Correspondences

Fetal brain development in chimpanzees *versus* humans

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It is argued that the extraordinary brain enlargement observed in humans is due to not only the human-specific pattern of postnatal brain development, but also to that of prenatal brain development [1,2]. However, the prenatal trajectory of brain development has not been explored in chimpanzees (*Pan troglodytes*), even though they are our closest living relatives. To address this lack of information, we tracked fetal development of the chimpanzee brain from approximately 14 to 34 weeks of gestation (just before birth) in *utero* using three-dimensional ultrasound imaging. The results were compared with those obtained for the human brain during approximately the same period. We found that the brain volume of chimpanzee fetuses was only half that of human fetuses at 16 weeks of gestation. Moreover, although the growth velocity of brain volume increased until approximately 22 weeks of gestation in both chimpanzees and humans, chimpanzee fetuses did not show the same accelerated increase in brain volume as human fetuses after that time. This suggests that maintenance of fast development of the human brain during intrauterine life has contributed to the remarkable brain enlargement observed in humans.

Earlier studies have suggested that, compared with other primates, human neonates show a more immature brain size relative to that of the adult, followed by a rapid rate of brain development after birth [1,2]. This has been attributed to the constraints imposed on neonate head size by the structure of the maternal pelvis [3]. But although gestational length is slightly longer in humans than in chimpanzees (human, 38 weeks; chimpanzee, 34–35 weeks) [4], human neonates do have larger brains than chimpanzee neonates [2]. It has been suggested that the extraordinary brain enlargement in humans is due to unique features in the human pattern of brain development during both the prenatal and postnatal periods [1,2]. It has been argued that all primates conform to a 12% ratio of brain mass to body mass from the fetal period to birth [5,6], though a recent study [7] suggested that the brain of a chimpanzee neonate accounts for 10% of its body weight, whereas that of a human neonate, on average, accounts for 12.3%, an increase due to accelerated brain growth, known as encephalization, in humans.

We looked for empirical evidence for the remarkable enlargement of the human brain during the fetal period. We performed three-dimensional ultrasound imaging on two chimpanzee fetuses from approximately 14 to 34 weeks of gestation (Figure 1A and Tables S1–S4 in the Supplemental Information) and compared the results with previously estimated numerical data from human fetuses from 16 to 32 weeks of gestation [8] — up until a few weeks before birth (Tables S5 and S6; see the Supplemental Experimental Procedures for details).

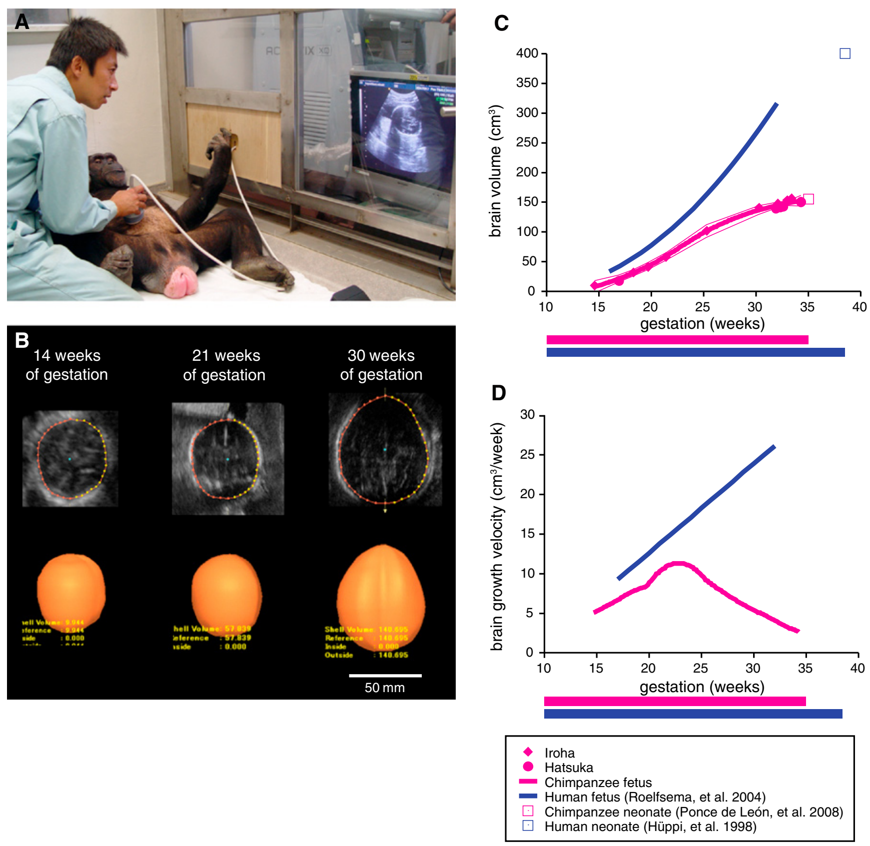

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Figure 1. Evaluation of fetal brain volume relative to gestational age.
Three-dimensional ultrasound images were acquired from two chimpanzee fetuses as they developed from 14 to 34 weeks of gestation. (A) Three-dimensional ultrasound scanning of a chimpanzee fetal brain. (B) An ontogenetic series of images of the chimpanzee fetal brain. Three-dimensional ultrasound brain images from one chimpanzee fetus (Iroha) at 14 weeks, 21 weeks, and 30 weeks of gestation are shown. The upper row shows sonographic axial images of the brain. The lower row shows three-dimensional renderings of the brain. (C) Gestational age-related changes in the brain volume in chimpanzee fetuses (Hatsuka and Iroha) and human fetuses (n = 68) (see details in [8]). The magenta solid line represents the LOESS fit of the chimpanzee fetus. The blue line represents the median value (50th percentile) of the human fetus. The fine magenta lines represent the 95% confidence band of the LOESS fit. (D) Gestational age-related changes in the growth velocity of brain volume in chimpanzee fetuses (Hatsuka and Iroha) and human fetuses (n = 68) (see details in [8]). The color bars below the graphs represent the gestational time based on the time of conception in chimpanzees (magenta) and humans (blue), respectively.

The chimpanzee fetuses used in our study showed a significant age-related change in brain volume over the course of the study period (Figure 1B,C). The volume of the chimpanzee brain increased nonlinearly from 14 to 34 weeks of gestation ($F = 634.28$; cubic effect, $p < 0.0001$) (Figure 1C). The brain volume of the chimpanzee was only half that of the human fetus at 16 weeks of gestation (15.8 cm^3; Figure 1C). The estimated volume of the human brain at the same gestational age is 33.6 cm^3 [8]. At 32 weeks of gestation (just before birth), the volume of the chimpanzee brain reached approximately 40.3% of the adult volume. By contrast, the corresponding value for humans was 23.4%. However, the volume of the fetal human brain appears to continue to increase after this gestational age, as the volume of the human neonatal brain is ~30% of the adult volume (see Supplemental Experimental Procedures for details).

Chimpanzee fetal brain growth velocity continued to increase from ~17 to 22 weeks of gestation (as also observed in human fetuses), although it was slower than that in human fetuses during this period. However, the velocity of brain growth in chimpanzee fetuses did not continue to increase after 22 weeks, whereas it did in human fetuses (Figure 1D). At 32 weeks of gestation, the velocity of chimpanzee brain growth slowed down to approximately 20% of that observed in humans (Figure 1D). The estimated rate of chimpanzee brain growth was 4.1 cm^3/week at ~32 weeks of gestation (Figure 1D); in humans, the corresponding value was 26.1 cm^3/week at the same gestational age (Figure 1D).

These results demonstrate that the remarkable enlargement of the human brain already begins before ~16 weeks of gestation. Moreover, the growth velocity of brain volume increased until ~22 weeks of gestation in both chimpanzees and humans; however, after that time, brain growth in the chimpanzee fetus slowed down as birth approached. By contrast, brain growth in the human fetus continued to accelerate until around 32 weeks of gestation. Therefore, we infer that prenatal patterns of human neuronal enhancement changed from those of the chimpanzee during the rapid brain evolution of modern humans [9,10]. These ontogenetic patterns during intrauterine life appear to have emerged after the split of humans from chimpanzees and have contributed to the more marked brain size in our species.

Supplemental Information

Supplemental Information includes six tables and can be found with this article online at http://dx.doi.org/10.1016/j.cub.2012.06.062.

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The lifespan of Korean eunuchs

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Although many studies have shown that there are trade-offs between longevity and reproduction, whether such trade-offs exist in humans has been a matter of debate [1,2]. In many species, including humans, males live shorter than females, which could be due to the action of male sex hormones. Castration, which removes the source of male sex hormones, prolongs male lifespan in many animals, but this issue has been debated in humans [3]. To examine the effects of castration on longevity, we analyzed the lifespan of historical Korean eunuchs. Korean eunuchs preserved their lineage by adopting castrated boys. We studied the genealogy records of Korean eunuchs and determined the lifespan of 81 eunuchs. The average lifespan of eunuchs was 70.0 ± 1.76 years, which was 14.4–19.1 years longer than the lifespan of non-castrated men of similar socio-economic status. Our study supports the idea that male sex hormones decrease the lifespan of men.

In many mammalian species, including humans, the lifespan of males is shorter than that of females. One explanation for this is that male sex hormones reduce the lifespan of men because of their antagonistic role in immune function [4]. Male sex hormones also predispose men to adverse cardiovascular events [5]. Therefore, male sex hormones could be responsible for the reduced lifespan of men. The effects of male sex hormones on lifespan have been examined by observing the effects of castration, which typically prolongs lifespan in animals [6], but studies on its influence in humans have yielded limited and debatable findings. Castration prolonged the lifespan of mentally ill, institutionalized men [7], whereas the lifespan of castrato singers was not markedly different from that of non-castrated singers [8].

A eunuch is a castrated human male, and historically, eunuchs have been employed as guards and servants in harems across the Middle East and Asia. The Imperial court of the Korean Chosun Dynasty (1392–1910) also had eunuchs.