dental eruption and sexual maturation. The developmental stage in chimpanzees corresponds to early infancy (red), late infancy (orange), and juvenile stage (green). The black dashed lines represent the study range in chimpanzees. See also [Supplemental Experimental Procedures](#) for the statistical analysis; [Supplemental Results, Figure S2](#), and [Figure S3](#) for the comparison with the results of the total, WM, and GM volumes of the prefrontal and nonprefrontal portions in humans and macaques; [Supplemental Discussion](#) for the demarcation of the prefrontal portion; and [Figure S1](#) for the definitions of the developmental stages in chimpanzees.

language, and social interaction [1, 2]. The executive role played by the prefrontal region critically depends on its reciprocal connections to the diencephalon, mesencephalon, and limbic systems, as well as numerous brain regions that mediate higher sensory functions [1, 6]. Therefore, focusing on the augmentation of WM volume in the prefrontal region, which is attributable to the myelination of axons that connect the posterior processing regions [1], is key to understanding human brain evolution.

Whether or not the human prefrontal region or any of its subdivisions are proportionally enlarged remains controversial [6, 10–18]. In particular, comparative studies have not reached a consensus as to whether the prefrontal WM enlargement is an evolutionary specialization of humans [6, 18]. Unfortunately, few studies have compared the developmental patterns of the prefrontal region in humans and nonhuman primates. Moreover, brain developmental patterns have not thus far been explored in the great apes. An understanding of the developmental processes in the prefrontal region is expected to provide powerful insights into the evolution of adult brain morphologies and function.

We have performed the first longitudinal analysis of brain developmental trajectory in the closest relative of humans, the chimpanzee. Despite the relatively small sample size in the current chimpanzee study, our results successfully illustrate similarities and differences in brain volume trajectories among chimpanzees, humans, and rhesus macaques. The prefrontal WM maturation in chimpanzees, as in humans, showed a less mature and more protracted course compared with the maturation of the nonprefrontal portion throughout prepuberty. However, the rate of increase of prefrontal WM volume during infancy was slower in chimpanzees than in humans.

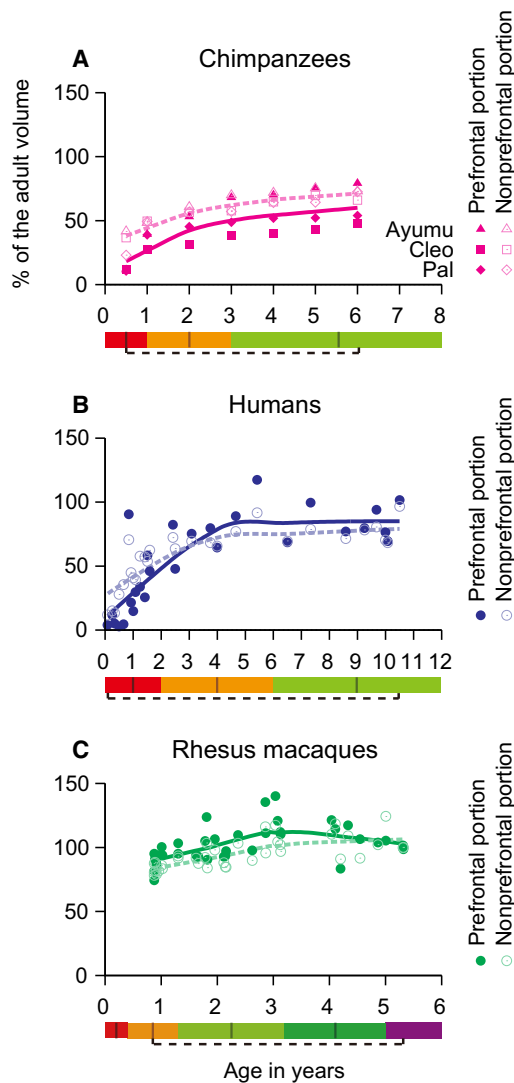
Recent imaging studies of human brain development emphasized the more protracted course of development in the frontal region, based on the time frame in which the cortex and fiber trajectories matured. A recent MRI study investigated the development of the cortical GM density and reported that maturation of the frontal region, a high-order association

96.5% and 97.1%, respectively, at the end of the juvenile stage (3.2 years) (Figure 4C).

Although chimpanzees and humans shared a markedly immature prefrontal WM volume at the middle of early infancy, the prefrontal WM volume in chimpanzee infants developed along a slower trajectory compared with human infants. In chimpanzees, the proportional WM volume in the prefrontal portion reached 31.8% of the adult value at the end of early infancy (1 year), 49.7% at the end of late infancy (3 years), and 55.7% in the second half of the juvenile stage (6 years) (Figure 4A). The proportional WM volume of the nonprefrontal portion was 54.0%, 64.2%, and 73.6% at each respective developmental stage (Figure 4A). By contrast, in humans, the proportional WM volume in the prefrontal portion attained 48.9% of the adult value at the end of early infancy (2 years), 76.2% at the end of late infancy (6 years), and 83.9% in the second half of the juvenile stage (10.5 years) (Figure 4B). The corresponding values of the nonprefrontal portion were 63.6%, 77.2%, and 84.3% at each respective developmental stage (Figure 4B).

## Discussion

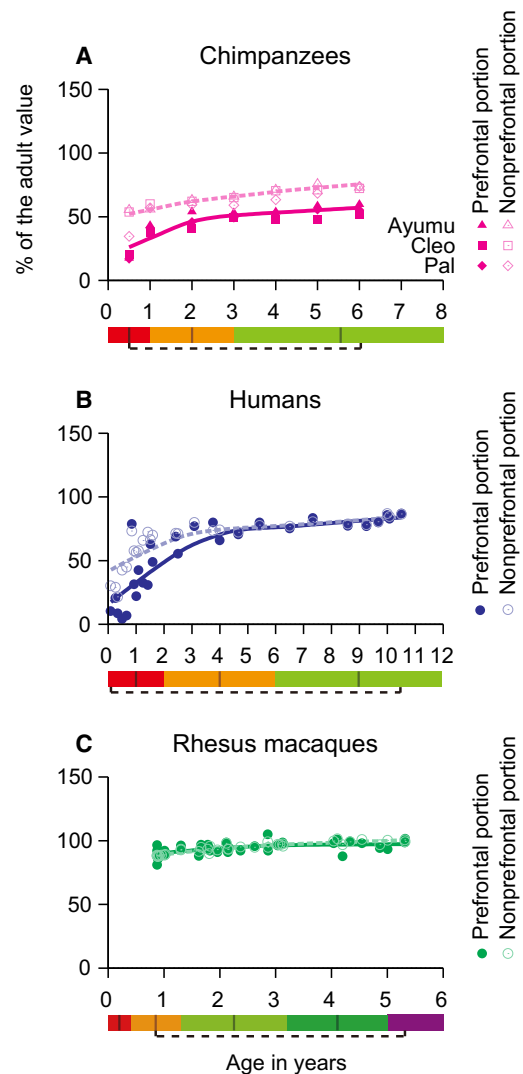
The human prefrontal cortex mediates evolutionarily advanced functions such as working memory, temporal integration, motivation, decision making, self-awareness, creativity,



**Figure 3.** Evaluation of White Matter Volumes Relative to the Adult Volume in the Prefrontal and Nonprefrontal Portions during Early Infancy and the Juvenile Stage

Age-related changes in the relative WM volumes are shown in the prefrontal and nonprefrontal portions in chimpanzees (Ayumu, Cleo, and Pal) (A), humans ( $n = 28$ ) (B), and rhesus macaques ( $n = 37$ ) (C). The color bars below the graphs represent the developmental stages based on combined dental eruption and sexual maturation. The developmental stage in chimpanzees, humans, and macaques corresponds to early infancy (red), late infancy (orange), juvenile stage (green), puberty (dark green), and adult stage (purple). The black dashed lines represent the study ranges in chimpanzees, humans, and macaques. See also [Supplemental Experimental Procedures](#) for the developmental trajectories in humans and macaques and the statistical analysis; [Supplemental Discussion](#) for the demarcation of the prefrontal portion and the demarcation of the cerebrum and the prefrontal portions in humans and macaques; and [Figure S1](#) for the definitions of the developmental stage in chimpanzees, humans, and macaques.

area, progresses in a back-to-front direction [19]. The progression begins in the low-order sensorimotor regions and spreads anteriorly over the superior and inferior frontal gyri, with the prefrontal region developing last. We have demonstrated that, in a similar fashion, regional differences of WM maturation between the prefrontal and nonprefrontal portions in chimpanzees appear to be involved in the differential maturation



**Figure 4.** Evaluation of Proportional White Matter Volumes Compared with the Adult Value in the Prefrontal and Nonprefrontal Portions during Early Infancy and the Juvenile Stage

Age-related changes in the proportional WM volumes in the prefrontal and nonprefrontal portions in chimpanzees (Ayumu, Cleo, and Pal) (A), humans ( $n = 28$ ) (B), and rhesus macaques ( $n = 37$ ) (C). The color bars below the graphs represent the developmental stages based on combined dental eruption and sexual maturation. The developmental stage in chimpanzees, humans, and macaques corresponds to early infancy (red), late infancy (orange), juvenile stage (green), puberty (dark green), and adult stage (purple). The black dashed lines represent the study ranges in chimpanzees, humans, and macaques. See also [Supplemental Experimental Procedures](#) for the developmental trajectories in humans and macaques and the statistical analysis; [Supplemental Results](#) for more detailed results about the proportional WM volumes of the prefrontal and nonprefrontal portions in humans and macaques; [Supplemental Discussion](#) for the demarcation of the prefrontal portion and the demarcation of the cerebrum and the prefrontal portion in humans and macaques; and [Figure S1](#) for the definitions of the developmental stages in chimpanzees, humans, and macaques.

between the prefrontal executive function and the sensory and motor systems after birth.

Previous developmental diffusion tensor imaging studies indicated that certain frontal connections in humans, particularly frontotemporal connections such as the uncinate fasciculus and the cingulum, tend to mature more slowly than the

projection connections and the other association connections [20, 21]. The patterns of connection elaboration of chimpanzees in this study appeared to reflect the same phenomena. We infer that the protracted connection maturation of the prefrontal portions in human and chimpanzees is attributable to the elaborations of reciprocal corticocortical connections rather than to the elaboration of projection connections.

Developmental delay is a key feature of human evolution [22] and is thought to play a role in the emergence of human-specific cognitive abilities through an extended period of high neuronal plasticity [13, 23, 24]. Delayed development of the human brain may affect its function by rendering it more susceptible to the influence of postnatal experiences [24]. Similarly, a recent imaging study of brain structure compared the maturity of cortical folds of human brains with that of macaque brains [25]. That study hypothesized that high-order association areas in postnatal development benefit from remaining less mature during the human early postnatal period. In this manner, the influence of postnatal experiences on the development of selected brain regions is increased. Therefore, our results suggest that less mature prefrontal connections during early infancy and a protracted developmental period of the prefrontal network in chimpanzee brains will likewise result in a strong influence of postnatal experiences on functional and behavioral outcomes.

A series of cognitive studies with the same three chimpanzee subjects employed in the current study revealed that chimpanzee infants share some common features with human infants with regard to cognitive development during early infancy (see [26] and references therein). These chimpanzee infants, similarly to human infants, demonstrated closed dyadic relationships (dyadic infant-adult and object interactions) with their mothers during early infancy, based on mutual gaze and social smiling [27]. Such interactions are not observed in macaque infants. Also similarly to humans, the three chimpanzees demonstrated first object-object manipulation, a precursor to tool use, during early infancy [28]. This was followed by first tool use, which consisted of the employment of a probing tool to obtain honey through a small hole [29]. Taking these data together, we hypothesize that brain connection development, particularly in the prefrontal portion, may have been under intense evolutionary pressure to remain immature, producing a brain that is more susceptible to acquiring chimpanzee- and human-specific social and technical skills based on early postnatal experiences.

However, these previous studies [26–29] reported crucial differences between chimpanzees and humans in behavioral and cognitive development during early infancy and the juvenile stage. Triadic interactions (triadic infant-adult and object interactions), based on sharing attention and additional important social interactions with the theory of mind [30], develop in humans between 9 months and 3 years (near the middle of early infancy and the first half of late infancy, respectively) [31]. Triadic interactions were lacking in the three chimpanzees even at the later juvenile stage [26, 27]. Furthermore, chimpanzees have a limited capacity to combine many objects in a hierarchical order, whereas humans can develop hierarchical combinatorial manipulations at infinite levels [28]. On the other hand, the working memory of chimpanzees aged 4 to 5 years (the first half of the juvenile stage) has more potential for expansion than that of chimpanzee and human adults [32]. One interpretation of this intriguing finding suggests that humans lose the memory skills over time that are required to obtain language-related skills, conceptual representation,

“chunking” (breaking down information or details into smaller parts), hierarchical organization, and syntactic rules [26, 32], because brain volume capacity becomes limited at a certain point in human life [33–38].

In this context, we hypothesize that the dramatic increase of the prefrontal WM volume during human infancy, which was not observed in chimpanzees, corresponded with opportunities for human-specific social learning and acquisition of technical and linguistic skills. Furthermore, the protracted period of the prefrontal connection elaboration in chimpanzees appeared to only affect specific social and cognitive processes based on direct and dyadic subject-object relationships and did not impart behaviors based on social reference frameworks.

In conclusion, our results suggest that, as groundwork for the reformatting of these expanded brain regions in humans, the prefrontal reciprocal connections to the posterior brain regions became enhanced during the course of evolution. This enhancement likely occurred through an extension of the period of prefrontal connection maturation in the common lineage after the last common ancestor shared by chimpanzees and modern humans split from macaques. However, the lineage leading to modern humans has undergone substantial evolutionary modifications, resulting in the rapid development of the prefrontal connections during infancy. This likely facilitates the development of complex social interactions and the shaping of neuronal connectivity through the acquisition of experience-dependent knowledge and skills.

#### Supplemental Information

Supplemental Information includes three figures, one table, Supplemental Experimental Procedures, Supplemental Results, and Supplemental Discussion, and can be found with this article online at [doi:10.1016/j.cub.2011.07.019](https://doi.org/10.1016/j.cub.2011.07.019).

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