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1 **Ontogeny of cranial base during the first two years of life**

2 Ontogénèse de la base du crâne durant les deux premières années de vie

3

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17

## 1 **Abstract**

2 The integration of the growth of the brain and the cranial base suggests that each system may influence the other,  
3 notably during the first three years of life, although this influence has never been proven to be exclusive.

4 **The aim of our work** was to analyse the dynamics of normal growth on the one hand, and the development and  
5 ontogenetic allometry of the cranial base in the infant on the other hand.

6 **Materiel and Method:** 32 infants (17 males/15 femeles) having been included in the unexpected infant death  
7 french protocol were analyzed. Three-dimensional reconstructions of the cranial base were performed from CT  
8 scans. The technique combined manual segmentation of regions of interest, contour extraction and surface  
9 reconstruction Nineteen landmarks were positioned on each of the bone surfaces

10 **Results:** No correlation was observed between sex assigned at birth and shape, weight, crown-heel length, or  
11 head circumference. Principal component analysis showed that 85.5% of the variance observed on the first  
12 component was secondary to growth. After Procrustes superimposition, 25% of the shape variance observed was  
13 explained by the first principal component. It showed anteroposterior lengthening of the cranial base. In addition,  
14 the height, width and length of the posterior fossa increased and the relative position of the basion was displaced  
15 inferiorly and anteriorly with flexion of the sphenoid angle. Negative allometry was also observed.

16 **Conclusion** Our study, carried out in a rigorously selected population of infants, presents a fundamental  
17 approach to ontogeny through study of shape, growth and ontogenetic allometry.

18 **Key words:** ontogeny; brain; cranial base; infant; growth; development; allometry.

19

## 20 **Résumé**

21 L'intégration de la croissance du cerveau et de la base crânienne suggère que chaque système peut influencer  
22 l'autre, notamment pendant les trois premières années de la vie, bien que cette influence ne se soit jamais avérée  
23 exclusive.

24 **Le but de notre étude** était d'analyser la dynamique de la croissance normale, et d'autre part le développement  
25 et l'allométrie ontogénique de la base du crâne chez le nourrisson.

26 **Matériel et méthodes :** 32 nourrissons (17 garçons / 15 filles) ayant été inclus dans le protocole français de mort  
27 subite du nourrisson ont été analysés.

1 Des reconstructions tridimensionnelles de la base crânienne ont été réalisées à partir de CT-scann. La technique  
2 combinait la segmentation manuelle de régions d'intérêt sélectionnées, l'extraction de contours et la  
3 reconstruction de surface Dix-neuf points de repère ont été positionnés sur chacune des surfaces osseuses

4 **Résultats** : Aucune corrélation n'a été observée entre le sexe assigné à la naissance et la forme, le poids, la  
5 longueur du talon ou la circonférence de la tête. L'analyse en composantes principales a montré que 85,5% de la  
6 variance observée sur la première composante était secondaire à la croissance. Après superposition Procrustes,  
7 25% de la variance de la conformation observée était expliquée par la première composante principale. Elle  
8 montrait un allongement antéropostérieur de la base du crâne. De plus, la hauteur, la largeur et la longueur de la  
9 fosse postérieure augmentaient et la position relative du basion était déplacée vers le bas et l'avant avec la  
10 flexion de l'angle sphénoïde. Une allométrie minorante a également été mise en évidence.

11 **Conclusion** : Notre étude, réalisée dans une population de nourrissons rigoureusement sélectionnée, présente  
12 une approche fondamentale de l'ontogénie à travers l'étude de la forme, de la croissance et de l'allométrie  
13 ontogénétique.

14 **Mots clés**: ontogénie; cerveau; base du crâne; nourrisson; croissance; développement; allométrie.

15

## 1 **Introduction**

2 Ontogeny is described as the development of an organism from conception to adulthood. It is defined as a  
3 process composed of three interdependent mechanisms: growth (changes of size with age), development  
4 (changes of shape with age) and ontogenetic allometry (changes in shape according to size) (1).

5 The integration of the growth systems of the brain and the cranial base suggests that each system may influence  
6 the other, notably during the first three years of life, although this influence has never been proven to be  
7 exclusive (2). It is thought to come into play during the foetal period and the first three years of life, when  
8 growth of the brain is greatest (3).

9 The brain is known to be the best indicator of maturation in foetal ontogenesis (4-5), and a continuum exists  
10 between development and maturation of the brain in the foetus and the infant (4-9). Changes in the cranial base  
11 may be considered as reflecting brain development.

12 Using geometric morphometric methods, shape can be considered independently of size (10-11). Needham's  
13 equation defines form as size and shape (12). Kendall (13) defined shape as "all the geometrical information that  
14 remains when location, scale and rotational effects are filtered out from an object". Using these methods, the  
15 shape changes that take place during growth can be quantified and visualised, notably in three dimensions (14).  
16 In this way, the ontogenetic trajectories of the foetal cranial base (15-19) and of the craniofacial complex in the  
17 neonate can be determined (20-21).

18 The aim of our work was to analyse the dynamics of normal growth on the one hand, and the development and  
19 ontogenetic allometry of the cranial base in the infant on the other hand.

20

## 21 **Materials and Methods**

### 22 **Sample**

23 The sample studied consisted of a retrospective series of infants aged 0 to 24 months and who had been included  
24 in the sudden infant death (SID) protocol in the public hospitals of Marseille (Assistance Publique des Hôpitaux  
25 de Marseille).

26 We studied 32 infants (17 males / 15 females) who had died between January 1, 2010, and 31 December, 2016  
27 (Fig. 1).

1 The deaths were due to sleeping accidents (positional mechanical asphyxia), infectious disorders (viral and  
2 bacterial) and surgical abdominal disorders (acute intestinal intussusception, peritonitis, volvulus) or sudden  
3 infant death syndrome.

4 Only infants with no disorder affecting growth and no brain disorder identified on imaging followed by autopsy  
5 and histopathological examination were included in the study. Autopsy completed by histopathological  
6 examination was considered the gold standard to exclude any disorder. Autopsy was performed after the written  
7 consent of the parents had been obtained. Any external or internal abnormalities were described.

8 The non-inclusion criteria were incomplete or insufficient quality of CT-scan (slice thickness  $\leq 1.5$  mm).

9 Information on pregnancy, term at birth, and medical and surgical history was also recorded.

10 For each infant, anonymized anthropological data were available: chronological age (or corrected age if the  
11 infant was born before 38 weeks amenorrhea), weight, crown-heel length, head circumference and sex.

12 The scans were obtained with a helical CT scanner (Somatom Sensation Cardiac 64; Siemens, Erlangen,  
13 Germany) and the following parameters: voltage 100–140 kVp, amperage 50–150 mA, and slice thickness 0.75–  
14 1.5 mm. These high-resolution native slices recorded in the Digital Imaging and Communications in Medicine  
15 (DICOM) format were anonymised before use.

16

## 17 **Data acquisition**

18 Three-dimensional reconstructions of the cranial base were carried out from the CT scans. The technique  
19 combined manual segmentation of selected regions of interest, contour extraction and surface reconstruction  
20 using Osirix software (Pixmeo, Switzerland) version 5.6. The reconstructions were recorded in STL format.

21 Nineteen landmarks (LDK) were positioned on each of the bone surfaces using Avizo Standard Edition software  
22 (v.7.0.0®, Visualization Sciences Group, SAS) (Fig. 2, Table 1). Bookstein (22) created a classification system  
23 where landmarks are categorized as Types I, II, or III based on their structural location and how informative the  
24 landmarks may be in terms of biological processes and epigenetic factors. Two of the landmarks were type I  
25 (point in space where three structures meet), 10 were type II (maxima of curvature or other local morphogenetic  
26 processes) and 7 were type III (landmark points characterised locally by information from multiple curves and  
27 by symmetry) according to Bookstein's classification (22).

1

## 2 **Statistical analysis**

### 3 **Reliability of measurements**

4 At the current time, there is no reliable and valid method for evaluating the error associated with the positioning  
5 of an individual landmark (23). The repeatability of landmark positioning was evaluated blindly at an interval of  
6 one month from the Procrustes coordinates using three different methods: Lin's concordance correlation  
7 coefficient (CCC), the Bland-Altman agreement method and the matrix correlation test (24). The CCC allow to  
8 approximate the coefficient of precision (average of the absolute differences between the two observations). The  
9 principle of the method proposed by Bland and Altman consists in assessing the difference observed between  
10 two values obtained for the same measurement. This method makes it possible to deduce, on the set of the  
11 population analyzed, the bias, the precision and the limits of the 95% confidence interval, allowing to rule on the  
12 concordance of the two series of values (25). The matrix correlation test was used to evaluate similarity between  
13 two covariance matrices of procrustes coordinates(26) in the absence of outliers. This tests the null hypothesis  
14 of independence of the matrices. A permutation test using 10,000 permutations was carried out to test the null  
15 hypothesis of absence of similarity. Global measurement error of shape was also evaluated following the  
16 protocol described by Claude (27) and derived from the work of Bailey and Byrnes (28). It consisted in carrying  
17 out a Procrustes ANOVA to evaluate shape variation between two landmark digitization sessions, and calculate a  
18 percentage of measurement of error (%ME).

### 19 **Growth**

20 The raw cartesian coordinates of the landmarks were extracted. Principal component analysis (PCA) of these  
21 coordinates was used to analyse morphological changes during growth by studying form (12). It allowed to  
22 visualise the distribution of the individuals and to evaluate morphological distances between specimens. A  
23 growth model was developed using Autocad software 2016 (AutoDesk, San Francisco, CA). This software is  
24 mainly designed to prepare technical drawings. All evaluations were done by a single trained professional. This  
25 growth model were aligned according to landmark 1 (hypophyseal fossa in sella turcica) and the midsagittal  
26 plane.

### 27 **Analysis of shape and centroid size**

1 A Generalized Least-squares Procrustes fit was then used to extract centroid sizes (CS) and shapes (represented  
2 by procrustes coordinates) from the original forms by removing variation due to relative size, position, and  
3 orientation (29-33)

4 . The raw landmark data were used to calculate CS and quantify the size of a specimen (34). Mathematically,  
5 centroid size corresponds of the squares of each of the distances between a landmark and the centroid of the  
6 landmark configuration.

7 The cranium was considered as a structure of object symmetry type (35) according to the definition of Mardia et  
8 al. (36). In our analysis, only the symmetric component of variation was used for study of shape.

9 A PCA was applied on the Procrustes coordinate to analyse the variation in shape and visualise the  
10 morphological changes that were the most characteristic of development in our sample.

11 Statistical significance was estimated using permutation tests with 10,000 iterations against the null hypothesis  
12 of independence between shape asymmetry and size asymmetry.

13

#### 14 **Study of allometry**

15 As morphological traits could be influenced by size following an allomeric relation, a multivariate regression of  
16 shape on centroid size was performed (14). Indeed, this analysis can characterise allometry by determining  
17 whether there is a statistical association between shape and size. Thus, it allowed to characterise morphological  
18 changes according to size and also to determine the growth trajectories (ontogenetic allometry). When  
19 examining early stages size changes are very important. Therefore, in order to obtain a better performance  
20 Klingenberg recommend to use the logarithm of centroid size (14). Statistical significance was estimated using  
21 permutation tests with 10,000 iterations against the null hypothesis of independence between shape and size  
22 (37).

23 Shape changes (dependent variable) were also analysed according to age, sex, head circumference, crown-heel  
24 length and weight (independent variables) using multivariate regression (38).

25 Statistical and geomorphometric analysis of the data was carried out using R software (39), the Geomorph  
26 software package version 3.1.3 (40), and MorphoJ® 1.06d software (29).

27

#### 28 **Results**



## 1 **Reliability of measurements**

2 The Procrustes coordinates yielded by landmark positioning showed excellent concordance (Lin's CCC >0.95).

3 According to Bland and Altman, the difference between the two measurements was normally distributed: 95% of  
4 the values of measurement differences were within the limits of agreement. The difference between two  
5 measurements was uniformly distributed. Bias (mean difference) was low [-0,0014;0,0014] and 0 was contained  
6 within the confidence interval of bias.

7 The matrix correlation test was statistically significant ( $p < 0.0001$ ,  $R^2 = 0.88$ ), rejecting the null hypothesis. The  
8 matrices of covariance were not statistically dissimilar that means that the two sessions of posing landmarks are  
9 not statistically different. Global measurement error of shape was 11.5%.

10

## 11 **Principal results**

### 12 **Study of shape**

13 PCA identified 27 principal components (PC). The distribution of PC is quite structured. About 60% of the total  
14 variance is explained by the first 4 PC (Fig. 3). The first PC (PC1) was largely preponderant, and it alone  
15 explained 25% of total variance. The next 3 PCs showed similar values, accounting together for 35.6% of  
16 variance (12.4%, 12.2% and 11% respectively). PC1 dominated in terms of explained variance, suggesting  
17 reliable statistical stability. The PC is an axis of largest variation that sometimes can be linked to a biological  
18 signal.

19 The principal shape changes of the cranial base were revealed (Fig. 4). In superior projection, PC1 was  
20 associated with lengthening of the posterior level in relation to the anterior level of the cranial base, due to  
21 enlargement of the posterior part of the temporal bone and reduction of its anterior part, together with widening  
22 of the interpetrous angle. In lateral projection, PC1 showed flexion of the cranial base, secondary to slight  
23 closure of the sphenoid angle, projection of the basion downwards and forwards, together with lengthening of  
24 the posterior level. In superior projection, PC2 was associated with anteroposterior lengthening of the temporal  
25 bone and of the posterior level. Lateral projection revealed superior and posterior reorientation of the petrous  
26 pyramids and superior and anterior reorientation of the small wings of the sphenoid, resulting in increased depth  
27 of the various levels of the cranial base.

1 Multivariate regression showed a statistically significant correlation between shape and the age of the infants ( $p$   
2 = 0.001,  $R^2 = 74$ ). According to these results, age explained 7.4% of variation of the shape of the cranial base.  
3 There was no statistically significant correlation between shape and sex ( $p = 0.50$ ), weight ( $p = 0.06$ ), head  
4 circumference ( $p = 0.60$ ) and size ( $p = 0.48$ ).

5

## 6 **Centroid size**

7 The centroid size of the cranial base increased during the first two postnatal years (Fig. 5).

8

## 9 **Study of allometry**

10 Multivariate regression of shape on centroid size exhibited significant allometry ( $p = 0.001$ ,  $R^2 = 71$ ). As the  
11 range of sizes was large, log-transformed centroid size was used as an independent variable in multivariate  
12 regression (14) and revealed allometry ( $p = 0.001$ ,  $R^2 = 31$ ) which explained 3.1% of total shape variation.

13 The geomorph package in R with PredLine (41).

14 was used to perform shape regression on centroid size. This generated a graph describing the relationship  
15 between centroid size and shape as derived from landmark data. It yielded a regression line that reflected  
16 negative ontogenetic allometry ( $b < 1$ ). Negative allometry corresponds to a change in shape that is less than  
17 could be expected in view of the increase in the size variable.

18

## 19 **Growth**

20 95.2% of total variation was explained by the first two principal components (85.5% and 9.7%, respectively).

21 This variance was explained by size (see section on Study of shape, above) and demonstrated the effect of  
22 growth (Fig. 6).

23

## 24 **Discussion**

25 To our knowledge, this study is the first to adopt a global approach to ontogeny of the cranial base in a  
26 population of infants with complete data, based on three-dimensional study of cranial base shape.

## 27 **Study population and acquisition techniques**

1 Our series was large compared with other studies, the population was of heterogeneous distribution but coherent  
2 with epidemiological data on SID (42). In France, sudden infant deaths are managed in a reference centre  
3 (specialised paediatric hospital department) following a protocol based on the recommendations of the High  
4 Authority for Health (42). In accordance with this protocol, medical investigations including imaging studies and  
5 full autopsy can be carried out as rapidly as possible in order to identify a cause of death. There was a clear  
6 majority of infants aged under 10 months and an unbalanced sex ratio, males being more numerous. Certain age  
7 groups were thus under-represented, limiting the scope of our conclusions for certain parameters.

8 The strength of our approach, however, lies in its three-dimensional geometric morphometric analysis of the  
9 cranial base, whereas the majority of studies are two-dimensional (2,16-18).

10 Infants were rigorously selected (only 54% of the original sample were finally included) in order to exclude any  
11 condition that could affect the biometric parameters chosen. The CT scan thicknesses gave good three-  
12 dimensional reconstruction of the cranial base.

13 Landmark positioning for geometric morphometric study was reproducible in spite of the presence of numerous  
14 type II and III Bookstein landmarks (22). Type II and III landmarks made it possible to include areas that  
15 otherwise would not have been sampled. This yields valuable information for studies of growth, clinical  
16 evaluation and volume measurements (43). As far as we are aware, no publication has yet established an  
17 acceptability threshold for general measurement error, and we consider that this should be a matter for the  
18 researcher's subjective judgment.

19 The acquisition of our imaging data (*post mortem*) was not however optimal, as section thickness was greater  
20 than that of other geometric morphometric studies that used high-resolution imaging techniques (17). Our  
21 medical images had been obtained with the aim of diagnosis rather than for research.

## 22 **Geometric approach**

23 Analysis of PC1 revealed three modes of variation (anteroposterior elongation of the cranial base, flexion of the  
24 cranial base and increase the opening of the posterior fossa). The latter two may be related to relative growth of  
25 the cerebellum. Similar observations have been made in the foetus and newborn (2, 15, 44). Growth was  
26 constant during the first two years of life. The increase in anteroposterior length of the cranial base has  
27 previously been described (45).

1 The other principal components of shape should be interpreted with caution, as only landmark 1 showed notable  
2 explained variance, suggesting reliable statistical reliability (46). It could thus reflect true biological correlation  
3 between the elements involved (47).

4 Our study emphasises that shape changes are greater in the infant than in the adult (3, 48-49), found that growth  
5 of the brain and skull slowed down after the age of two and a half years. The fact that infants are in a growth  
6 phase (unlike adults, in whom only intra- or inter-population variability plays a role) is of course an explanatory  
7 factor of the difference observed.

8 Multivariate analysis showed a statistically significant correlation between shape changes and age, as found by  
9 other authors (45). This correlation was only 0.074 so while significant it is not by any stretch a strong  
10 correlation. It may be worth commenting upon this comparing the strength of correlations in the literature.

11 The impact of sexual dimorphism on the ontogeny of the skull-brain complex is debated in the literature. The  
12 size and composition of our sample does not allow to discuss sexual dimorphism and specifically if there are  
13 differences in growth and development between females and males. Gkantidis and Halazonetis (50), observed no  
14 sexual dimorphism that could explain the shape but these findings conflicted with observations of the  
15 neurocranium by Bulygina et al. (51).

16 We found a statistically significant association between centroid size and shape based on a methodology that is  
17 widely used in the literature (14, 30, 52). Multivariate regression of shape on centroid size guaranteed optimal  
18 estimation of allometry (14,53). The allometric trajectory in immature subjects has principally been studied in  
19 the foetus (15-19). Our study has demonstrated that the allometric trajectory was linear in the morphospace  
20 during the first years of postnatal life. Allometry was of negative type, corresponding to an expected change of  
21 shape that was smaller than the relative increase in the size variable. After the foetal period, the skull and head  
22 segment developed more slowly than the rest of the body (54).

### 23 **Conclusion**

24 As far as we are aware, this is the first study to take an overall approach to ontogeny of the cranial base in a  
25 population of infants with complete data. Better knowledge of overall growth and normal development increases  
26 our understanding of the various disorders of the brain and the cranial base and of their pathophysiology, leading  
27 to improved surgical treatment.

28 Based on original analysis, we demonstrated that growth of the cranial base principally occurs by anteroposterior  
29 lengthening. The height, width and length of the posterior fossa increase. The relative position of the basion is

1 displaced inferiorly and anteriorly due to flexion of the sphenoid angle. Shape changes of the cranial base are  
2 mainly observed at the posterior level and are may be related to development of the cerebellum.

3

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6 improve the quality of the manuscript. We declare no conflict of interest.

#### 7 **Author contributions**

8 C. Delteil: conception and design, image selection and treatment, data analysis and interpretation, manuscript  
9 writing.

10 C. Mopin: data analysis and interpretation, manuscript revision and approval of the article.

11 A. Carballeira Alvarez: CT scan data.

12 P. Adalian and M.D. Piercecchi: conception and design, data interpretation, manuscript revision and approval of  
13 the article.

14

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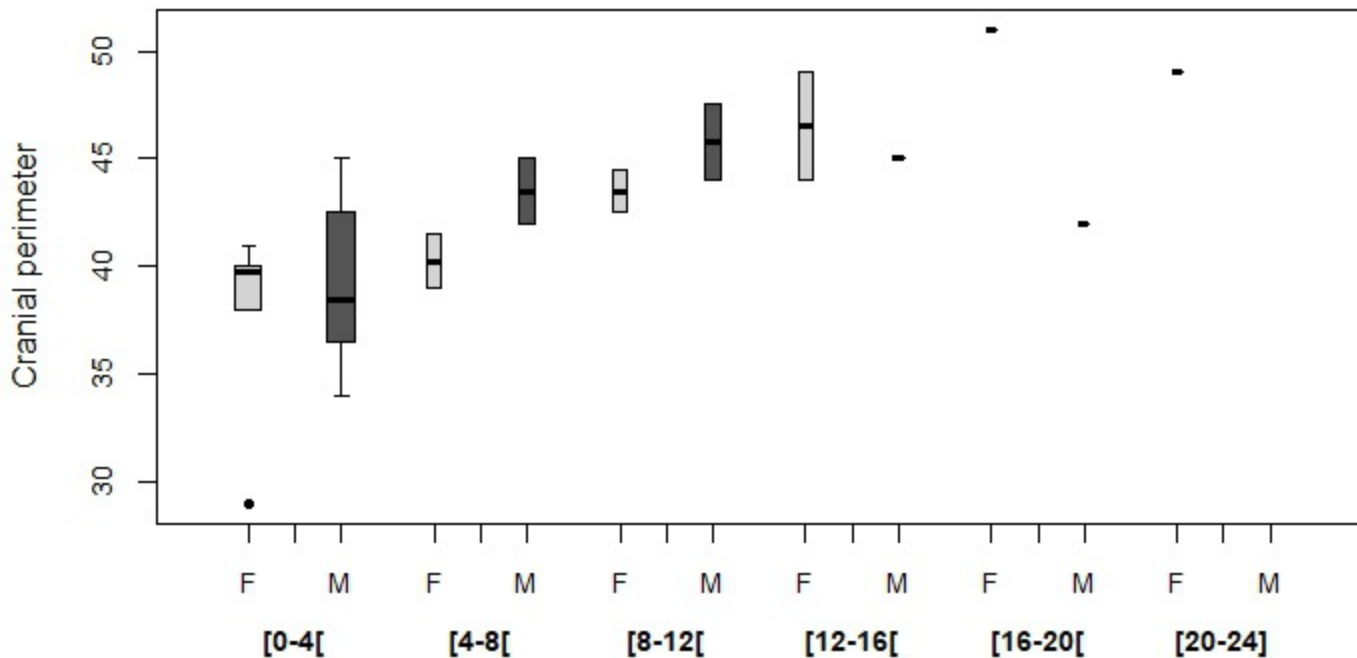
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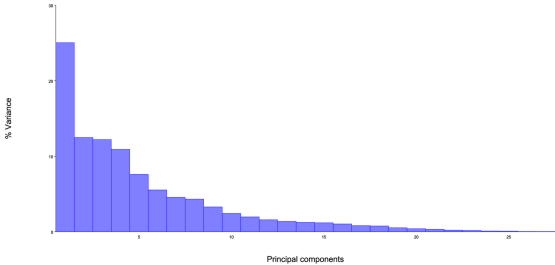
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- 26
- 27 Tables legends

- 1 Table 1 Definition of the landmarks used in our study and their classification according to Bookstein (1991).
- 2 Figure legends
- 3 Fig. 1 Cranial base with its 19 landmarks (superior view)
- 4 Fig. 2 Boxplot of the head perimeter according to sex and age group.
- 5 Fig. 3 Histogram of eigenvalues: variance according to principal components.
- 6 Fig. 4 Wireframe images show shape changes (superior and lateral views) between the youngest infant (0
- 7 months, soft grey lines) and the oldest infant (24 months, dark grey lines).
- 8 Fig. 5 Mean centroid sizes by age group.
- 9 Fig. 6 The growth normogram, characterised by raw superimpositions of landmarks, was carried out using
- 10 Autocad 2016 software.
- 11

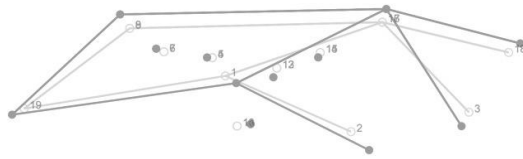
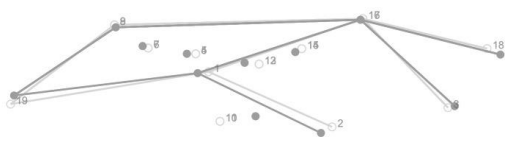
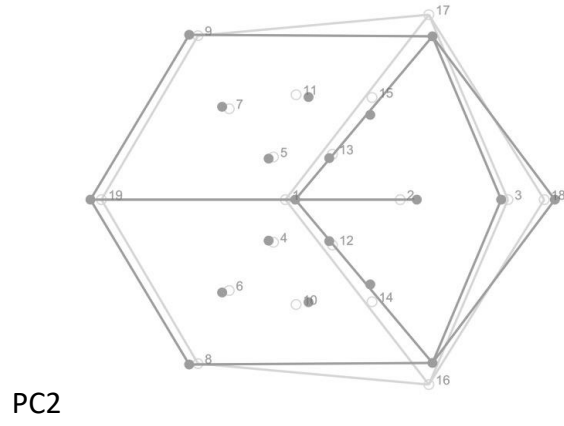
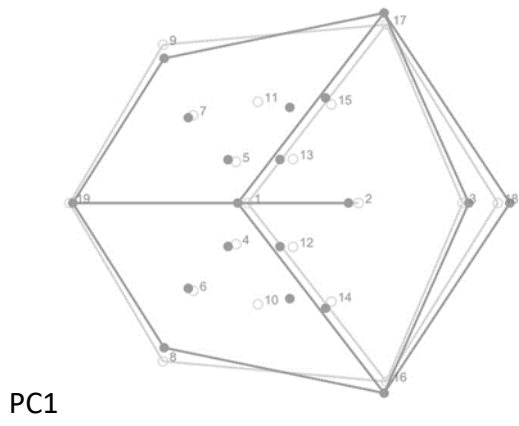
# Boxplot

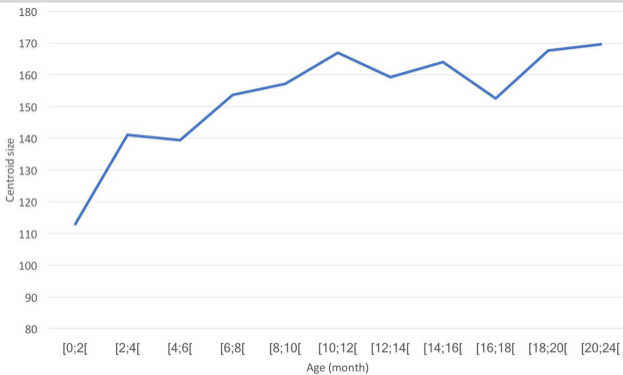


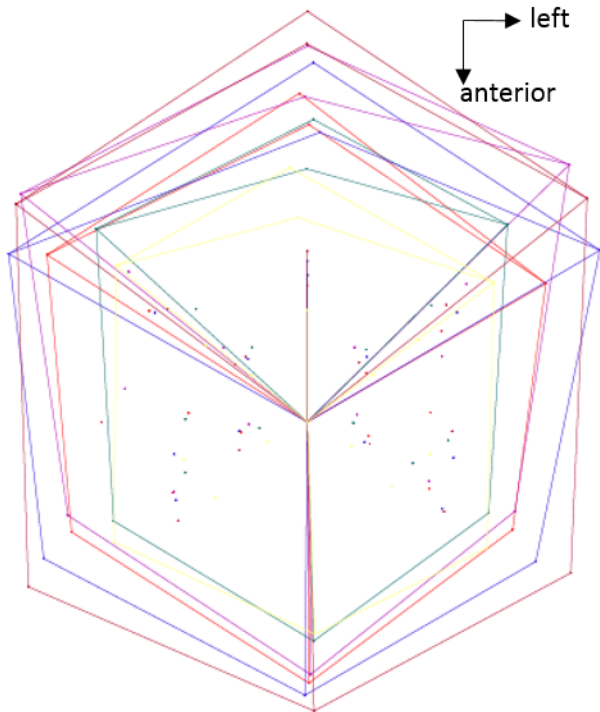




Anterior  
Left







color	Age (month)
yellow	0,43
green	1,03
red	4,96
blue	9
violet	16,76
maroon	18



**Table 1** Definition of the landmarks used in our study and their classification according to Bookstein.

Landmark number	Landmark type	Lateral/Midline landmark	Name
1	II	Mid	Hypophyseal fossa in sella turcica
2	II	Mid	Basion : anterior foramen magnum
3	II	Mid	Opisthion : posterior foramen magnum
4	I	Lat	Left anterior clinoid process
5	I	Lat	Right anterior clinoid process
6	III	Lat	Midpoint of left lesser sphenoid wing
7	III	Lat	Midpoint of right lesser sphenoid wing
8	II	Lat	Lateral border of left small sphenoid wing
9	II	Lat	Lateral border of right small sphenoid wing
10	III	Lat	Deepest point of left middle fossa
11	III	Lat	Deepest point of right middle fossa
12	II	Lat	Most internal point, upper border of left petrous part
13	II	Lat	Most internal point, upper border of right petrous part
14	III	Lat	Midpoint of left petrous part (between the most internal and the apex of petrous part points)
15	III	Lat	Midpoint of right petrous part (between the most internal and the apex of petrous part points)
16	II	Lat	Apex of left petrous part
17	II	Lat	Apex of right petrous part
18	III	Mid	Internal occipital crest
19	II	Mid	Foramen caecum