Growth-Related Shape Changes in the Fetal Craniofacial Complex of Humans (*Homo sapiens*) and Pigtailed Macaques (*Macaca nemestrina*): A 3D-CT Comparative Analysis

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ABSTRACT This study investigates whether macaques and humans possess a common pattern of relative growth during the fetal period. The fetal samples consist of 16 male pigtailed macaques (mean age, 20.5 gestational weeks) and 17 humans (9 males and 8 females; mean age, 29.5 gestational weeks). For each individual, three-dimensional coordinates of 18 landmarks on the skull were collected from three-dimensional computed tomographic (CT) reconstructed images and two-dimensional CT axial slices. Early and late groups were created from the human (early mean age, 24 weeks, N = 8; late mean age, 34 weeks, N = 9) and macaque samples (early mean age, 17.7 weeks, N = 7; late mean age, 23 weeks, N = 9). Inter- and intraspecific comparisons were made between the early and late groups. To determine if macaques and humans share a common fetal pattern of relative growth, human change in shape estimated from a comparison of early and late groups was compared to the pattern estimated between early and late macaque groups. Euclidean distance matrix analysis was used in all comparisons. Intraspecific comparisons indicate that the growing fetal skull displays the greatest amount of change along mediolateral dimensions. Changes during human growth are primarily localized to the basicranium and palate, while macaques experience localized change in the midface. Interspecific comparisons indicate that the two primate species do not share a common pattern of relative growth, and the macaque pattern is characterized by increased midfacial growth relative to humans. Our results suggest that morphological differences in the craniofacial skeleton of these species are in part established by differences in fetal growth patterns. Am J Phys Anthropol 120:339–351, 2003.

A number of investigations have documented the divergence of craniofacial growth patterns between primate species (Giles, 1956; Jungers and Hartman, 1988; Ravosa, 1991, 1992; Shea, 1983, 1985a,b) and between the sexes within primate species (Cheverud and Richtsmeier, 1986; German et al., 1994; Leigh and Cheverud, 1991; Ravosa, 1991; Richtsmeier et al., 1993; Zumpano and Sirianni, 1994). Lieberman et al. (2000) provided a comprehensive critique and review of primate cranial base studies. It is not surprising that most of these studies document postnatal growth, usually beginning with growth during the juvenile period. It is also not surprising that many comparative studies (e.g., Richtsmeier and Walker 1993; Krovitz, 2000; Ponce de Leon and Zollikofer, 2001) of craniofacial growth that have demonstrated early appearance of taxon- (or population-) specific features and the maintenance of this morphological distinctiveness later in postnatal ontogeny suggest that shape differences arise very early, perhaps during prenatal development. Only a few studies have incorporated the infant growth period (Ravosa, 1992; Richtsmeier et al., 1993; Shea, 1983) or examined the contributions of fetal craniofacial growth patterns to postnatal craniofacial morphology (Zumpano and Sirianni, 1994). The main reason for the rarity of fetal growth studies is the difficulty in obtaining fetal specimens and collecting fetal growth data. Fetal primate collections are rare and often contain specimens that result from devel-

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opmental abnormalities or spontaneous abortions. However, the consideration of fetal growth patterns is essential to construction of the complete ontogeny of morphological traits and to determine whether heterochronic processes are responsible for the changes that have occurred between human and nonhuman primates.

Age-based and size-based heterochronies both require an "onset" time for growth (Gould, 1977; McKinney and McNamara, 1991; Shea, 1985a). Using birth as an onset time is convenient, but ignores periods of morphological change and growth that occur during the fetal period (Zumpano, 1997). For example, the pigtailed macaque male has achieved 45–50% of its adult craniofacial dimensions at birth (Sirianni and Newell-Morris, 1980). Is the postnatal growth pattern a simple continuation of the prenatal pattern, or are they different? Do all primates share a common fetal growth pattern? Are there elements of the growth pattern that are species-specific? This study provides the first three-dimensional comparative analysis of fetal craniofacial growth and morphology between humans (*Homo sapiens*) and pigtailed macaques (*Macaca nemestrina*). Our purpose is to determine whether a common pattern of relative growth is shared by these two species, and to document and localize intraspecific and interspecific differences and similarities in fetal craniofacial morphology.

The pigtailed macaque (*M. nemestrina*) is one of many macaque species that is commonly used as an experimental model for human growth and development (Watts, 1985). Postnatal growth of the pigtailed macaque skull has been documented in two extensive cephalometric longitudinal studies (Sirianni and Swindler, 1985; Sirianni and Van Ness, 1978), and postnatal allometric relationships between the sexes have been documented (German et al., 1994). However, there are only two direct comparative investigations of postnatal craniofacial growth in humans and macaques (Duterloo and Enlow, 1970; Enlow, 1966).

Interspecific comparisons of adult craniofacial morphology show that the anterior cranial base (basion-nasion) in macaques is relatively longer and possesses a greater angle (nasion-sella-basion) as compared to humans (Sirianni and Swindler, 1985). The bitemporal and bizygomatic widths are larger in macaques relative to humans, in order to accommodate the larger macaque jaw musculature. In accordance with a larger masticatory apparatus, the lateral orbital rims are thicker and oriented more posteriorly in macaques (Duterloo and Enlow, 1970; Enlow and McNamara, 1973). Relative to humans, the macaque palate is elevated in the oral cavity, and the macaque midface is prognathic. The shape of the macaque neurocranium is ovoid, and not round like the human neurocranium (Sirianni, 1985). Relative to humans, the macaque neurocranium is longer anteroposteriorly and shorter superoinferiorly, while the splanchnocranium is situated anterior to, and not inferior to, the neurocranium (Sirianni, 1985).

Fetal growth of the pigtailed macaque craniofacial skeleton was examined in several cross-sectional investigations (Moore, 1978; Moore and Phillips, 1980; Sirianni, 1985; Sirianni et al., 1975; Zumpano, 1997). Cross-sectional investigations documenting growth of the fetal human craniofacial complex are numerous (Bjork, 1955; Bosma, 1976; Brodie, 1941; Burdi, 1965, 1969; Diewert, 1983, 1985; Ford, 1956; Grausz, 1991a,b; Houpt, 1970; Inoue, 1961; Johnston, 1974; Kraus, 1960; Kvinnsland, 1971a,b). Still, there are no direct comparisons of fetal craniofacial morphology between these two species. All comparisons are literature-based (Enlow and McNamara, 1973; Moore and Lavelle, 1974; Sirianni, 1985; Sirianni and Newell-Morris, 1980).

Literature comparisons have indicated that the fetal cranial base angle in macaques is larger than in humans (Siranni, 1985). The shape of the fetal macaque neurocranium is initially round like the fetal and adult human skull, but becomes more ovoid as fetal growth progresses in humans (Sirianni, 1985; Sirianni and Newell-Morris, 1980). The fetal macaque midface is more prognathic than the fetal human midface, and macaques have attained more of their adult craniofacial dimensions at birth (Sirianni and Newell-Morris, 1980). These literature comparisons of fetal craniofacial growth between macaques and humans provide a general description of interspecific morphological differences. However, they fail to provide information regarding the location of growth differences and the significance, statistical and/or biological, of these differences.

This project uses Euclidean distance matrix analysis (EDMA) and three-dimensional (3D) coordinate data collected from computed-tomographic (CT) images of the macaque and human fetal craniofacial complex to quantify intra- and interspecific 3D morphological changes in craniofacial form during late fetal growth. Specifically, EDMA is used to elucidate the changes that occur in the fetal craniofacial complex during late fetal growth within each species. EDMA is also used to test the null hypothesis that macaques and humans share a common fetal pattern of relative growth.

MATERIALS AND METHODS

Samples

The fetal monkey sample consists of 16 male pigtailed macaques from the Primate Fetal Collection located at the Department of Anthropology at the State University of New York at Buffalo. These specimens were collected to study craniofacial growth and development as part of a multidisciplinary research project funded by the National Institutes of Health during the 1960s and 1970s. The purpose of the NIH project was to establish baseline growth data for the pigtailed macaque (Sirianni, 1985). These fetuses resulted from timed matings in which

TABLE 1. Subsets of fetal human and pigtailed macaque samples created for growth comparisons

	Prenatal weeks	% of gestation completed
Macaca nemestrina		
Early group (N = 7)	16, 17, 17, 18, 18, 19, 19 (mean age, 17.7)	72
Late group (N = 9)	22, 22, 23, 23, 23, 23, 24, 24 (mean age, 23)	93
Homo sapiens		
Early group (N = 8)	22, 23, 23, 24, 24, 25, 25, 26 (mean age, 24)	60
Late group (N = 9)	32, 32, 33, 33, 34, 36, 36, 37, 37 (mean age, 34)	86

gestational age was known to within ±1 gestational day (Blakley et al., 1977). The fetuses were obtained by cesarean section. The estimated length of gestation for pigtailed macaques is 170 ± 8 gestational days (24.6 weeks) (Sirianni and Newell-Morris, 1980).

The fetal human sample consists of digital CT image data for 9 males and 8 females (Grausz, 1991a). Specimens were obtained from the Maryland State Anatomy Board. Ages were obtained from mortuary records, and only fetuses free of pathologies affecting the craniofacial complex were included (Grausz, 1991a). The estimated length of human gestation is 280 days (40 weeks) (Falkner and Tanner, 1986). Since numerous cephalometric investigations have shown that there are no significant differences between the sexes within the human fetal craniofacial complex, males and females were combined to increase the sample size of the fetal human sample (Burdi, 1969; Lavelle, 1974; Levihn, 1967; Trenouth, 1985).

The mean age for the macaque sample is 20.5 weeks, indicating that the monkeys in this study have completed approximately 83.5% of their estimated gestation. The mean age for the human sample is 29.5 weeks, indicating that the humans in this study have completed approximately 73.8% of their estimated gestation. These mean ages fall within the third trimester of fetal growth for both species.

In order to quantify morphological changes during late fetal growth between and within both species, the human and macaque samples were divided into early and late age groups (Table 1). These age groups were constructed to maximize sample size and minimize differences in gestational age. An ideal experimental design would have developmental ages within early and late age groups equally distributed between macaques and humans. This ideal is very difficult to realize in any growth study, but is particularly difficult to achieve in studies that incorporate fetal specimens. Since our data are cross-sectional, we cannot study particular aspects of growth, such as the adolescent growth spurt, that are more readily observable using longitudinal data sets. We accept the intraspecific comparison of early and late age groups as representative of changes in morphology through time during late fetal growth. The authors acknowledge that the percentage of gestation completed is not necessarily equal in the two species, so the conclusions drawn from the interspecific age-matched form comparisons (i.e., early human group vs. early macaque group, and late human group vs. early macaque group) are given with caution.

Data and landmark acquisition

CT scans were acquired for each pigtailed macaque at Millard Fillmore Hospital (MFH, Buffalo, NY). The human fetuses underwent scanning at the Johns Hopkins Medical Institutions (JHMI). The CT scanners at both institutions possess third-generation CT technology (Seeram, 1994; Zonneveld, 1987), and a similar CT scanning protocol was used at both institutions. All specimens were scanned using a slice thickness of 1.5 mm. Validation studies have shown that accurate and precise image data are acquired by both scanners (for the JHMI scanner, Richtsmeier et al., 1995; for the MFH scanner, Zumpano, 1997). Measurement error studies have been conducted for the collection of landmark data (Richtsmeier et al., 1995) from image data.

A total of 36 landmarks was digitized by one of the authors (M.P.Z.) on 3D-CT reconstructions and axial slices for each macaque and human skull on a desktop personal computer (PC) running VoxBlast, a 3D measurement and visualization software package (Colburn et al., 1998). Landmarks were modified from Corner and Richtsmeier (1992), and were used by the authors in recent publications (DeLeon et al., 2001; Zumpano et al., 1999).

These landmarks were digitized three times, with a period of 3 weeks separating each session. These separate digitizations were used to calculate precision (the absolute difference between repeated measures of the same image) along all three axes local to each landmark, following procedures detailed by Richtsmeier et al. (1995). In both samples, all landmarks were digitized with an average precision of less than 0.5 mm along all axes (x, y, and z axes).

Measurement error for specific landmarks resulted from many factors. The large expanse of the human fontanelles relative to those of the macaque prevented landmarks such as bregma and lambda to be located with acceptable precision on the 3D surface of the fetal human skulls. Suture locations and completeness of neurovascular foramina were more varied in the human sample than in the macaque sample. Additionally, several landmarks were originally defined on the macaque skull and lacked a corresponding location on the human skull. The 18 landmarks that were included in this study where those located on the human skull with an average precision of 0.5 mm (Table 2 and Fig. 1).

TABLE 2. List of landmarks digitized from 3D-CT reconstructions[1]

Landmark number	Landmark abbreviation	Landmark definition and abbreviation name
1	nas	Nasion, junction of the frontonasal suture
2	nal	Nasale, anterior DMH and inferiormost tip of the nasal bone
3 and 4	zms	Superior zygomatico-maxillary suture (right and left)
5 and 6	fzj	Posterior aspect of the frontal-zygomatic suture (right and left)
7 and 8	ptnp	Pterion posterior, frontal-zygomatic-parietal intersection (right and left)
9 and 10	tzj	Temporal-zygomatic junction, inferior surface of suture
11 and 12	iam	Superior aspect of external auditory meatus (right and left)
13 and 14	ast	Asterion (right and left)
15	bas	Basion, the most inferior and posterior point on the anterior margin of the foramen magnum
16	pns	Posterior nasal spine, posteriormost point of contact between the two palatine bones
17	sella	Center of bony hypophyseal fossa
18	ids	Infradentale superior (supradentale), most anterior inferior point on the maxilla at its labial contact with the maxillary central incisor

[1] Two numbers are given for landmarks that occur bilaterally. These landmarks are illustrated in Figure 1.

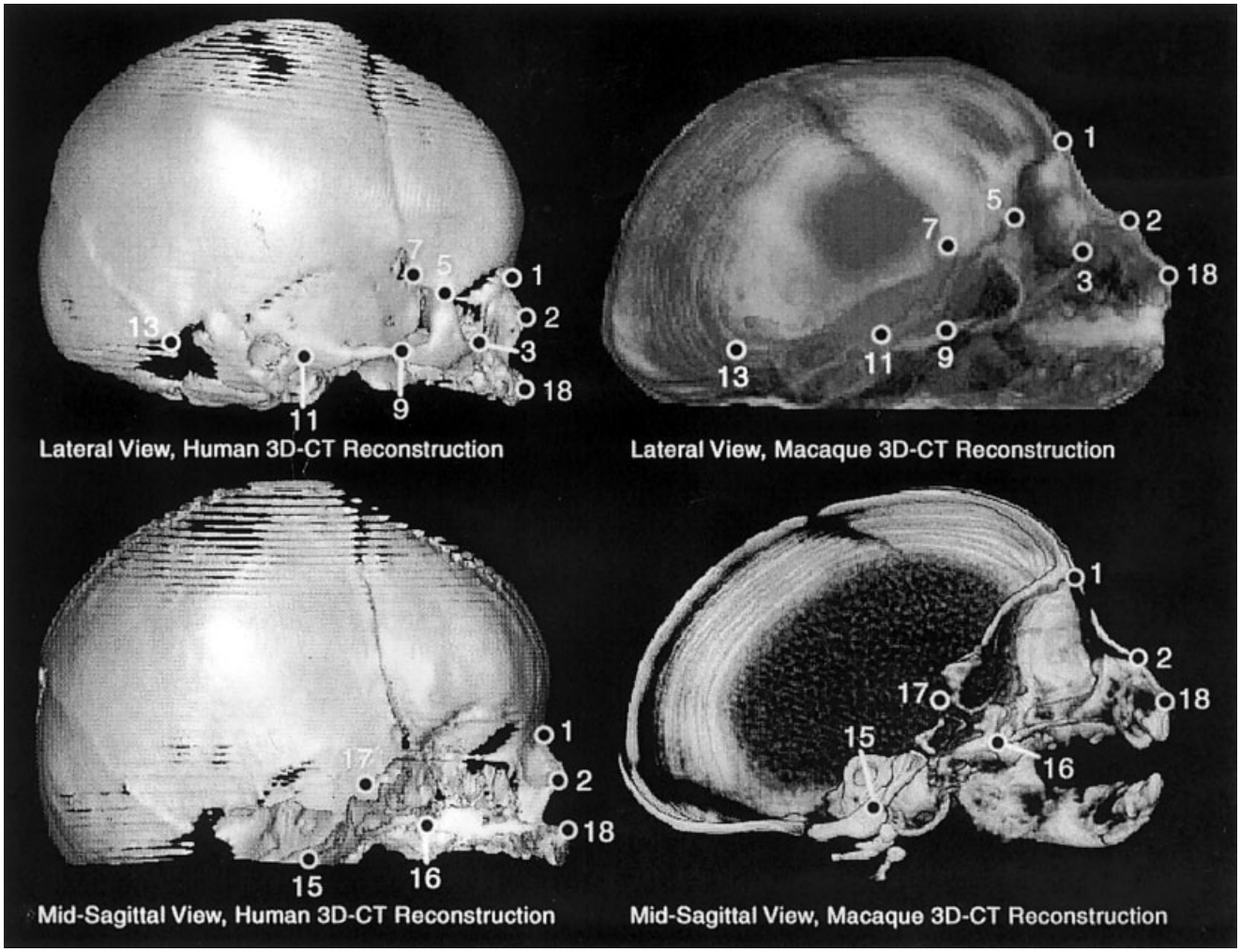

Fig. 1. Landmarks used in analyses are defined in Table 1 are illustrated on midsagittal and lateral 3D-CT reconstructions of a fetal human and fetal pigtailed macaque skull. Only right-sided landmarks are illustrated for those that occur bilaterally.

Comparisons and statistical method

Euclidean distance matrix analysis was used to compare craniofacial morphology between the early human and early macaque groups and between the late human and late macaque groups. EDMA was also used to determine patterns of relative growth within the human and macaque fetal craniofacial complex by comparing the early and late macaque groups to one another and the early and late human groups to one another. Finally, the null hypothesis that human and macaques share a common pattern of relative growth was tested for specific landmark

subsets, and nonparametric confidence intervals were used to determine localized differences in relative growth between the two species ($P < 0.05$).

EDMA is a landmark-based method that compares forms and/or growth patterns between two samples in two or three dimensions (Lele, 1993; Lele and McCulloch, 1999; Lele and Richtsmeier, 1991, 1995, 2001; Richtsmeier and Lele, 1993). EDMA compares forms by first calculating a mean form matrix (FM) from landmark coordinate data for each population. A FM contains mean linear distances computed for all unique landmark pairs within each sample. The FMs for two samples are compared by computing a form difference matrix (FDM). The FDM reports a ratio (sample 1/sample 2) of like linear distances for all landmark pairs within each sample.

When like interlandmark distances are the same between the two samples, the FDM ratio equals 1. If an interlandmark distance in the numerator sample is larger relative to the same interlandmark distance in the denominator sample, the FDM ratio will be greater than 1. If an interlandmark distance in the numerator sample is smaller relative to that same interlandmark distance in the denominator sample, the FDM ratio will be less than 1. The actual value of the FDM provides a relative measure of a specific linear distance in the two samples being compared. The further the value of the FDM ratio is from 1, the greater the difference is for a given interlandmark distance. Significant differences between samples are determined on the basis of nonparametric null hypothesis-testing and the estimation of confidence intervals. The null hypothesis states that average forms of the two samples are similar. If the null hypothesis is rejected, then the two forms are considered to be significantly different in shape.

Rohlf (2000) recently criticized the EDMA testing procedure for relatively low power. We recognize fully (as acknowledged originally by Lele and Cole, 1996) that the EDMA testing procedure, in every biological situation, does not have the best statistical power to detect a real shape difference (the probability of rejecting a false null hypothesis). Importantly, neither of the tests proposed by Rohlf (2000) are uniformly most powerful (UMP) tests. Simulation studies like those presented by Rohlf (2000) can be misleading because they report the power of one test relative to others in *a specific situation.* A situation where any particular test behaves badly or favorably can always be found. As emphasized elsewhere (Lele and Richtsmeier, 1995), shape differences should be studied using confidence interval testing procedures instead of concentrating solely on the testing of a simple null hypothesis of equality of shapes. In this study, we include a nonparametric procedure that calculates confidence intervals for each linear distance to determine those linear distances that are significantly different between the two samples (Lele and Richtsmeier, 1995). This provides a test for localized differences in shape between the two groups.

Patterns of relative growth can also be compared using EDMA (Richtsmeier and Lele, 1993). Instead of comparing two mean forms, two growth intervals are compared. For example, in this study, there are two age groups for each species (Table 1). The pattern of relative growth that occurs between the early macaque and late macaque age groups will be compared to the pattern that occurs between the early human and late human age groups.

EDMA compares growth patterns between two age intervals in a series of steps. First, a form matrix (FM) is calculated for each sample being considered: early macaque, early human, late macaque, and late human age groups. Next, the pattern of growth that occurs within the macaque interval is expressed as a growth matrix (GM) by comparing the FMs of the early macaque and late macaque age groups. A GM reports a ratio of like linear distances for every possible landmark pair (and therefore is mathematically equivalent to an FDM). Another GM is created for the human interval. Finally, the patterns of growth between the macaque and human intervals are contrasted by calculating a growth difference matrix (GDM).

The GDM compares the two GMs by calculating a ratio of the change recorded for each linear distance in the two intervals. For any specific linear distance, this ratio uses the value of the GM calculated for the macaque interval in the numerator and the value of the GM calculated for the human interval in the denominator. In this study, if the relative growth observed for an interlandmark distance in the macaque interval is greater than growth of the same interlandmark distance in the human interval, the ratio will be greater than 1. If the ratio is less than 1, then the amount of relative growth experienced local to an interlandmark distance in the macaque interval is less than the amount of growth experienced by that same interlandmark distance in the human interval. The collection of these localized values enables comparison of relative growth patterns. The further the value of the GDM ratio is from 1, the greater the difference in relative growth for a given interlandmark distance between the two populations being compared.

To compensate for size differences in all interspecific form and relative growth comparisons, each individual was scaled by dividing each linear distance by the geometric mean of all linear distances for that individual (Lele and Cole, 1996). In order to test for statistically significant differences in relative growth, we conducted null hypothesis-testing, using subsets of landmarks such that the sample size of the larger sample was greater than the number of landmarks in the subset (Table 3). For each subset, the null hypothesis states that the relative growth of fetal macaques is similar to the relative growth of fetal humans. The subsets were designed to represent functionally meaningful craniofacial

TABLE 3. Landmark subsets that were analyzed to permit statistical testing of shape differences

Subset name	Landmark number
Cranial Base	1, 17, 19
Face	1, 3, 4, 5, 6, 11, 12
Midface	2, 3, 4, 18, 20
Neurocranium	7, 8, 13, 14, 15, 16

components. All raw EDMA outputs are available upon request. EDMA is available for download at http://c.faculty.umkc.edu/colet (Cole, 2002).

RESULTS

Intraspecific EDMA comparisons

The early (24 weeks) human and late (34 weeks) human age groups were compared using EDMA. This comparison determines if the overall form of the human fetal craniofacial complex is significantly different between these age groups. Our results indicate that the form of the early human craniofacial complex is significantly different ($P < 0.05$) from the late human age group in all subset comparisons (Table 4, row 1). Confidence intervals (CIs) were calculated to determine the specific sites of significant localized differences ($\alpha = 0.10$) within the time period studied, and are illustrated in Figure 2. Solid lines indicate linear distances that are significantly larger in the older human age group, and dotted lines indicate linear distances that are significantly smaller in the older human age group. Linear distances that did not demonstrate significant CIs are not labeled, representing regions of no significant morphological change, or maintenance of craniofacial form between the early and late human age groups (Fig. 2).

The length of the anterior cranial base (1–17) is relatively larger in the older human age group, while the length of the posterior cranial base (15–17) is relatively smaller. Additional linear distances that are significantly smaller in the older human age group relative to the young human age group are localized between the pterions and the frontozygomatic sutures (5–7 and 6–8). The height of the posterior palatal shelf (16–17) and the distance between basion and the posterior nasal spine (15–16) are also smaller in the older human age group, relative to the young human age group.

Upper facial height is relatively larger along the oblique mediolateral and superoinferior axes in the older human group (1–3 and 1–4). The anteroposterior length of the fetal skull is relatively longer in the older human group (3–13, 4–14, 9–11, and 10–12). Linear distances summarizing midfacial prognathism did not display any differences between the two human age groups (1–2, 1–16, 1–18, 2–3, 2–4, 2–16, 3–18, and 4–18), but the length of the palate as defined by posterior nasal spine to infradentale superior (16–18) was relatively larger in the older human age group. Changes were greatest along the mediolateral axis, indicating that the width of the human fetal skull displays markedly disproportionate increases during this interval (3–4, 5–6, 7–8, 9–10, and 13–14).

The early macaque and late macaque age groups were also compared using EDMA to determine if the overall form of the macaque craniofacial complex is significantly different between these two age groups. Results indicate that the shape of the early macaque fetal craniofacial complex is significantly different ($P < 0.05$) from the late macaque age group in all subset comparisons (Table 4, row 2). CIs were calculated to determine the specific sites of significant localized differences ($\alpha = 0.10$) within the time period studied, and are illustrated in Figure 3. Solid lines indicate linear distances that are significantly larger in the old macaque age group, and dotted lines indicate linear distances that are significantly smaller in the older macaque age group (Fig. 3).

The lengths of the anterior and posterior cranial base (1–17 and 15–17) and the distance between nasion and basion (1–15) are larger in the old macaque group, relative to the young macaque group. There is no difference in lengths between sella and the posterior nasal spine (16–17), indicating no change in height of the posterior palatal shelf between these two macaque age groups.

Upper facial height is relatively larger in the old macaque age group (1–2, 1–3, and 1–4). Linear distances related to midfacial prognathism are larger in the old macaque group, relative to the young macaque age group (1–2, 3–4, 3–18, 4–18, and 16–18). The distance between nasale and infradentale (2–18) and nasale and posterior nasal spine (2–16) are relatively smaller in the old macaque age group.

These decreases, combined with an increase in palatal length (16–18), results in an elongation of the inferior aspect of the nasal cavity and a shortening of the superior aspect of the nasal cavity, creating the characteristic slanted nasal aperture of the macaque snout. Finally, the same mediolateral interlandmark distances that displayed significant relative increases in the older human age group displayed significant relative increases in the older macaque.

Interspecific EDMA comparisons

To determine if the overall shape of the fetal craniofacial complex is similar ($P < 0.05$) between both species, the early macaque group was compared to the early human group (early interspecific comparison), and the late macaque group was compared to the late human group (late interspecific comparison). To compensate for size differences, each individual was scaled by dividing each linear distance by the geometric mean of all linear distances for that individual (Lele and Cole, 1996). All subset comparisons for both early and late interspecific comparisons demonstrated significant differences in shape between species (Table 4, rows 3 and 4). CIs were calculated to determine the specific sites of significant localized differences ($\alpha = 0.10$)

TABLE 4. Results of test of null hypotheses of similarity in shape or similarity of shape change due to growth for all EDMA subset comparisons

EDMA comparison	Subset name			
	Cranial base *P*-value	Face *P*-value	Midface *P*-value	Neurocranium *P*-value
1. Human intraspecific growth	0.03	0.02	0.03	0.02
2. Macaque intraspecific growth	0.01	0.01	0.01	0.01
3. Early interspecific form	0.01	0.01	0.01	0.01
4. Late interspecific form	0.01	0.01	0.01	0.01
5. Relative growth comparison	0.02	0.01	0.01	0.01

within the time period studied, and are illustrated for the early interspecific (Fig. 4) and the older interspecific (Fig. 5) comparison.

The overall pattern of significant localized differences between early and late interspecific comparisons are very similar (compare Figs. 4 and 5). Linear distances that summarize midfacial prognathism were larger in the macaques, relative to humans for both age groups (1–3, 1–4, 3–4, 3–5, 3–18, 4–6; and 4–18). The length of the posterior cranial base (15–17) is larger in the macaques from both age groups, while the length of the anterior cranial base (1–17) is smaller in the macaques. The length of the cranial base (1–15) is larger in the macaque age groups, relative to the human age groups.

There are several differences in the pattern of significant localized differences between the early and late interspecific comparisons. In the early interspecific comparison, distances along the mediolateral axis were significantly larger in the macaque, relative to humans. In the late interspecific comparison, these distances became relatively smaller in macaques (compare Figs. 4C and 5C).

EDMA comparison of relative growth

The null hypothesis that macaques and humans share a common craniofacial growth pattern was tested using EDMA by comparing the pattern of relative growth between the early and late macaque age groups (hereafter the macaque interval) to the pattern of relative growth between the early and late human age groups (hereafter the human interval) ($P < 0.05$). The results of this comparative growth analysis indicate that there are significant differences between human and macaque fetal relative growth patterns in all subset comparisons (Table 4, row 6). We reject the null hypothesis of shape similarities between macaques and humans in the fetal craniofacial complex due to relative growth, and provide data that define significantly different fetal craniofacial patterns of relative growth in macaques and humans. Finally, we remind the readers that these results are based on a small sample size of macaque and human fetuses that are organized into similar, though not identical age intervals.

Confidence intervals were calculated to determine the specific sites of significant localized growth differences ($\alpha = 0.01$) and are illustrated in Figure 6. Solid lines indicate linear distances that display significantly more relative growth in the macaque in-

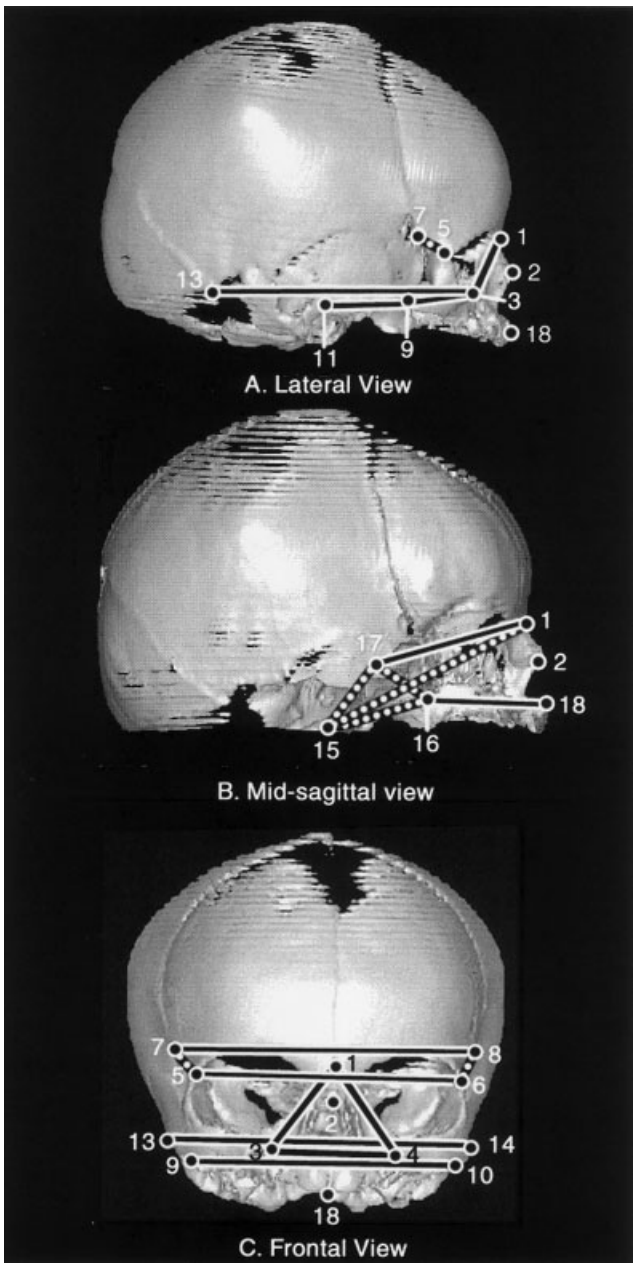

Fig. 2. Human intraspecific EDMA comparison. Linear distances that display significant confidence intervals are illustrated on 3D reconstructions of lateral (**A**), mid-sagittal (**B**), and frontal (**C**) views of a fetal human skull. Solid lines indicate linear distances that are significantly larger in the old human age group relative to the early human age group. Dotted lines indicate linear distances that are significantly smaller in the old human age group relative to the early human age group.

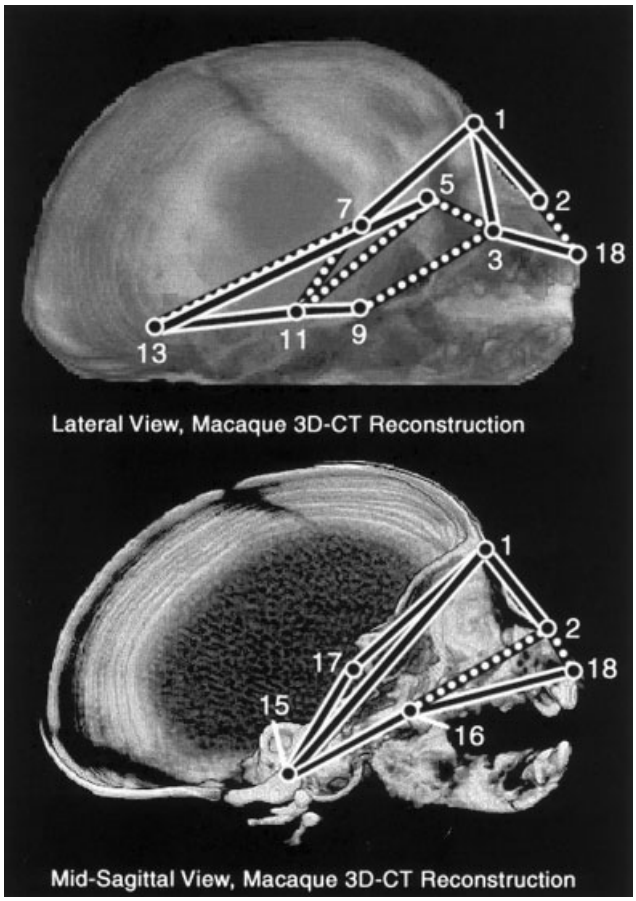

Fig. 3. Macaque intraspecific EDMA comparison. Linear distances that display significant confidence intervals are illustrated on 3D reconstructions of lateral (**A**) and midsagittal (**B**) views of a fetal pigtailed macaque skull. Solid lines indicate linear distances that are significantly larger in the old macaque age group relative to the early macaque age group. Dotted lines indicate linear distances that are significantly smaller in the old macaque age group relative to the early macaque age group.

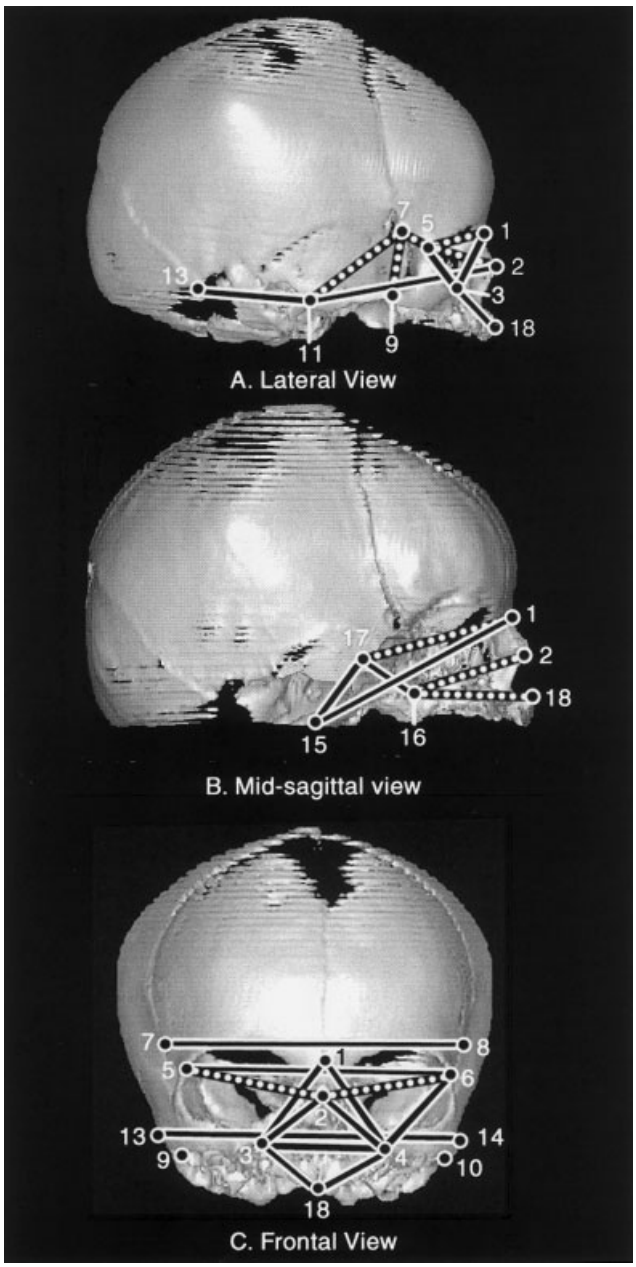

Fig. 4. Comparison of human and macaque fetal craniofacial morphology for the younger age group. Linear distances that display significant confidence intervals are illustrated on 3D reconstructions of lateral (**A**), mid-sagittal (**B**), and frontal (**C**) views of a fetal human skull. Solid lines indicate linear distances that are significantly larger in the early macaque age group relative to the early human age group. Dotted lines indicate linear distances that are significantly smaller in the early macaque age group relative to the early human age group.

terval as compared to the human interval, and dotted lines indicate linear distances that display significantly less relative growth in the macaque interval. Linear distances that are not illustrated indicate regions that display similar localized patterns of relative growth between macaques and humans.

Linear distances in the macaque midface that display the greatest growth differences are localized between the zygomatico-maxillary sutures and infradentale superior (3–18 and 4–18), followed by linear distances connecting nasion and nasale to the zygomatico-maxillary sutures (1–3, 1–4, 2–3, and 2–4). Our data suggest that macaque midfacial prognathism is produced by relatively increased growth magnitudes localized between the zygomatico-maxillary sutures and infradentale superior. These distances are obliquely oriented along the mediolateral and superoinferior axes. Within the fetal midface, macaques and humans display no significant differences in relative growth for the linear distances between nasion and nasale (1–2), nasion and infradentale superior (1–18), and nasale and infradentale superior (2–18). These distances are located along obliquely oriented anteroposterior and superoinferior axes. Increased magnitude in the relative growth of the palate (16–18) in the macaque also contributes to a prognathic midface in the fetal macaque.

The anterior cranial base (1–17) displays less growth in the macaque, relative to humans. The

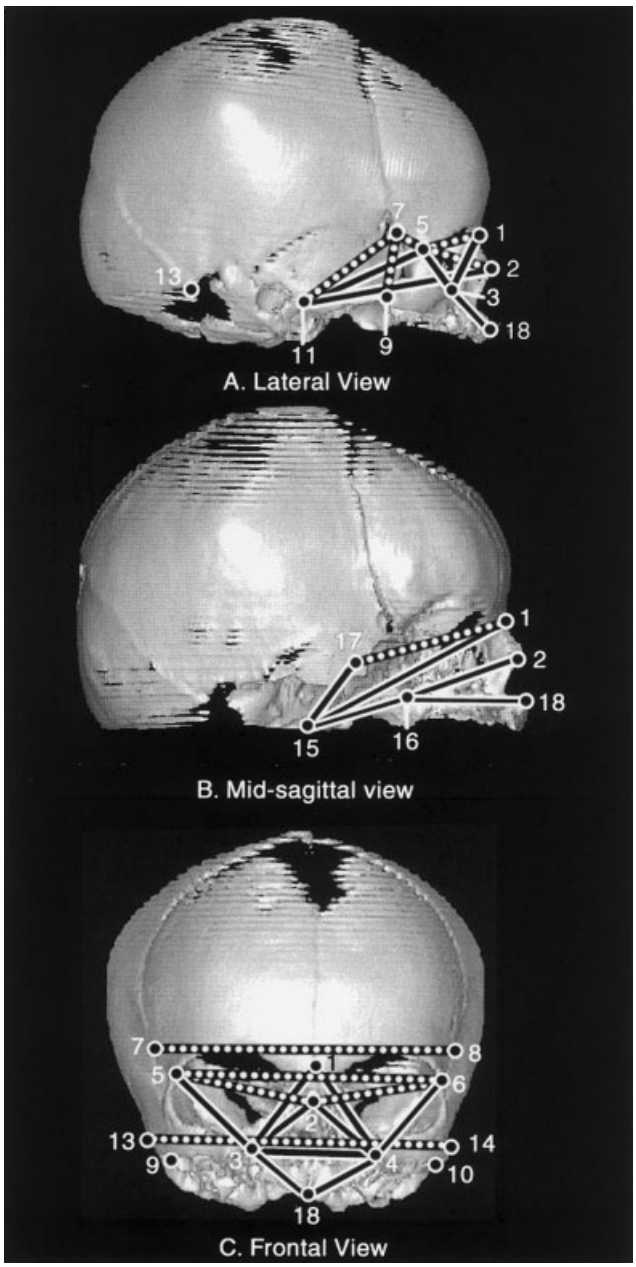

Fig. 5. Comparison of human and macaque fetal craniofacial morphology for the older age group. Linear distances that display significant confidence intervals are illustrated on 3D reconstructions of a lateral (**A**), mid-sagittal (**B**), and frontal (**C**) views of a fetal human skull. Solid lines indicate linear distances that are significantly larger in the late macaque age group relative to the late human age group. Dotted lines indicate linear distances that are significantly smaller in the late macaque age group relative to the late human age group.

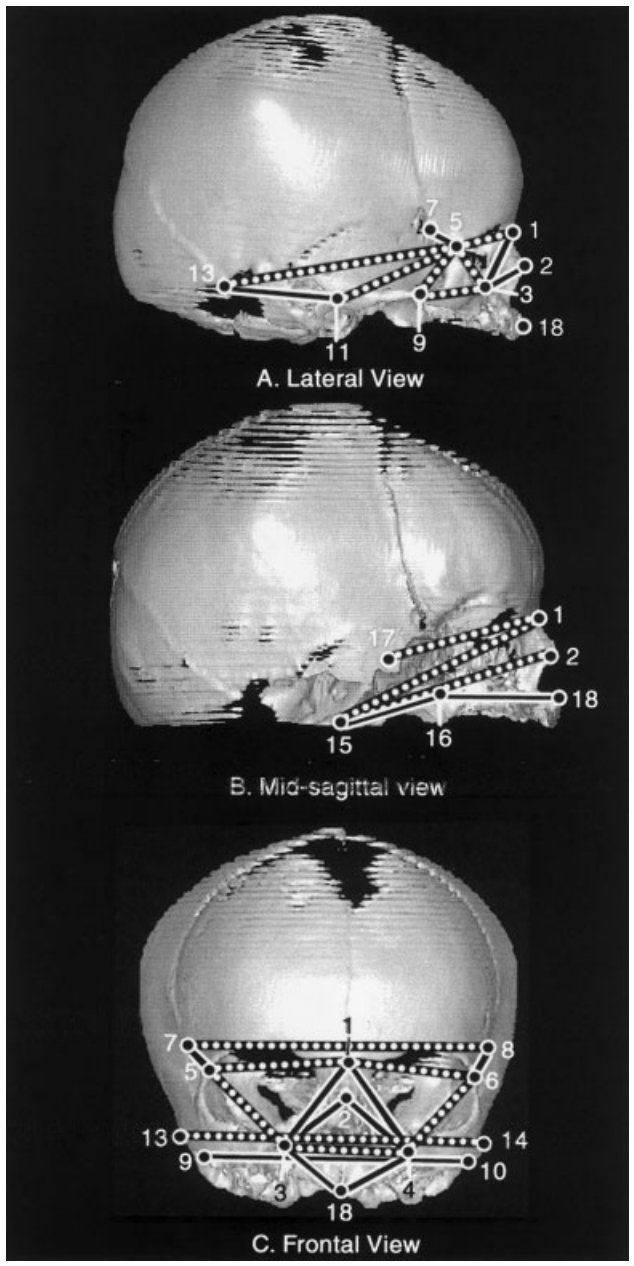

Fig. 6. Growth comparison of fetal macaques and humans. Linear distances that display significant confidence intervals are illustrated on 3D reconstructions of lateral (**A**), mid-sagittal (**B**), and frontal (**C**) views of a fetal human skull. Solid lines indicate linear distances that are significantly larger in the macaque interval relative to the human interval. Dotted lines indicate linear distances that are significantly smaller in the macaque interval relative to the human interval.

posterior cranial base (15–17) exhibits similar relative growth patterns between the macaque and human intervals. Overall cranial base length (1–15) grows less in macaques relative to humans.

Other linear distances that display significantly larger growth magnitudes in the macaque interval relative to the human interval are between asterion and the external auditory meatus (11–13 and 12–14), pterion and the frontozygomatic suture (5–7 and 6–8), and the basion and the posterior nasal spine (15–16). The distance between basion and the posterior nasal spine possesses the greatest growth difference between the macaque and human intervals. Linear distances that display significantly less growth in macaques relative to humans are between the frontozygomatic sutures and the zygomaticomaxillary sutures (3–5 and 4–6) and all linear dis-

tances oriented along a mediolateral axis (1–5, 1–6, 3–4, 7–8, and 13–14), with the exception of bizygomatic width (9–10).

Many studies of craniofacial growth track changes in the cranial base angle. To provide data that are directly comparable to more traditional studies, we compared early and late measures of the cranial base angle in these two species, using landmark coordinate data. The linear distance between the nasion and sella was chosen to represent the anterior cranial base, and the linear distance between the sella and basion to represent the length of the posterior cranial base. The linear distances nasion to basion, nasion to sella, and basion to sella were calculated for each specimen, using the landmark coordinate data collected in this study. Given these distances, the cranial base angle (nasion-sella-basion) was known for each individual, and average measures of the cranial base were calculated for the early and late age groups for both species.

The human cranial base angle decreased from 139.83° (SD = 1.813) in the early group to 125.63° (SD = 1.15) in the older group. The macaque cranial base angle was more stable than the human cranial base angle, decreasing only slightly from 147.29° (SD = 0.897) in the early macaque group to 144.25° (SD = 3.04) in the late macaque group.

DISCUSSION

This study compared fetal craniofacial morphology and craniofacial growth patterns between macaques and humans, using cross-sectional samples of CT image data during late fetal growth. For our samples, we identified local significant differences in shape and relative growth between the human and macaque fetal craniofacial complex, and enabled the rejection of the hypothesis that macaques and humans possess a common fetal pattern of relative growth.

Growth and morphology of the cranial base have been the focus of numerous studies (see Lieberman et al., 2000). The impetus for most studies of the primate cranial base is to determine the angle of the cranial base, the sites of cranial base flexure, and the sites of growth of the cranial base in these two species (Bjork, 1955; Bosma, 1976; Dubrul and Laskin, 1961; Ford, 1956; Houpt, 1970; Lavelle, 1974; Lestrel and Moore, 1978; Moore, 1978; Ross and Henneberg, 1995; Ross and Ravosa, 1993; Sirianni and Newell-Morris, 1980; Sirianni and Van Ness, 1978). Previous investigations showed that over 50% of the adult length of the cranial base (basion to nasion) is achieved during the fetal period in both species (Burdi, 1965; Ford, 1956; Sirianni, 1985). During the third trimester, anterior cranial base length increases faster than posterior cranial base length in these two species (for macaques: Sirianni, 1985; Sirianni and Newell-Morris, 1980; for humans: Bjork, 1955; Burdi, 1965; Ford, 1956).

In humans, decreases in cranial base length are achieved through the differential growth of anterior and posterior elements. There are increases in the length of the anterior cranial base length, while the length of the posterior cranial base decreases. Linear distances connecting the basion to other points on the cranial base experience reduction within the intervals studied (1–15, 15–17, and 15–16). We found that a decrease in cranial base angle may contribute to an overall reduction in cranial base length in fetal humans. Our data do not demonstrate a similar reduction in the fetal macaque cranial base (increased basicranial flexion) for the comparable interval. This difference in the progression of prenatal cranial base flexion, coupled with differences in midfacial growth, most likely contribute to the difference in midfacial projection between the two species.

Bjork (1955) and Burdi (1965) showed that the human cranial base maintains an angle ranging from 129–132° from the second trimester to term. However, Ford (1956) noted a decrease of the human cranial base angle during the third trimester. Our calculations indicate that the cranial base undergoes a flexure (or decrease) of 14.88°, from 139.83° in the early age group to 125.63° in the late human group, during the third trimester. These observations contradict previous cephalometric investigations that showed the human cranial base to maintain a constant angle throughout the fetal period (Bjork, 1955; Burdi, 1965; Ford, 1956), and indicate that basicranial flexion is underway during the fetal period.

In macaques, the cranial base elongates during late fetal growth. Both anterior and posterior cranial base length display increases, with the anterior cranial base displaying a larger magnitude of change. Linear distances connecting the basion to other points on the cranial base are also lengthening (Fig. 3B: 1–15, 15–17, and 15–16;). Our results suggest maintenance of, or a slight decrease in, the macaque cranial base angle during the third trimester. While the measures we report are less than the angle reported in previous studies (153°), we concur with previous investigations that showed the maintenance of the macaque cranial base angle during fetal growth (Lestrel and Moore, 1978; Sirianni and Newell-Morris, 1980).

Similarities and differences in the relative growth of the cranial base between macaques and humans were elucidated using EDMA (Fig. 6). The macaque anterior cranial base experiences less relative growth than the human anterior cranial base. No significant growth differences between species were observed for the posterior cranial base. Finally, the length of the cranial base displays more relative growth during this fetal interval in the human sample than in the macaque sample. The increases in relative length of the anterior cranial base in humans may reflect the faster rate of growth of the frontal lobes of the cerebral cortex in humans, relative to macaques (Enlow and McNamara, 1973;

Moss, 1973; Moss and Salentijn, 1969; Sirianni and Newell-Morris, 1980).

The greatest relative growth differences between macaques and humans are localized to the midface. Macaques possess more growth between the zygomatico-maxillary sutures and nasion, nasale, and infradentale superior. The length of the macaque palate experiences more relative growth than the length of the human palate.

Differences in adult facial morphology between these two primate species are attributed to the large amount of midfacial prognathism present in macaques relative to humans (Sirianni and Swindler, 1985). The morphology of the large masticatory apparatus in adult macaque males has been related to allometry between body size and canine size, sexual selection and diet, and phylogenetic constraints operating on postnatal growth (Clutton-Brock et al., 1977; Harvey and Bennett, 1985; Leutenegger, 1978; Leutenegger and Cheverud, 1982). Macaques are weaned relatively early as compared to humans, and must be prepared to masticate adult food sources before humans of comparable chronological age (Sirianni and Swindler, 1985; Swindler, 1985). Accordingly, macaques are born with their crowns fully calcified and ready to erupt soon after birth (McNamara et al., 1977; Swindler, 1976; Swindler and Emel, 1990; Trotter et al., 1977), while dental eruption of the human deciduous dentition begins several months later (Bhaskar, 1976; Hillson, 1996).

Our results indicate that the development of the adult prognathic macaque midface is well underway during the time period studied. This is evidenced by significant localized increases in the length of several linear distances in the fetal macaque midface (Fig. 3). Furthermore, macaques display significantly more relative growth, than do humans, in the dentofacial complex (Figs. 4C, 6C). Since previous investigations reported nonsignificant differences in the initial time (onset time) of calcification of the deciduous canines, incisors, or first molars (Anemone and Watts, 1990; Swindler, 1985), midface differences between macaques and humans probably reflect either an accelerated rate of development of the macaque deciduous dentition or delayed rate of maturation of the human deciduous dentition.

Pre- and postnatal growth of the craniofacial complex in both human and pigtailed macaques has been characterized by increases in dimensions orientate along the anteroposterior and superoinferior axes (Bergland, 1963; Broadbent et al., 1975; Brodie, 1941; Burdi, 1965; Diewert, 1983; Ford, 1956; Inoue, 1961; Kvinnsland, 1971a; Kvinnsland, 1971b; Lavelle, 1974; Levihn, 1967; Mestre, 1959; Ortiz and Brodie, 1949; Siebert, 1986; Sirianni and Swindler, 1985). These studies have employed cephalometric methods to describe the growth and development of the craniofacial complex. A limitation of cephalometry is its reliance on a registration system to describe changes in morphology (Lele and Richtsmeier, 1991; Moyers and Bookstein, 1979; Richtsmeier and Lele, 1993). Another shortcoming of these investigations is that the data are two-dimensional, as cephalograms are usually taken in norma lateralis. Growth is therefore depicted as to a two-dimensional process, ignoring growth along the mediolateral axis. Results from our investigation reveal that a significant amount of morphological change occurs along the mediolateral axis during fetal development (Figs. 2C, 4C, 5C, 6C).

Lastly, previous investigations suggest that the last trimester of fetal craniofacial growth is characterized by isometric growth (e.g., the fetal skull undergoing only increases in size, with no corresponding changes in shape; Houpt, 1970; Kvinnsland, 1971a,b; Lavelle, 1974; Levihn, 1967; Mestre, 1959; Moore and Phillips, 1980; Sirianni and Newell-Morris, 1980). More recent investigations suggest that shape changes do occur within the fetal craniofacial complex during the last trimester of fetal growth (Grausz, 1991a,b; Plavcan and German, 1995; Zumpano, 1997). Results from our intraspecific form comparisons of early and late fetal human age groups and early and late fetal macaque age groups support these recent investigations. We have shown that the shape of the craniofacial complex is significantly different in each subset comparison (Table 4), demonstrating the specifics of shape change that occur during the third trimester in both species.

This study provides the first 3D comparison of fetal craniofacial morphology and growth between pigtailed macaques (*M. nemestrina*) and humans (*H. sapiens*). The last trimester of fetal growth of the craniofacial complex is characterized by an increase in midfacial prognathism in the macaque, and anteroposterior lengthening of the cranial base in humans. While fetal macaques and humans do not share a common pattern of relative growth of the craniofacial complex, both species undergo increases in mediolateral dimensions (widening) of the skull and increases in palatal and anterior cranial base length. The development of many postnatal craniofacial traits (e.g., macaque midfacial prognathism and cranial base flexion in humans) is established and accentuated during the third trimester of fetal growth.

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