Radial symmetry molding skull roundness: a human fetal MR study

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Abstract

The aim of this study consists in evaluating the morphological integration and molding shape of the human fetal craniofacial complex development on MR sagittal images. The *sella point* has been used as a reference point to build eleven dimensional parameters encompassing the craniofacial complex. Data and measurements obtained were statistically analyzed by PCA. The designed rays were significantly correlated, normally distributed and characterized by linearity over the overall fetal development. These findings showed that the *craniofacial* units are clustering together, whereas *craniobasal* and *craniopharyngeal* traits are spread. The data analysis supported the efficacy of specific morphological traits to evaluate differences emerging during the modeling growth processes. Skull modeling seems to be characterized by a rotational symmetry around the sella as inertial point. We firstly present the intriguing hypothesis through which the skull development grows along a dihedral angle symmetry made of a both rotational and reflection vector.

Introduction

Within the human body, different organs, tissues and cell groups are organized in a modular fashion generating a network of interacting units which are organized in a hierarchical way. Organism is, therefore, an arrangement of many modules, each one acting as a self-assembled and interactive *morphological unit*. The morphological unit may represent an inductive abstraction of the whole or a part of an organism. It can be defined as a series of linear, straightforward and often important measurements¹. Different kinds of interaction justify a different partitioning in the setting of a hierarchical system. Valid organizational morphological modules can be identified as structural or functional units. The cooperation of each part makes the organization as a result of functional integration and performance of modules that set the individualized unit aimed to the organism survival and reproduction. Since during the developmental processes structures are molded for specific functions²⁻⁴, consequently, different functions require different traits.

The skull can be modeled like an integrate and interactive module resulting from over millennia of co-evolution processes. These interactions include breathing, food tasting and processing, exploration of smells, noises and objects recognition in our environment, and vocalization. The senses of vision, olfaction, balance, hearing, taste, mechanoreception might be capable of influencing the craniofacial compartment size. At a glance the skull is composed of three parts: the cranial vault, the cranial base, and the face. The growth of the cranial vault relies mostly on the growth of the brain, the cranial base depends by the growth of the brainstem and cerebellum, and the face by the sense organs encased within it. With the application of a reciprocal causality logic principle^{5,6}, the brain acts as a scaffold for each component of the human face⁷⁻⁹.

Increased encephalization, which is one of the main processes that led to hominization, contributed to the development of a larger and more globular cranial vault. Human evolution seems to prefer certain directions of shape molding (variation axes) and the roundness of our species' braincase would represent

one of these favored axes. The relevant autapomorphy in modern humans' head included the expansion of the anterior neuroepithelium into a brain, the novel sensory systems assembly on the craniofacial skeleton, the reorganization of the pharynx, the introduction of muscles for eye movement, the jaws, the throat, the larynx and the tongue^{7,10-13}.

Due to the continuous evolutionary pressure, the neural mechanisms which are dependent upon a sensory transduction that preside contextual behaviors by the integration of every bodily, environmental, and neural systems, have a purpose of optimizing homeostatic efficiency or energy utilization¹⁴. The brain pursues two objectives: the survival of the individual and the survival of the species. It ensures that the organism is in a safe environment and has enough to sustain (i.e. water and food). In this context, one of the most important brain functions is to integrate emotional information with voluntary motor response. In humans, an interesting example are oral (branchial) and lingual (somitic) movements inherent in swallowing and vocalization strictly controlled by the voluntary motor system, however there exists complementary pathways that produce movements in the context of emotional expression¹⁵. The emotional motor system controls all vegetative basic effector activities such as blood pressure, heart rate, respiration, and vocalization. Eating, drinking, digestion of food, activities of the pelvic organs, such as micturition, defecation, sexual activities, and parturition can take place only in a safe environment, pinpointed by mental processing and strictly dependent on both vegetative and voluntary motor systems. When circumstances can jeopardize the safety of the setting, the execution of these activities results in being inhibited at a brain level¹⁶. All outliving activities are mainly organized on the medial brain cortical surfaces, moreover, major craniofacial growth occurs in the sagittal plane¹⁷.

In the 70's, Rakic first described the modality of neuronal migration as a radial process. The identity and function of different neurons depends on the location achieved along the dorsal-ventral, latero-lateral and anterior-posterior axes pathways during the early embryonic period. In no other organ is observed such a radical and precisely preprogrammed rearrangement of cell positions^{18,19}. The ontogenesis that occurs in the neurogenic placodes also recalls the radial migration of neuronal cells from the ventricular zone, suggesting a common mechanism for both processes^{20,21}. Two endocranial features are representative of the radial expansion; the optical pathway with the diencephalic evagination underlined by optic nerve and tract in middle cranial fossa, that continue like optic radiations on posterior cranial fossa; and a hollow telencephalic evagination from which bulb and olfactory tract elongate under the frontal lobe orbital surface along the anterior cranial fossa floor. From this structure the lateral and medial olfactory tract are generated and reach the temporal surface lobe hippocampo-entorhinal area. Furthermore, approximately at the level of the skull base angle, the corona radiata organizes axonal bundles that converge/diverge in/from the cerebral peduncles. In the fully developed encephalon, the corona radiata retains traces of the ontogenetic sequences and that's why it seems oriented towards principal directions of craniofacial molding axes. The skull base angle seems to provide the inertial point, from which the pathway for a harmonic expansion of each axis moves. If the corona radiata is the structure that better fits the brain case roundness, sense organs and brain development play a determinant role on skull shaping, then a first null hypothesis predicts that the correlations between expansion from the sella point

and the cranial traits should be high and significant. Functional modularity refers to the interactions of morphological units in performing one or more functions. Accordingly, traits within modules are tightly correlated with each other, but relatively independent in respect to traits in other modules. A second null hypothesis predicts that correlation between skull modules should be different.

Results

Growth analysis

All designed rays are significantly correlated ($0.57 < r < 0.97$, $p < 0.001$), normally distributed and characterized by linearity according to the variables correlation matrix (Table 2). It is evident that the *craniofacial* units (spg, s_antipg, sans and s_antians) and the supplementary GW, CBL variables are clustering together, whereas *craniobasal* (sfc, s_antifc, sb, s_antib), and *craniopharyngeal* (sh, s_antih) traits are spread (Figure 6). This positioning is handled by multidimensional scaling of the absolute values of the correlations. The biplot of individuals and variables on the PC1 versus PC2 plane (Figure 4) shows respectively 81.66% and 6.04% of the total variance. The biplot on the PC2 versus PC3 plane (Figure 6) shows respectively 6.0% and 3.5% of the total variance. The arrangement of the subjects along the PC1 follows approximately the order of their respective gestational age (Figure 4). The first PC has all coefficients of the same sign and it is interpreted as a measure of the actual variation on development events of the craniofacial complex in a population of 63 fetuses of different GW age.

The orthogonality constraint in PCA, then demands that subsequent PCs are contrasts between variables, other features may be unrelated to size or measures of 'shape'. The relative contributions of variables to PCs are showed in Figure 5. All the ten rays contribute approximately positively equally and concordantly to the PC1, albeit the craniofacial variables prevail. The craniobasal variables (sfc and s_antib) positively and (sb and s_antifc) negatively predominate to contribute in PC2. The correlation between the rays sfc, sb and the anti-rays s_antifc e s_antib seems to define two modules with an inverse correlation. Of these modules, one corresponds to the posterior cranial fossa (sb, s_antifc), the other one to the anterior fossa (sfc, s_antib). The craniopharyngeal variables, sh positively and s_antih negatively, prevail to contribute in PC3 (fig 5). The craniopharyngeal chord seem to represent a true boundary and follows a subdivision that linked modules by relatively few or weak interactions, the craniofacial traits, the anterior and posterior cranial fossae.

The PC2 versus the PC1 biplot analysis showed the following findings: i) sans, spg, s_antipg, s_antians and supplementary variables such as GW and CBL have positive coordinates on PC1. Therefore, this component contributes to the craniofacial covariation and size expansion throughout the gestation; ii) sfc and s_antib have positive coordinates whereas sb and s_antifc have negative coordinates on PC2. Therefore, this component focuses on craniobasal covariation but with opposite contribution like the roof of the nasal cavity, anterior cranial fossa floor and frontal portion of the cranial vault, against the posterior edge of the face, posterior cranial fossa anterior wall and supraoccipital portion of the cranial vault.

Independently from the gestational age, the patients fall in the four quadrants, indicating levels of variation and correlation of craniometric traits through a development of the human fetuses' skull.

The PC3 versus the PC2 biplot analysis showed the following: i) GW and BCL contributes are not statistically significant to indicate that the shape does not depend on age whereas it is weakly connected with the craniobasal trait; ii) shape seems to be molded by the relative contribution on opposite direction of craniobasal traits; iii) sh has large positive whereas s_antih has large negative coordinates on PC3. Therefore, this component focuses on craniopharyngeal module, where sh in a broad sense correspond to the supralaryngeal vocal tract module, and s_antih roughly to motor-cortex–parietal area engaged on breathing, feeding, vocalization and speaking.

Gender analysis

Because placement of both gender categories nearby the origin of both biplots, the presence of a sexual dimorphism seems not supported by data (fig.4, 6).

Discussion

In our cohort sexual dimorphism does not seem to be influent in the craniofacial development, probably because facial growth starts during the postnatal period and the phenotypic changes between genders mostly occur at puberty²².

Traditional craniometric length measurements are appropriate to quantitatively assess the shape variation or covariation within and between modules². The concept of morphological integration encompasses the pattern and the amount of correlation between different morphological traits (the so-called variables), which is detected by the analysis of correlation coefficient matrices²³. Recently, *Sodini et al.* supported the correlation between the morphological traits and the genetic and phenotypic features²⁴. We have found that the correlation among the landmarks set within a single linear module (i.e. splacno- and neurocranium traits) is significantly higher than those between the different linear modules. Therefore, the true boundary between the different linear modules is emerging by their relative weak reciprocal interaction. According to the Goswami mathematical formalism model, the morphological traits are integrated only if they are jointly represented within the same spatial direction, otherwise, they do not act as integrated traits because they are represented in a perpendicular or opposite direction³. *Esteve-Altava et al.* formally modelled the human skull as an undirected/unweighted network, whose nodes and links are respectively represented by each bone and suture²⁵. According to a such human skull network paradigm, we showed that two specific modules demonstrate a significant integration: firstly, an anterior facial module, related to the face and palate; and, secondly, a posterior cranial module, related to the cranial vault and base.

According to these foreword principles, the data analysis of the correlation matrix and the principal components biplot showed the definition of three different modules: *anterior cranial fossa*, *posterior*

cranial fossa and craniopharyngeal space modules. BCL is highly correlated to the craniofacial complex growth, with spg (0,93), sans (0,90), sfc (0,91) and sb (0,85) (Table 2). The sphenoid and occipital bones constitute the core of the *anterior and posterior cranial module* and contribute to the topology of the skull base in relation to the vault and the face. Indeed, the morphological traits which define the clivus (sb) and the anterior cranial fossa floor (sfc) are weakly correlated (0.61), whereas the correlation is higher between the expansion of the anterior cranial fossa (defined as the angle between the sfc and s_antib 0,82) and the posterior cranial fossa - pars subtentoriale expansion (defined as the angle between the sb and s_antifc 0,80). The occipital base supports the inferior parts of the brain and the occipital vault protects the cerebellum and the occipital lobe. The sphenoid and frontal bones constitutes the floor of the frontal lobes, the roof of the nasal cavity and the posterior edge of the face²⁶.

The PC3 versus the PC2 analysis or the so-called 'shape biplot' confirms the *craniopharyngeal module* (defined as the angle between the sb and spg) to be a real boundary between the posterior cranial fossa (sb, s_antians) and the portion of the anterior cranial fossa (sfc, s_antipg, s_antib) over the viscerocranium (sans, spg). This is consistent with Shoja et al. whereas the posterior fossa is subdivided into two regions, the lower bony region (sb, s_antifc) and the expansile upper tentorial region (s_antifc, s_antians)^{27,28}.

To our knowledge this is the first time that a clear correlation between viscerocranium (sans, spg) and cranial vault (s_antians, s_antipg) expansions is described (Fig. 3). A structural need for optimal alignment of the sensors located in the facial cavities and a developmental push induced by sensory afferents on the vault region that encase primary sensory and multimodal associative and efferent processing cerebral areas may represent the two complementary needs at the basis of our finding. According to the Bruner's model where anatomically modern humans are characterized by a rounded braincase, there is a good correspondence between the brain and vault shape¹². The facial skeleton surrounds nasal, orbital, oral, and pharynx cavities, thus the facial module has a hierarchical organization that supports the functions of breathing, smelling, watching, feeding, vocalizing and speaking^{25,29}.

Moving within the surrounding environment represents one of the most fundamental activity of daily life, and the ability to be precisely oriented in the space is a vital cognitive function that processes the relations between the self to space (places), time (events), and person (people)³⁰. Locations are redundantly encoded by several cerebral regions that processes multiple orientation mechanisms from a variety of sensory inputs including visual, auditory and somatosensory signals³¹.

The primary purpose of olfaction relied on the discrimination of smells in nature, then, alongside with the evolution of the human race, it evolved to organize the olfactive stimuli into functional associative memory structures. A narrower human nose could have allowed an increased sensitivity to odorants, improved the accuracy of directional orientation, with greater survival possibilities in the wild environment. The existence of two symmetrical nostrils suggests that humans might use bilateral sampling to extract information about the location of a specific odorant source^{32,33}. On the other side, the development of the visual perception allowed humans to gather precious information from the

environment concerning threat and safety, successful foraging and sexual opportunity³⁴. Furthermore, in terms of peripheral receptors, the oral cavity is one of the most densely innervated part of the human body. The gustative molecular recognition system - intercalated in several tissues and organs throughout the body - developed itself to acknowledge the nutrient content, palatability and potential toxicity of food, guide appetite and trigger metabolic processes³⁵. The oral cavity afferents represent cables through which immunity conveys information to the brain, too³⁶. This special sensory richness is linked to a dominant role in generating the 'conscious mouth image', which strongly contributes to the human homeostasis. Under the evolution pressure, the egocentric representation of the organism became a separated neural network from what is perceived as "other" to achieve an integration that optimize homeostatic efficiency³⁷. An operative navigation system requires both a "compass" (i.e., spatial perception) and a "map" (i.e., a storage system)³⁸. These functions employ cognitive maps that can be broadly separated into a posterior network (subserving visual and spatial processing) and an anterior network (dedicated to memory and navigation planning)³⁹. Cortical areas that belong to the medial prefrontal, medial frontal, mid-parietal, inferior parietal, hippocampal and entorhinal cortex, set up the neural network navigation key structures^{30,40,41}. Specifically, i) the human hippocampus and entorhinal cortex support map-like spatial codes; ii) posterior brain regions such as parahippocampal (PPA) and retrosplenial cortices (RSC) provide critical inputs that allow cognitive maps to be anchored to stable environmental landmarks; iii) hippocampal and entorhinal spatial codes are used in conjunction with frontal lobe to plan routes during navigation; and iv) medial prefrontal cortex plays a key role in maintaining useful information in working memory and in selecting the most appropriate navigational strategy^{42,43}. Moreover, given the advanced nature of the human visual system, spatial navigation requires a high-level integration of salient visual information. The PPA (closely located to the parahippocampal and lingual gyri) plays a role in landmark processing; the RSC is supposed to play a role in the translation of information between egocentric and allocentric representations; and the occipital place area (OPA) seems to encode potential future pathways involved in the spatial navigation³⁹. As an evolutionary shaped trait that rules the human motivational system, the reward network it is the key driver of human development. Reward networks are located in the prefrontal cortex, portions of the orbitofrontal cortex, insula, and anterior cingulate cortices allocated on medial surface brain, as well as subcortical limbic structures such as nucleus accumbens (NAc), ventral pallidum (VP), and amygdala^{44,45}. The neuroanatomical architecture of the feelings coming from the body (in the insular cortex), the sensations of pleasure and disliking (linking reward and punishment information, core reactions to hedonic impact which condition behavior), the craving (motivation process of incentive salience), the reward that comes from learning and memory (reward value information stored in episodic memory), substantialize homeostatic motivations that guide adaptive behaviors (in the cingulate cortex). It is clear that all these vital cognitive functions represent the core of the elaboration of the receptor's stimuli from the sensorial cavities of the viscerocranium. This tight connection might justify to our opinion, a close link in terms of expansion of the sensorial cavities and the cranial vault which encases the areas where the sensitive stimuli themselves are organized.

Conclusion

Our findings confirm the sella as the topographic center of the development of the skull and the close relation between the sensory receptor structures and the cerebral areas designated to the integration between receptive stimuli, organic and cognitive responses. During human fetal development, the craniofacial complex growth process follows a radial symmetry pattern, which is responsible for the roundness of our specie braincase. The brain and the neurocranium grow above, ahead and behind of the skull base, whereas the face and many sensory placodes grow below and ahead, but both grow along preferred directions. We observed that skull roundness is the result of the development towards these preferred axes. The correlation between the expansion of the craniobasal, craniofacial and craniopharyngeal traits from the sella point are highly concordant and significant (Table 2). Therefore, the first null hypothesis cannot be rejected. Because developmental processes mold structures that perform functions, different functions demand different traits. PC3 versus the PC2 biplot shape analysis showed the existence of a small angle between the anterior cranial fossa (sfc and s_antib traits) and posterior cranial fossa (sb and s_antifc) modules to indicate a positive correlation; whereas an almost perpendicular angle between cranial fossae and the craniopharyngeal modules means that the variables are not correlated. Therefore, for the shape molding, the second null hypothesis is not rejected. Additionally, the craniopharyngeal trait seems to represent a true boundary between the anterior and posterior cranial fossa modules. Larger data are mandatory to support and confirm our preliminary findings on the dihedral symmetry which rules the modern skull development assembly strategy.

Subjects And Methods

MR imaging

The Authors retrospectively reviewed sixty-three sagittal images selected from an archive-database of 2000 fetal magnetic resonance (MR) scans of the Department of Radiology and Neuroradiology at V. Buzzi Children's Hospital in Milan. MRI scans were performed as third level diagnostic procedures for diagnostic purposes. Fetuses (34 males and 29 females) aged between 20th and 35th gestational week (GW) were included if not carrying any central neurological malformation and/or head and neck dysmorphology. Age in gestational week was determined by ultrasound criteria.

Every mother signed a specific medical consensus regarding MRI diagnostic procedure and the use of imaging data for retrospective research purposes. Internal Review Board authorized the collection of imaging information in a database for retrospective research purposes⁴⁶. Imaging data were retrieved from the MR facility in an anonymized format. All scans were obtained with a 1.5 T machine (Philips Achieva), using phased-array coils or abdominal surface in relation to the gestational week, the fetal head and the placenta's position. A multiplanar single-shot fast spin T2 sequence was performed (TE: 180 ms, TSE factor: 85, vibration angle: 90°, matrix 256x256, FOV: 320 mm, slice thickness: 3-4 mm, gap: 0.1 mm, slice number: 11, acquisition time: 12s). No maternal-fetal sedation was given. All data were used respecting Helsinki Declaration principles.

A median sagittal image was selected in which the brainstem, the fourth ventricle, the pituitary stalk, the foramen cecum of the frontal bone and the facial profile were clearly visible⁴⁷. Measurement were performed by using cephalometric landmarks: sella-foramen cecum (*sfc*), sella-basion (*sb*), sella-anterior nasal spine (*sans*), sella-pogonion (*spg*) and sella-hyoid (*sh*) (Figure 1). In order to assess the roundness expansion, according to Bookstein, we have adopted type 3 landmarks extremal points⁴⁸. Ross and Williams reported that extremal type 3 landmarks are fairly accurate when derived as linear distances⁴⁹. Since their specular arrangement and the common sella origin, the complementary rays are defined as follows: anti-sella-foramen cecum (*anti_sfc*), anti-sella-basion (*anti_sb*), anti-sella-anterior nasal spine (*anti_sans*), anti-sella-pogonion (*anti_spg*) and anti-sella-hyoid (*anti_sh*). On the median sagittal surface (Figure 1) the landmarks areas are: *sans-sfc*, encompassing the nasal capsule, orbitosphenoid, presphenoid (chondrocranium), postsphenoid (chondrocranium); *sfc-anti_sb*, frontal lobe (desmocranium); *anti_sb-anti_sh*, paracentral lobule (desmocranium); *anti_sh-anti_spg*, parietal (desmocranium), *anti_sans* occipital (desmocranium), *anti_sfc* supraoccipital (chondrocranium), and the *sb* (chondrocranium). The segment sella-hyoid bone passes through the supralaryngeal vocal tract (SVT)⁵⁰.

Statistical analysis

Reliability

Measurement precision was evaluated by comparison of five repetitive measures for five randomly selected fetuses, over five nonconsecutive days. *Intraclass Correlation Coefficients* (ICC) function computes intra-rater reliability coefficients under Mixed Factorial ANOVA Model and *Confidence Interval of ICC* - formulated as a measure of intra-rater reliability coefficient – computes the lower and upper confidence bounds of the confidence interval. These analyses were performed by the *irrICC Package*⁵¹. The report of reliability is shown on Table 1.

Principal Components Analysis (PCA)

PCA of the ten designed rays was performed on 63 fetuses as a morphometric method with the use of the package *FactoMineR*^{52,53}. The correlation coefficient is the most meaningful expression of association when dealing with the morphological integration, the PCA was therefore done on interlandmark distances correlation matrix⁴⁹ (Figure 3). A biplot of individuals and variables on one graph assess the data structure and the *coordinates* of two components. *FactoMineR* package *PCA* function uses word *coordinates* for *standardized loadings*. The *contributions* of variables accounting for the variability to a given PC are expressed in percentages. To easily extract and visualize PCA results we

used the *factoextraR* package. To determine the number of PC to be considered we evaluate eigenvalues and the proportion of variances. The scree plot (Figure 2) shows the first three principal components explaining 91% variability, so we decide to truncate at the PC3. On the PCA biplot (Figure 3 and 6), the distance among fetus variable and origin it is a variable quality measure. The angle belonging to vectors is an approximation of the correlation between the variables. Small angle indicates that the variables are positively correlated, an angle of 90° means the variables are not correlated, and an angle close to 180° that the variables are negatively correlated. Length of the line indicate how well the variable is represented in the biplot. The qualitative variable 'gender' (F, M), and the quantitative variables 'cranial base length' (CBL, measured as the distances sfc + sb)⁵⁴ and 'GW' were projected on the biplots as supplementary variables. Fetuses are labeled on GW ascending order.

Declarations

CONFLICTS OF INTEREST

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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Tables

Due to technical limitations, the tables are only available as downloads in the supplementary files section.

Figures

Figure 1

Fetal magnetic resonance image.

Legend	PC1	PC2	PC3	PC4	PC5	PC6	PC7	PC8	PC9	PC10
Eigenvalue sqrt	22.601	5.011	4.53	4.029	3.145	2.606	2.140	1.876	1.602	1.054
Variance %	81.664	6.042	3.487	2.533	2.357	1.363	1.163	0.855	0.380	0.156
Cum Variance %	81.664	87.706	91.193	93.726	96.083	97.446	98.609	99.464	99.844	100.000

Figure 2

Eigenvalues scatter plot

Figure 3

Correlation matrix plot

Figure 4

PC1-PC2 Biplot of individuals and variables

PC report the coordinates for the variables, ctr contributions (in percentage) of the variables to the PC.

	PC1	PC2	PC3
sfc	0.8474375	0.42630867	0.11120877
s_antifc	0.8656089	-0.35416906	0.02881915
sb	0.8621373	-0.37032928	-0.12287764
s_antib	0.8791757	0.32251084	-0.02178055
sans	0.9380524	0.10114745	0.07392519
s_antians	0.9520235	-0.07737760	-0.03683507
spg	0.9610219	0.06767979	0.06880131
s_antipg	0.9596451	-0.05450627	-0.08110865
sh	0.8792857	-0.15337188	0.37958795
s_antih	0.8824916	0.09284989	-0.39709211

Figure 5

Contributions of Variables to PCs.

Figure 6

PC2-PC3 Biplot of individuals and variables

Supplementary Files

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- [tables.docx](#)