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AAO Foundation Final Report Form
(a/o 1/3/2018)

In an attempt to make things a little easier for the reviewer who will read this report, please consider these two questions before this is sent for review:

- *Is this an example of your very best work, in that it provides sufficient explanation and justification, and is something otherwise worthy of publication? (We do publish the Final Report on our website, so this does need to be complete and polished.)*
- *Does this Final Report provide the level of detail, etc. that you would expect, if you were the reviewer?*

Please prepare a report that addresses the following:

Type of Award **Research Aid Award**

1. Name(s) of Principal Investigator(s) **Sara Adabi, Snehlata Oberoi**

Institution **UCSF**

Title of Project **Geometric Morphometric Analysis of the Influence of three dimensional Basicranial Shape on Facial Asymmetry**

Period of AAOF Support (e.g. 07-01-18 to 06-30-19): **07-01-17 to 12-31-18**

Amount of Funding **$5000**

Summary/Abstract

The basicranium is a key organizer of the skull. Importantly, the basicranium ossifies early during craniofacial development and is centrally located in the skull, thus it is thought to act as

a structural “foundation” that organizes later growth of the facial skeleton. The goal of this study is to test the hypothesis that basicranial asymmetry directly and additively influences asymmetry of the facial skeleton. To do this, we used cone beam computed tomography (CBCT) scans obtained from the Orthodontic Clinic at the University of California San Francisco and analyzed them with Geometric Morphometrics (GM), a set of methods for quantifying and comparing three--dimensional shape. This approach enables us to evaluate hypotheses about the nature of craniofacial patterning and variation in different planes, including deviations from midline symmetry. In this study, we first obtained homologous 3D coordinates from the basicranium and facial skeleton of adolescent and adult patients (N=105). Next, we used Principal Components Analysis (PCA) and Partial Least Squares (PLS) to test between alternative models of covariation between basicranial and facial asymmetries. Our results support the hypothesis that the basicranium plays a significant role in patterning facial asymmetry, and this relationship is consistent with an additive model. Given the earlier relative timing of ossification of the basicranium, this suggests that basicranial shape is important for establishing the direction of later facial growth, which is relevant for clinical considerations.

Detailed results and inferences:

1. If the work has been published please attach a pdf of manuscript OR
2. Describe in detail the results of your study. The intent is to share the knowledge you have generated with the AAOF and orthodontic community specifically and other who may benefit from your study. Table, Figures, Statistical Analysis and interpretation of results should be included.

1. <u>Specific Aims</u>

Hypotheses

We assume that the basicranium and face are structurally associated with one another, but there are developmentally distinct. There are many reasons to think that this assumption is valid as described above. Based on these ideas, we hypothesized that asymmetry in the basicranium contributes to asymmetry in the face. We test three alternative hypotheses:

1) H0: There is no relationship between basicranial shape and facial shape. In this case the relationship is predicted to be random.
2) H1: Basicranial shape has a direct influence on facial shape and asymmetry, and the effect is additive. In this case we would predict that asymmetries of the basicranium and face are coordinated and in the same direction.
3) H2: Basicranial shape has a direct influence on facial shape and asymmetry, however the effect is compensatory, such that basicranial asymmetries are balanced by facial asymmetries in the opposite direction. Therefore the effect is predicted to be coordinated but in opposite directions.

2. Studies and Results

Generalized Procrustes Superimposition was completed on a total of 173 landmarks for 105 subjects. One might assume, as things grow larger, they would be more likely to become asymmetric. As a preliminary step, we looked to see if there was an effect of allometry on our results. Allometry is the study of the relationship between the body size and shape and since this could affect patterns of morphological integration (Klingenberg, 2009). Thus we performed a multivariate regression of Procustese coordinates on the logarithm of centroid size (LCS) to identify significant size--shape relationship. After performing permutation test against the null hypothesis of independent and looking at regression tests, we did not find any evidence that there was any relationship between size and shape, hence the conclusion that size does not affect asymmetry because the P value was not significant (= 0.3215). This only explains a small 1% variation in the sample, lower than almost all the PC axes.

In order to explore the structure of variation of facial and basicranium asymmetry as one unit, we next performed a PCA on the asymmetric component of variation (Figure 3). The goal of this analysis was to understand whether and how asymmetric variation of the face and basicranium covary when you look at them as one set of data.

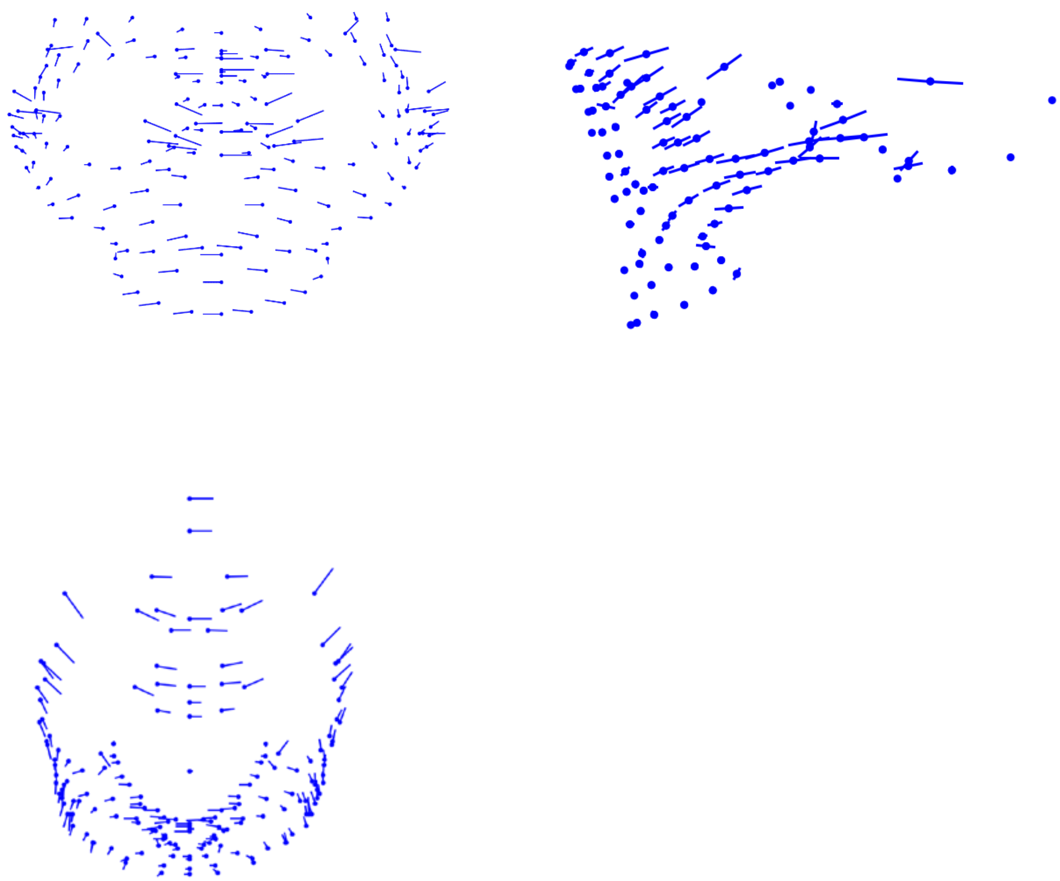


Figure 3. Principle component analysis 1 (PC1) for all landmarks and all subjects (a) Frontal view;; (b) Sagittal view;; (c) Superior--inferior view.

A total of 104 principal components were identified. Individual PCs can be visualized as vector deviations from the mean configuration of the total sample (Figure 4). In this case PC1 accounted for 9.97% and PC2 accounted for 7.26% of the variance observed in the subject population. The other principal components will not be discussed as the next largest PC, PC3 accounts for only 5.71%. Table 2 shows how variation is distributed amongst the first 10 principle components.

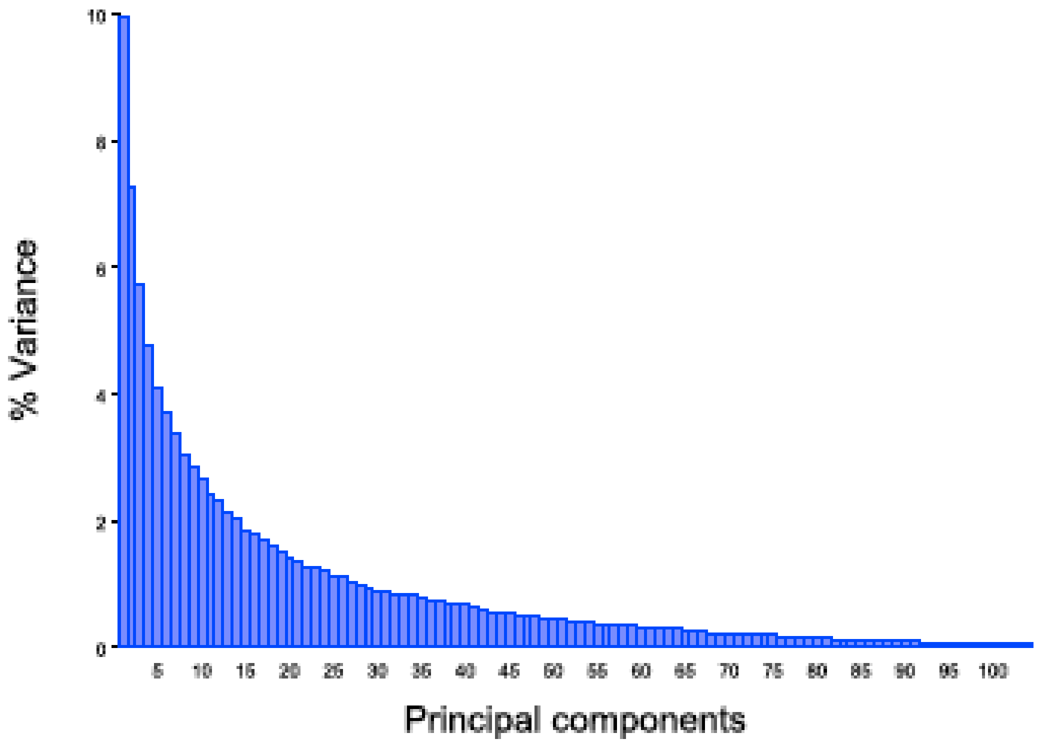


Figure 4. Screen plot of principal components and their associated percentage variance.

Table2. Percentage variance of first ten of 104 principal components of the asymmetric component of variation.

Principal Component	Eigenvalues	%Variance	Cumulative %
1	0.00004504	9.967	9.967
2	0.00003279	7.256	17.223
3	0.00002581	5.710	22.933
4	0.00002159	4.778	27.711
5	0.00001857	4.109	31.820
6	0.00001674	3.704	35.524
7	0.00001520	3.3363	38.888
8	0.00001375	3.043	41.930
9	0.00001283	2.840	44.770
10	0.00001201	2.658	47.428

Fluctuating asymmetry is a type of asymmetry that has a normal distribution of right and left differences around a mean of zero (Figure 5). The analysis of asymmetric components of basicranial and face variation from PC1--2 are consistent with fluctuating asymmetry and are suggestive of a strong relationship was found between the face and basicranium asymmetries. PC1 appears to reflect a general asymmetry across the basicranium and face, whereas PC2 appears to reflect a more limited asymmetry of the lateral basicranium and the upper jaw.

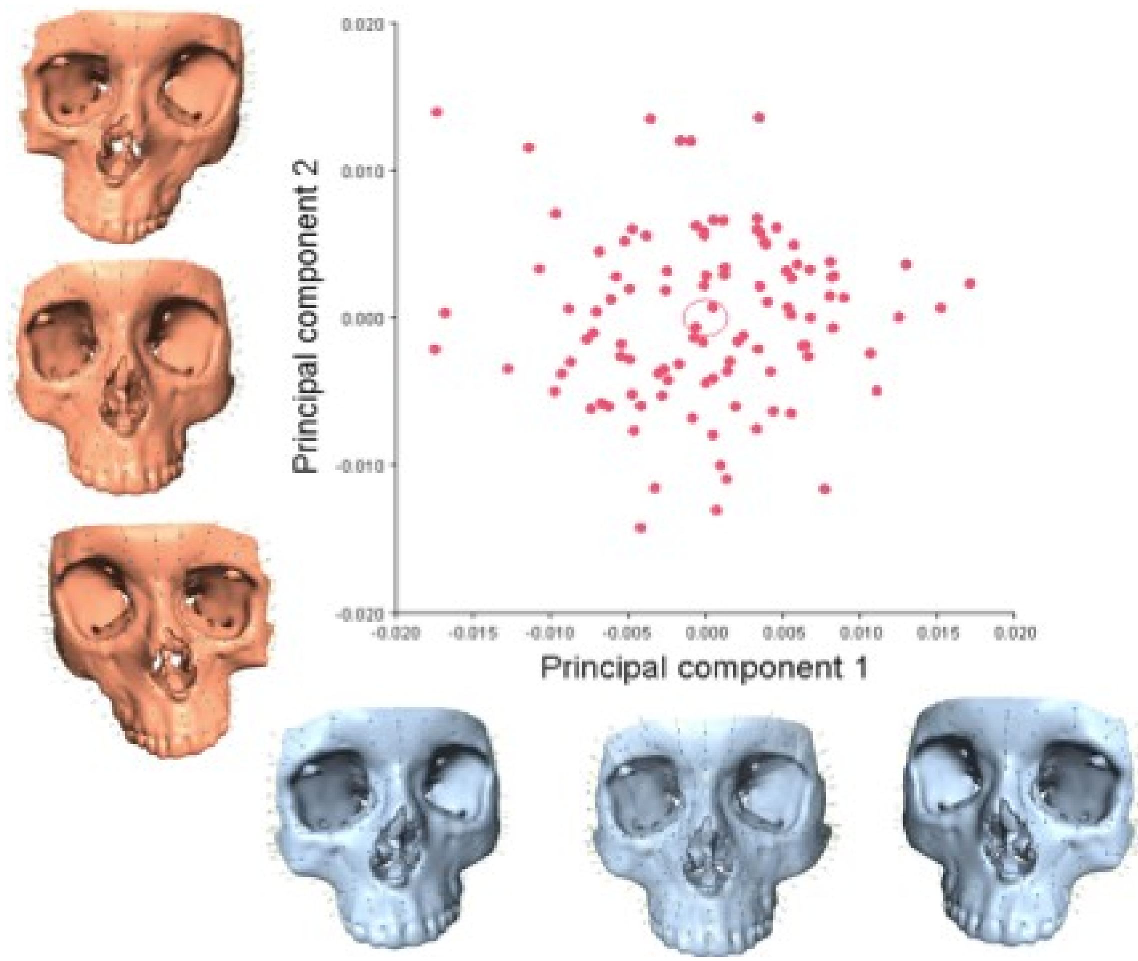


Figure 5. PC1 versus PC2 from the PCA of asymmetric variation of both basicranium and face with the confidence ellipse of the mean shown. Note that the mean is centered on "0" with approximate normal distributions on each axis, consistent with fluctuating asymmetry. Facial transformations show shape changes associated with the extremes of PC1 a general asymmetry across the face and PC2 showing a more limited asymmetry around the TMJ and upper jaw.

Partial Least Square (PLS) analysis

We next sought to test the strength and direction of this relationship using Partial Least Squares (PLS). This analysis identifies significant axes of covariation in asymmetric variation between the face and basicranium and tests for significance, and can be used to directly test our hypothesis about the covariation between the variation of the face and basicranium.

We examined the first ten PLS axes. A histogram of the PLS axes (Figure 6) shows that PLS1 explains 53% of total covariation, while PLS2 explains 12% (Table 3). Only PLS1 and PLS2 explained a significant proportion of total covariation (P--value <0.001) while only PLS1 had a significant correlation between basicranium and face blocks (P--value =0.084). The remaining axes did not explain a significant proportion of covariation, thus we do not consider them further here.

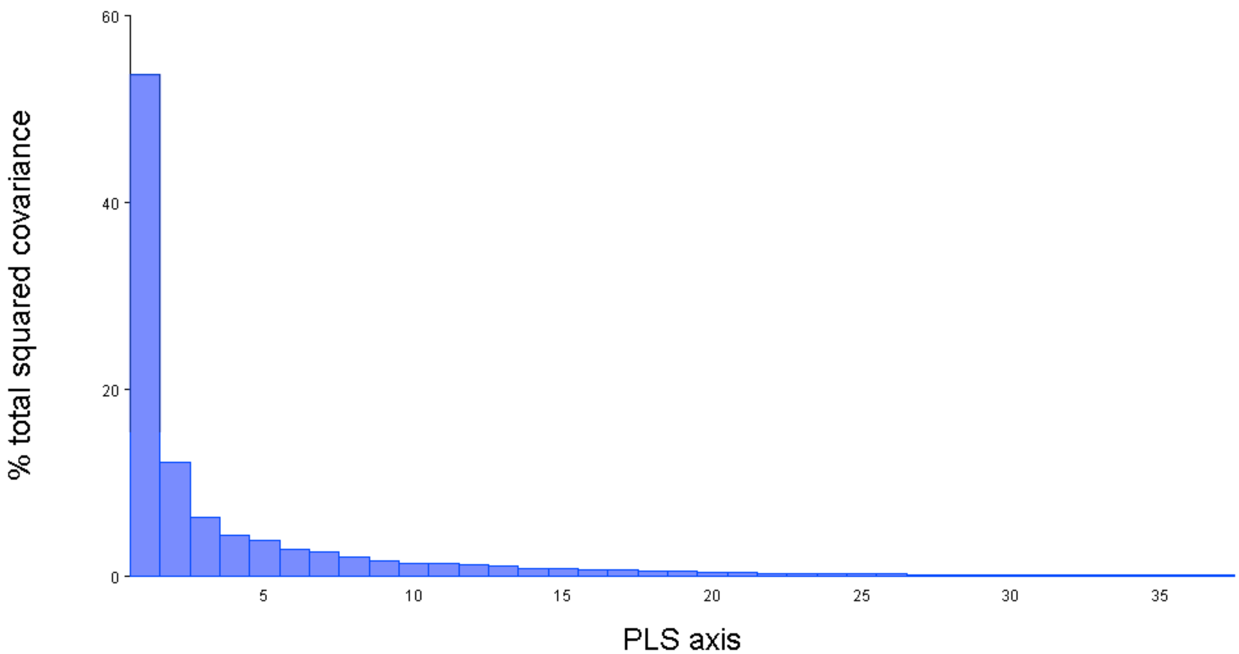
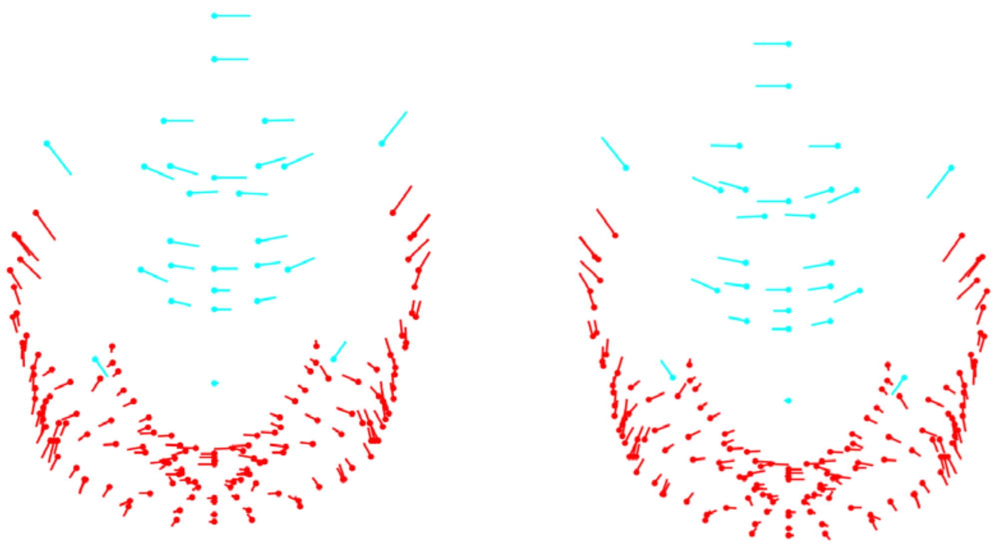


Figure 6. Screen plot of Partial Least Squares axes and their associated percentage covariance

Table 3. The first ten Partial Least Squares (PLS) and their corresponding singular value, P--value of the singular value, %total covariation, correlation, and P--value of total covariance.

	Singular value	P--value (perm.)	%total covar.	Correlation	P--value (perm.)
PLS1	0.00002026	<0.001	53.735	0.88508	<.001
PLS2	0.0000962	<0.001	12.104	0.63494	0.084
PLS3	0.0000693	0.124	6.279	0.54236	0.016
PLS4	0.0000573	0.404	4.304	0.55731	0.740
PLS5	0.0000538	0.148	3.784	0.61924	0.564
PLS6	0.0000464	0.380	2.816	0.61924	0.112
PLS7	0.0000440	0.092	2.540	0.66807	0.012
PLS8	0.0000384	0.316	1.935	0.66840	0.032
PLS9	0.0000350	0.404	1.606	0.55314	0.720
PLS10	0.0000318	0.548	1.321	0.57446	0.648

We found that the first PLS accounts for significant portion of covariation. Since there is a positive correlation between them, it shows that the relationship is additive meaning that the asymmetries of the face and basicranium are coordinated in the same direction (Figure 7). Therefore, the null hypothesis is falsified because we found a significant correlation between these two variables (Figure8).



A B

Figure 7. PLS1 showing the relationship between the asymmetries of the face (red) and basicranium (blue) in both positive (Figure 7A) and negative scale factors of 0.1 (Figure7B).

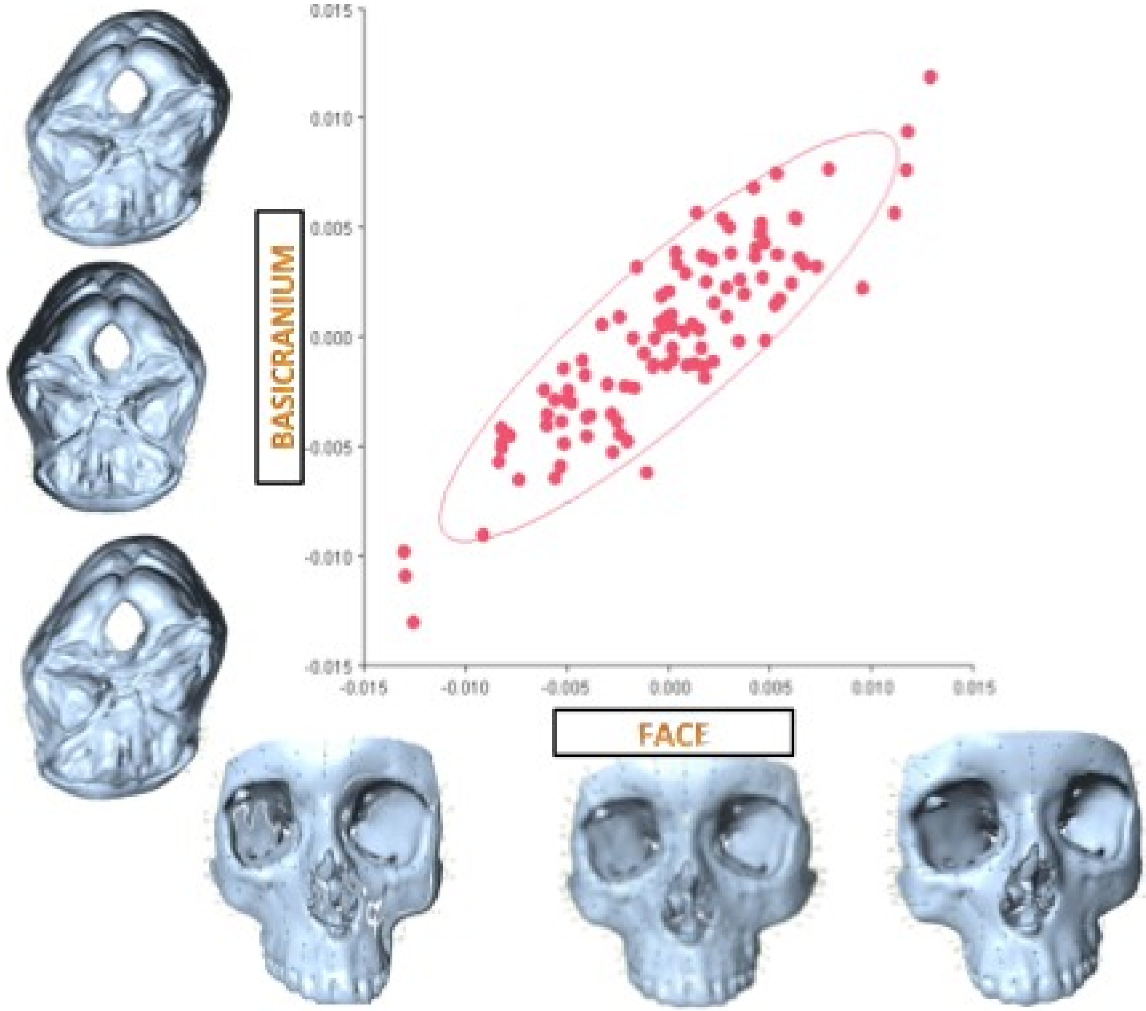


Figure 8. PLS analysis of external facial surface (Block 1) and internal basicranium skeleton (Block 2) asymmetry covariation. Facial and skeletal transformations show shapes associated with the extremes of each PLS applied to a representative cranium and face

Response to the following questions:

1. Were the original, specific aims of the proposal realized? **Yes**
2. Were the results published? **Not yet**
    a. If so, cite reference/s for publication/s including titles, dates, author or co-authors, journal, issue and page numbers
    b. Was AAOF support acknowledged? **Yes**
    c. If not, are there plans to publish? If not, why not? **Yes**
3. Have the results of this proposal been presented? **Yes**
    a. If so, list titles, author or co-authors of these presentation/s, year and locations
    Sara Adabi, Nathan Young, Gerald Nelson, Snehlata Oberoi
    Presented an E-poster at 2017 AAO Annual session.
    b. Was AAOF support acknowledged? **Yes**

c. If not, are there plans to do so? If not, why not?

d. 4. To what extent have you used, or how do you intend to use, AAOF funding to further your career?

The Resident Aid Award from the AAOF has allowed us to study Geometric Morphometric Analysis of the Influence of three dimensional Basicranial Shape on Facial Asymmetry. Additionally, Sara Adabi was able to present her work at the AAO Annual session and was able to use some funds for travel. Sara Adabi is now in Private practice in the Bay Area. This research has allowed her to gain experience in understanding facial asymmetry and she will continue to use her experience in her career. This also allowed her to appreciate the level of support from the AAOF for residents entering a career in Orthodontics, for which we both are grateful.

We thank the AAOF for the continued support that has enabled us to shed more light on facial asymmetry.

Respectfully submitted,
Snehlata Oberoi