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Integration of Cranial Base and Face in Growing Subject

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Abstract: Background: many papers investigate the role of the cranial base in facial development, but the results are not in agreement. This can be due to a difference between the central and lateral parts of the cranial base. The aim of the present study is to evaluate the relationship between the central and the lateral cranial base and the facial skeleton in pre-pubertal peak subjects and at the end of growth. Material/Methods: a total sample of 52 latero-lateral cranial teleradiographs were analyzed. To test the correlation between structures, the "Partial Least Square" analysis was performed. Geometric morphometric analysis were applied and partial least square analysis was used to test correlation. Integration was studied removing the effect of allometry. Results: facial skeleton has no significant relation with central cranial base. Facial skeleton has significant relationships with the lateral portion of the cranial base. This relationship is higher in the post-peak phase of growth. Conclusion: the Integration between facial structures and cranial base is significant. The Spatial orientation and shape of the facial structures are both influenced by cranial base. This is mainly due to the lateral portion of cranial base.

Keywords: geometric morphometric analysis; integration; cranial base; facial skeleton; craniofacial orthopedic

1. Introduction

The cranial base has a fundamental role in craniofacial growth. Many authors have investigated the relationship between the shape and the size of the cranial base and those of the face [1–7]. However, not all studies have identified this relationship [1–3,7,8]. In 2006, Bastir and Rosas [9] observed that these discordant results in the literature could be due to a difference between the growth in the central part and the lateral part of the cranial base. The first is linked to a sutural growth, determined early in the child; the second is linked to the sutural and appositional growth. The two authors conclude that the cranial base is composed of two distinct modules: a "lateral cranial base" module and a "central cranial base" module. Three-dimensional images are useful tools to analyze skull shape and dimension in physiological and pathological conditions [10,11]. In 2013, Neaux [12] and colleagues used three-dimensional images to investigate the relationship between the lateral and central cranial base with the face, both in humans and in chimpanzees. Their results confirmed a correlation of the lateral cranial base with the facial skeleton.

The work of Bastir and Rosas in 2006 was resumed by Gkantidis and Halazonetis in 2011 [13], in a cross-sectional study of two groups. The authors identify a significant relationship between the central portion of the cranial base and the face in the subjects before the pubertal peak; this relationship is no longer identified in the subjects after the pubertal peak. The latter subjects present a statistically significant relationship between the lateral portion of the cranial base and the facial skeleton.

Other authors [14] divide the cranial base into 3 different modules: anterior cranial fossa, the middle cranial fossa, and the posterior cranial fossa. Yet, the middle cranial fossa was divided into the central and lateral portion. The relationship between the anterior cranial base and the fronto-naso-maxillary complex was confirmed by the work of McCarthy and Lieberman [15]. Their work proposed that a rotation of the fronto-naso-maxillary complex aimed at correctly guiding the visual axis plane, as opposed to the posterior-maxilla (PM). The relationship between the middle and posterior cranial fossa and mandibular branch has been identified by several authors [1,16].

New types of analysis are used in all fields of dental and craniofacial science [17–20]. The analysis used in most of this paper is a geometric morphometric type of analysis. This type of analysis has two major characteristics: it allows one to analyze shape and size separately, it gives a visual form of the results which is easy to interpret. In particular, the analysis used to investigate integration and modularity are described by Klingenberg [21]. These analyses are principal component analysis, partial least square analysis, vector analysis. Although most of them can be found in some mentioned paper, some of them can't (Ex: partial least square analysis with single superimposition). None of the previous authors systematically used all the analyses to investigate integration and modularity between cranial base and facial features in a longitudinal sample, as suggested by Klingenberg.

The aim of the present study is to evaluate the relationship between the central and the lateral cranial base and the facial skeleton longitudinally (using historical archives of untreated subjects).

2. Materials and Methods

In total, samples of 52 latero-lateral cranial teleradiographs from the American Association of Orthodontists Foundation (AAOF, http://www.aaoflegacycollection.org) website were analyzed. In particular, the authors used the subjects belonging to the "Denver studies group" and the "Michigan" study.

The analysis of each subject was performed two times both before and after the growth peak.

Sample inclusion criteria:

- Aged from 7 to 18 (assessed by Gkantidis and Halazonetis Study criteria and cervical vertebrae maturation [4,13], we used these criteria to get comparable results);
- Male sex;
- No diseases, no craniofacial dysmorphism;

Ten female subjects were also included to test gender differences;

Twenty-seven landmarks (as described by Gkantidis and Halazonetis [13]) were selected on each teleradiograph using the TPSdigt software. Through the TPSutil software, the data were prepared to be analyzed using the MorphoJ software [22]. The data were divided into two different "projects" for the analysis of pre-peak and post-peak pubertal subjects. For each subject, 17 landmarks to describe the facial skeleton and 10 landmarks to describe the entire cranial base (6 landmarks to describe only the lateral cranial base and 4 landmarks to describe only the medial cranial base) were analyzed (Table 1).

Table 1. Landmarks.

Structures	Landmarks
facial structures	Glabella
	Nasion
	Rhinion
	Anterior nasal spine
	A Point
	Supradentale
	Posterior maxillary alveolar (most posterior cementoenamel junction not including 3rd molars)
	Posterior nasal spine
	Infradentale
	B Point
	Pogonion
	Menton
	Inferior mandibular border
	Antegonial notch
	Gonion
	Ramus flexion
	Mandibular Condyle (most superior point)
midline cranial base structures	Anterior end of Cribriform plate
	Posterior end of Cribriform plate
	Posterior end of Sphenoid plane
	Base of Dorsum Sellae
	Basion
lateral cranial base structures	Anterior orbital roof (intersection between Orbital roof and inner frontal table)
	Posterior orbital roof (intersection between Lesser and greater sphenoid wing)
	Spheno-parietal junction (center)
	Anterior greater sphenoid wing
	Inferior on middle cranial fossa.
	Petroso-parietal junction (center)

Twenty subjects were analyzed twice by G.O. and R.Z. Squared Dahlberg's error was not significant. Procrustes superimposition was applied to the samples of each group. This kind of superimposition rotates, translates and scales all the subjects of the sample. This allows analyzing the difference remained after the superimposition and to separate shape differences from size differences.

2.1. *Analysis of Outliers and Intragroup Variability*

The analysis of the outliers was carried out, in order to identify and correct errors in the digitization of the landmarks and to identify samples that differ significantly from the average form.

Principal component analysis (PCA) was used to study the variability present in the examined sample. This analysis leads one to find the main directions of variability inside the sample and to visualize this variability on landmarks relative position.

2.2. *Allometry and Dimension Correction*

In order to study the influence of allometry (the study of the relation between size and shape) in subsequent analyses, we used a multivariate regression of the Procrustes coordinates on the logarithm of the "centroid size" [23]. The "residues" identified between the "shape coordinates" and the logarithm of the "centroid size" were used in the subsequent analyses.

2.3. Sexual Dimorphism

To analyze the influence of sex in the skeletal morphology, we used a regression between form and sex in the subjects, before the pubertal peak and after the pubertal peak. The significance of this regression was investigated using the Goodall F test and the permutation test for 10,000 permutations, with an alpha error set at 0.05.

2.4. Integration between the Cranial Base and the Facial Skeleton

Partial least square analysis (PLS) was used to analyze the integration patterns between the cranial base and the facial skeleton. Two methods for the PLS analysis are described in the literature [21]. The analysis finds the direction that changes simultaneously in two groups. In morphological analysis, two groups are often two sets of landmarks. If they are both part of a larger set of landmarks, they can be first divided into two "blocks", and then each block is superimposed separately, and then the PLS is performed. A second way is to superimpose the lager set of landmarks, separate it into two blocks and perform the PLS analysis. The second procedure can not only visualize common change between the shape of the two blocks, but also the "spatial rotation" of the two blocks due to the changes.

Both of the described PLS analyses were performed on the sample. The overall correlation values were summarised by the Escoufier (RV) coefficient. To test the significance of the results of these analyses, a "permutation test" was carried out with 10,000 permutations and alpha error set at 0.05, as described by Rohlf and Corti [24].

2.5. Angular Comparison between the Results of the PCA and PLS

The relationship between PCA and PLS was studied by analyzing the angle between the vectors resulting from the two analyses. Through the "random vector permutations" method, the significance of these angles was tested with 10,000 permutations and alpha error set at 0.05. This analysis tries to understand if the direction of variability found inside one sample is the same one that is mostly related to changes in the second sample (the two sample are the two blocks of the PLS analysis) and if this relation is due to chance or is statistically significant.

3. Results

The analysis of the outliers did not identify any errors in the digitization of the landmarks, or subjects who should be eliminated from the sample. The PCA was used to describe intragroup variability. Figure 1 shows the main components 1 and 2, which were obtained for the pre-peak and post-peak subjects.

The first principal component (PC1) describes a reduction of the divergence in the facial skeleton (in particular the anterior vertical dimension) and a reduction in the depth of the average cranial fossa, with a clockwise rotation of the entire cranial base around the average cranial fossa. The second principal component (PC2) describes sagittal changes for both the facial skeleton and the cranial base. In the group before the pubertal peak, the submandibular incision is highly variable.

3.1. Sexual Dimorphism

The effect of sex was statistically significant, with a p-value of less than 0.01 for both groups. Subsequent analyses were conducted exclusively on males, to avoid errors due to sexual dimorphism.

3.2. Integration between the Cranial Base and the Facial Skeleton

The PLS analysis, with two superimpositions, was conducted between the central cranial base and the facial skeleton. Then, the analysis was conducted between the lateral cranial base and the facial skeleton in subjects before pubertal peak and again after pubertal peak (Figure 2).

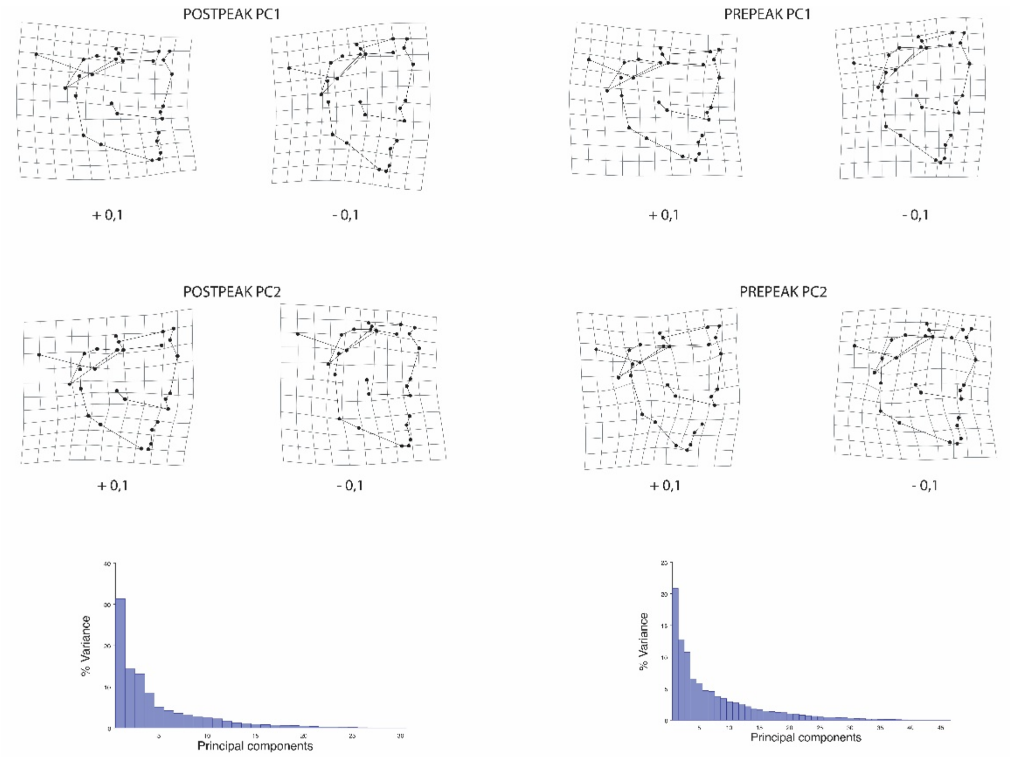

Figure 1. Variation in the position of the landmarks, coinciding with a variation of 0.1 of the main components 1 and 2 obtained by a PCA on the whole set of landmarks and the variance explained by the components themselves.

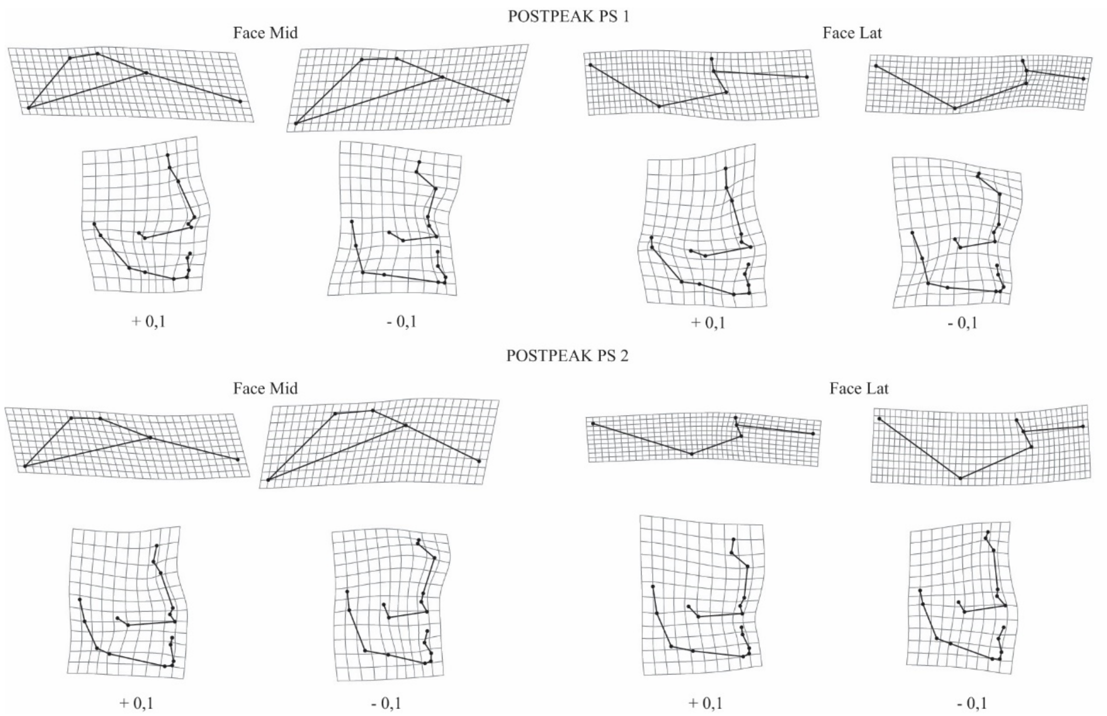

Figure 2. The figure shows Principal axes (PS) 1 and 2 for all groups.

From the permutation test with 10,000 repetitions (Table 2), it appears that the only statistically significant relationship is between the lateral cranial base and the facial skeleton in post-peak subjects

(p-value: <0.01). The effect of allometry seems to generally reduce the strength of the correlation but does not otherwise modify the significance.

PLS analysis with one superimposition was conducted between the groups.

All correlations are statistically significant from the permutation test with 10,000 repetitions (Table 3).

Table 2. Values of the overall correlation (RV) for the Partial Least Square (PLS) analyses and the results of the permutation test (p-value).

Maturity Stage	Structure Compared to the Facial Skeleton	RV (p-Value)	Allometric Analysis—RV (p-Value)
Pre-peak	Central cranial base	0.12 (0.4)	0.11 (0.5)
	Lateral cranial base	0.14 (0.34)	0.14 (0.34)
Post-peak	Central cranial base	0.13 (0.25)	0.12 (0.3)
	Lateral cranial base	0.20 (< 0.01)	0.19 (0.01)

Table 3. Values of the overall correlation (RV) for the PLS analyses, with a single overlap of landmarks and the results of the permutation test (p-value).

Maturity Stage	Structure Compared to the Facial Skeleton	RV (p-Value)	Allometric Analysis—RV (p-Value)
Pre-peak	Central cranial base	0.42 (<0.01)	0.42 (<0.01)
	Lateral cranial base	0.41 (<0.01)	0.41 (<0.01)
Post-peak	Central cranial base	0.45 (<0.01)	0.43 (<0.01)
	Lateral cranial base	0.50 (<0.01)	0.47 (<0.01)

The spatial orientation of the three structures therefore seems to be closely connected. As with the previous analysis, allometry reduces the degree of correlation (especially in the post-peak), but does not change the statistical significance of the analyses (Figure 3).

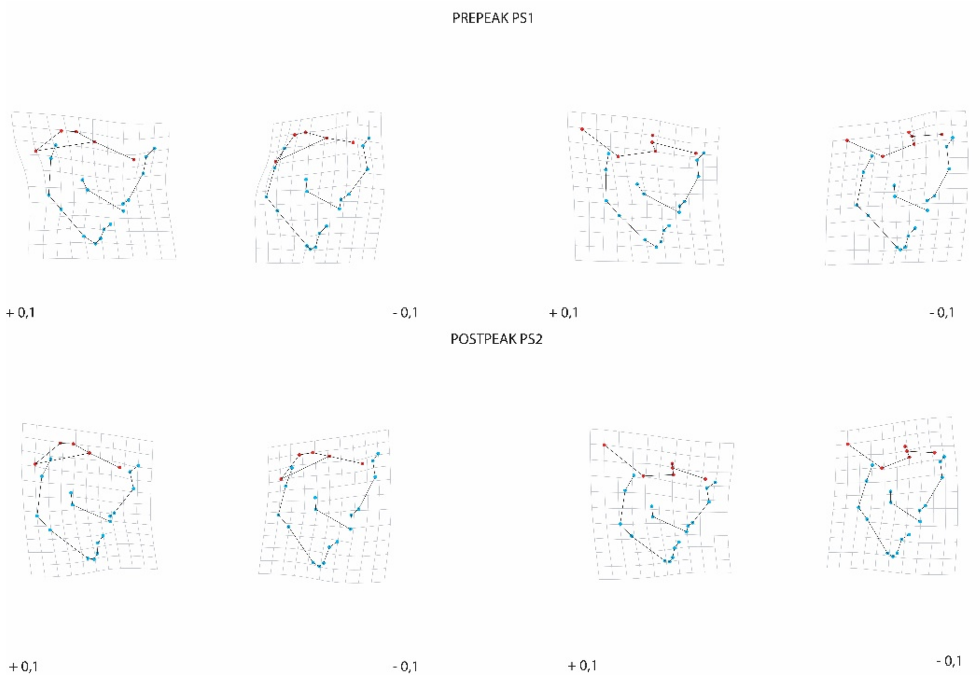

Figure 3. Deformation grids for an increase or a reduction of 0.1 in the single axis 1 for the different PLS analysis with a single superimposition. The structures of the cranial base are indicated in red, those of the facial skeleton in blue.

3.3. Angular Comparison between PCA and PLS

The 5 statistically significant PLS analyses were compared to the respective PCAs (Table 4). The results of the comparisons between PC1 and PLS1 are shown in Table 3. The probability of accidentally identifying lower angles than those shown in the table by analyzing the sample through a permutation test at 10,000 permutations has always been lower than 5%.

Table 4. Shows angular values between PC1 and PLS1 in different maturity stage, type of PLS and bone structures.

Type of PLS	Maturity Stage	Structure Compared to the Facial Skeleton	PC1-PLS1 Angular Value
Two superimposition	Post-peak	Lateral cranial base	28°
One superimposition	Pre-peak	Central cranial base	25°
		Lateral cranial base	24°
	Post-peak	Central cranial base	40°
		Lateral cranial base	13°

4. Discussion

The aim of the study is to investigate the relationship between the cranial base and the facial skeleton. The hypothesis that the facial skeleton is more closely linked to the lateral portion of the cranial base rather than the central portion has been proposed in the literature, but there are no studies that analyze the same subjects before and after the pubertal peak or using morphometric methods of analysis. The first type of analysis performed on the sample was the principal component analysis to study intragroup variability. The results of this study indicate that principal component 1 describes variations in the vertical dimension, and the principle component 2 describes variations in the sagittal dimension. This is true both before and after pubertal peak. These results are in agreement with those of Wellens and colleagues [25]. The analysis shows that an important area of variability pre-peak is in the submandibular notch, and the same is not found in the post-peak subjects. The role of this notch for development and mandibular growth is already reported in studies that used implants for the study of growth and mandibular rotation [26].

4.1. Sexual Dimorphism

The importance of sexual dimorphism in growth studies has already been stressed by Wellens and colleagues [27]. In the study of Gkantidis and Halazonetis [13] concerning the relationship between the cranial base and the facial skeleton, the authors report that in the group before pubertal peak there is no difference between the shape of the skeletal structures between males and females; this difference is present after pubertal peak. The same difference was identified in our study, both in the pre-peak group and in the post-peak group. Like the previous authors, the results underline the importance of gender differences; however, it is not necessary for sexual dimorphism to imply different patterns of correlation between the skeletal structures.

4.2. Integration between the Cranial Base and the Facial Skeleton PLS with Two Superimpositions

The first type of analysis undertaken to study the degree of integration between the three skeletal structures (lateral cranial base, central cranial base and facial skeleton) is the partial least square analysis of two blocks.

From the analysis of the deformation grids obtained from the sample of the pre-peak subjects analyzed in this study, there was no statistically significant relation between the structures.

In the post-peak subjects, the integration between central cranial base and facial skeleton was not statistically significant.

The analysis of the deformation grids of the lateral cranial base with respect to the facial skeleton was statistically significant. The analysis shows that the reduction of the anterior part of the lateral cranial fossa is associated with a reduction of the superior maxillary dimension, even if a tendency occurs to the forward displacement of the points under the influence of the alveolar bone and of the dental elements. According to the authors, this could be due to a compensation for the reduction of the maxillary bone base that occurs with sufficient systematic nature to be significant in the morphometry of the facial skeleton. The middle part of the lateral cranial fossa rotates in a clockwise direction, with the petromastoid portion moving up and the sphenoid wing down and in the back. The depth of the central lateral cranial fossa is significantly increased, due to a lowering of the central point to the fossa. This is associated with a lowering of the condyle, with a reduction of the posterior facial height and increase of the anterior facial height: this results in biprotrusion of alveolar components and an opening of the anterior bite.

Comparing these results with those present in the literature: both the statistical results and the deformation grids are found to be similar to those obtained by Bastir and Rosas [9]. The authors report that there is a difference present in the deformation grids that describes the Pls between the lateral cranial base and the facial skeleton in adults. This difference is associated with a narrower and deeper middle cranial fossa, a biprotrusion of the alveolar components with an opening of the anterior bite, simultaneously with a reduction of the anterior facial height. This reduction is not present in our results. Nevertheless, the relationship between the middle cranial fossa, the condylar position and the mandibular branch is confirmed by the results obtained, as is the relationship between the anterior cranial fossa and the nasomaxillary complex. Similar differences are also reported in the work of Baccetti and colleagues [28]. Compared to the work of Gkantidis and Halazonetis [13], the first difference is found in the pre-peak group, and our results do not identify a statistically significant correlation between the central cranial base and the facial skeleton in the pre-peak group, with differences also present in the deformation grids. To explore deeper and further explain the differences identified, it will be necessary to conduct studies that divide the subjects on the basis of skeletal maturity indexes that allow a division within the subjects before the pubertal peak. According to these authors, however, in the post-peak group, there is a statistically significant relationship between the lateral cranial base and the facial skeleton. Gkantidis and Halazonetis emphasized how this "inversion" of integration between the lateral and central cranial base may suggest an "evolution" over time of the modules that make up the craniofacial skeleton; this hypothesis is confirmed by the data reported in this study.

Comparing our results with those obtained by the two authors, similar results have been obtained for the analysis of allometry. This generally reduces the strength of the relationship between the various structures, but does not modify the direction of the vectors in any way.

The relationship observed between the facial skeleton and the anterior cranial fossa both in its central and lateral component, and the relationship between maxillary and ethmoidal plane, confirm the results published by McCarty [15]. The relationship between the petromastoid portion and the gonial angle confirms the results obtained by Bastir [16].

4.3. PLS with one Superimposition

The analyses previously shown permit us to compare the shapes of two different skeletal structures, but they lose the spatial relationships that one structure has when compared to the other. If the objective is to analyze the influence that the cranial base structures have on the final shape of the facial skeleton, then preserving the spatial relationship between the two structures is essential. The second type of PLS analysis allows this relationship to be preserved [21].

From the analysis of the deformation grids of the pre-peak subjects, a large "bending" is immediately noticed in the area of the mandibular branch when we compare the central cranial base and the facial skeleton. A retro positioning of the posterior cribriform point corresponds to a rearward lengthening of the mandibular branch, and to a retro positioning and raising of the basion, which reduces and rotates the sphenoid occipital clivus clockwise. All of this is associated with an opening of the gonial angle which generates, as mentioned above, a large deformation in the grid. Anteriorly, a forward displacement of the central anterior cranial fossa corresponds to an advancement of the nose-maxillary complex; the rotation of the palatal plane follows that of the ethmoidal plane. Similar results were obtained in the post-peak group.

The analysis of the lateral cranial base in the post-peak subjects reveals that: the forward and lower displacement of the landmarks which identify the middle cranial fossa leads to a mandibular postero-rotation with pogonion shifting backwards and downwards. In the same way the nose-maxillary complex moves downwards and forwards.

The results obtained for the three skeletal structures are all statistically significant, both in the pre-peak and in the post-peak subjects.

These results are difficult to compare with the results reported in the literature and previously discussed, due to the different type of analysis employed. The preservation of spatial relationships between the structures of the cranial base and the facial skeleton is better suited to verify the hypotheses espoused by Enlow on the relationships between these components of the craniofacial skeleton. The results we have identified are consistent with the author's theory, especially with regard to the variation of the middle cranial fossa and the tendency towards vertical growth.

4.4. Angular Comparison between PLS and PCA

The examination of the angles between the vectors identified by the PCA and PLS analysis allows us to more correctly interpret the relationships identified. Although all the angles are statistically significant at a permutation test and therefore with vectors that do not differ between the PCA and PLS analysis, it is evident that, from the pre-peak stage to the post-peak stage, the direction of the vector that explains the greater intragroup variability deviates from the direction that correlates most with the central cranial base (reaching an angle of 40 degrees).

The opposite occurs for the lateral cranial base that during the phase of the pubertal peak continues to grow with the facial skeleton; the two angles diverge by just 13 degrees. We can summarize this fact by saying that the direction in which the facial skeleton varies most within the population is very similar to the direction in which the facial skeleton "covaries" with respect to the lateral cranial base. The results obtained through the study of the angles are in agreement with the theories of Bastir and Rosas on the different timing of growth between central and lateral cranial base and with the theory of Gkantidis and Halazonetis on a "dynamic modularity" of the craniofacial complex: during growth, the lateral cranial base module would increase its relationship with the facial skeleton.

The advantage offered by morphometric analyses in research is reduced in clinical applicability. In the literature there are methods for applying these analyses in the diagnostic evaluation of the individual patients [25]. By taking advantage of the results obtained through our analyses, it will be possible in the future to guide a clinical diagnosis in the evaluation of the correct relationships between the cranial base and the facial skeleton. The PLS analysis with an initial overlap allows us to understand how the facial skeleton is positioned and how it changes its shape in relation to the shape and position of the cranial base. This analysis can be applied to deepen and confirm the relationships between other parts of the facial skeleton and the cranium, such as the ethmoidal plane and the nasomaxillary complex.

5. Conclusions

From the analyses conducted in this study, it appears that the facial skeleton has significant relationships with the lateral portion of the cranial base.

The use of modern morphometric analyses to preserve the relationships between these structures suggests influences in the growth of the two structure.

The difference between pre-peak and post-peak pubertal subjects is highlighted in the growth modules and in the relationships between the modules.

Future research will have to investigate the relationships between the two structures in situations of non-physiological growth. Three-dimensional images will be a fundamental component of any future study.

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