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Review Article

Three-dimensional analysis of craniofacial asymmetry and integrated, modular organization of human head

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Abstract: To achieve craniofacial symmetry is one of the important goals of orthodontic and orthognathic treatment planning. With the increasing popularity of cone beam computed tomography (CBCT) in recent years, it is frequently considered for three-dimensional evaluation of craniofacial asymmetry. Currently, there are no published reviews reporting craniofacial modularization to explain the aggravated asymmetry from the upper to lower face. This review highlights the characteristics of craniofacial asymmetry; the covariance and integration of the brain, cranium, and face; and the evolutionary development pattern of craniofacial modularization. In addition, the relationship between the brain and the facial midline is discussed in this context. We have proposed a new method to determine the midsagittal plane and three-dimensional analysis of craniofacial asymmetry using the bilateral hemisphere midline structure (cerebral falx) as a reference plane. The cerebral falx is a dura mater separating the cerebral hemispheres and a potential gold standard midline reference for assessing the brain midline shift during computed tomography (CT).

Keywords: Craniofacial asymmetry, integration, modularization

Introduction

Human craniofacial structures develop in a bilateral symmetry, resulting in identical right and left sides [1]. Symmetry can be defined as an equality and correspondence in the form of parts distributed around a center or an axis or to opposite sides of the body [2]. However, the complex process of organogenesis and involvement of various biological and environmental factors results in some kind of asymmetry [1]. Clinically, craniofacial asymmetry can be observed by comparing both sides and can range from hardly detectable to gross imbalance of the right and left sides [3]. The craniofacial asymmetry may be limited to soft tissues or may extend to underlying skeletal tissues, hence requiring radiographic investigations. Conventional radiography (such as panoramic, anteroposterior views) is not very helpful due to the two-dimensional presentation of three-dimensional objects. In addition, rotational movements of patients, radiographic magnification, and lack of reproducibility further compromise the interpretation [4].

In recent years, the use of computer tomography (CT), particularly cone beam computed tomography (CBCT), has been used widely. This technique has emerged with certain benefits such as accurate and comprehensive three-dimensional craniofacial images [5, 6].

In the study of craniofacial asymmetry, the establishment of a three-dimensional coordinate system and a reference plane is especially important. Currently, varying methods have being used for plane establishment, including the craniofacial midline landmarks midsagittal plane [7-11], and Frankfort plane as the axial (horizontal) plane [7, 12, 13]. The craniofacial midline anatomic landmarks include the nasion (N), anterior nasal spine (ANS), posterior nasal spine (PNS), sella (S), basion (Ba), crista galli (Cr), and opisthion (Op) (**Table 1**). Alternatively, an external reference system that is unrelated

Table 1. Nomenclature of anatomical landmarks used in this review

Landmark	Abbreviation	Description
Menton	Me	The most inferior midline point on the mandibular symphysis
Gonion	Go	The most inferior and posterior points at the right and left angles of the mandible
Anterior nasal spine	ANS	The tip of the bony anterior nasal spine in the median plane
Nasion	N	The most anterior of the frontonasal suture in the median plane
Basion	Ba	Middorsal point of the anterior margin of the foramen magnum
Opisthion	Op	Midpoint of the posterior arch of the foramen magnum
Posterior nasal spine	PNS	The most posterior midpoint of the posterior nasal spine of the palatine bone
Crista galli	Cr	The most superior edge of the crista galli

to the intracranial anatomical structures has been suggested. However, it can be influenced by the head position. Therefore, in order to guarantee the reliability of this system, the natural head position is required during the CBCT scanning [14]. A number of researchers have used a mathematical algorithm to calculate the craniofacial symmetry plane [15, 16]. For instance, Damstra *et al*. [16] obtained a craniofacial symmetry plane through morphological measurements and named it as the morphometric midsagittal plane.

The landmark method can be operated easily, but the combination of marks is random, with no scientific basis. In addition, the probability of error increases with the number of marks. Although the external reference system does not rely on intracranial structures, it requires patients to maintain a natural head position, which is difficult for patients with craniofacial malformation [5]. The mathematical algorithms obtain a "median" midsagittal plane, but it is a nonexistent calculated plane that does not follow the developmental axis during the evolutionary process of vertebrates.

In order to find more reasonable ways to analyze craniofacial asymmetry, the authors reviewed studies of evolutionary development, clinical medicine, and molecular biology. In addition, they proposed that as the brain, cranium, and face are interactive structures, they should be perceived as an integrated and modularized evolutionary development system. The brain midline and facial midline are highly consistent. However, there are no published reviews reporting craniofacial modularization to explain the aggravated asymmetry from the upper to lower face. This review highlights the characteristics of craniofacial asymmetry; the covariance and integration of the brain, cranium, and face; and the evolutionary development pattern of craniofacial modularization. Moreover, the relationship between the brain and facial midline is discussed in this context. We propose a new method to determine the midsagittal plane and three-dimensional analysis of craniofacial asymmetry using the bilateral hemisphere midline structure (cerebral falx) as a reference plane. The cerebral falx is a dura mater separating the cerebral hemispheres and a potential gold standard midline reference [17] for assessing the brain midline shift during computed tomography (CT). Furthermore, the characteristics of craniofacial asymmetry as well as the organizational features of head integration and modularization are reviewed.

The characteristics of craniofacial asymmetry and aggravated symptoms

Numerous studies have demonstrated that the main reason for craniofacial asymmetry is due to the lower jaw, including an abnormal mandibular morphology. In addition, the asymmetry is gradually aggravated from top to bottom [18, 19]. The lower face landmarks present a higher possibility of asymmetry and larger deviations, compared to the upper face landmarks. In terms of the distribution of craniofacial asymmetries, a wide range of variations have been reported. Park *et al*. [11] found that a normal occlusion sample and asymmetric patients had a similar pattern of asymmetry in the upper third of the face, while the asymmetry of the lower jaw landmark was of statistical significance. Meanwhile, in patients with facial asymmetries, apparent asymmetric sites include the mandibular central incisors, menton (Me), and lower first molar. Janson *et al*. [20] found that among patients with Angle's class II malocclusions, a majority (61%) had a consistent maxillary and facial midline, but the mandibular mid-

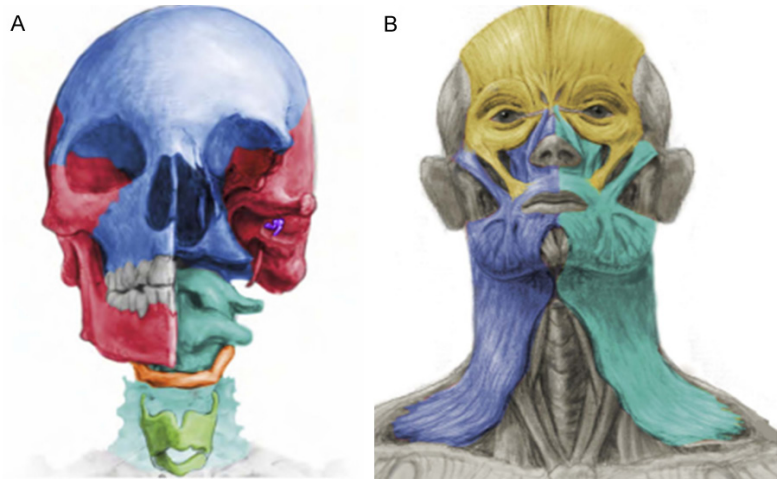

Figure 1. Esteve-Altava skeleton and muscle modules of the human head based on anatomical networks [33] showing (A) skeletal modules: cranial complex (red), facial complex (blue), and thyroid complex (green); and (B) muscular modules: the ocular/upper face complex (yellow) and orofacial complexes (light and dark blue).

line was deviated to the class II side. Similarly, Alavi *et al*. [21] examined patients with Angle's class II subdivision and reported that the deflection mainly occurs in the lower jaw. The asymmetric molar relationship in 61% of patients with Angle's Class II malocclusion is due to mandibular asymmetry, in which the lower jaw is 1.95 mm shorter at the corresponding side [22]. In the case of Angle's class III facial asymmetries, the mandibular deviation remains independent of the cranial base morphology. However, it is associated with functional or inherent potential of the mandibular asymmetry. Moreover, Haraguchi *et al*. [19] concluded that although facial asymmetries are present, the mandibular asymmetries are greater than the maxillary asymmetries.

Integration of the developing brain, cranium and face

It is well known that multiple tissues including nerves, bones, and muscles form an interactive development system in vertebrates. Therefore, the development of the head is a complicated, integrated and modularized process involving multiple genes. The central and peripheral nerves influence skeletal formation directly. A number of studies have confirmed the role of induction and regulation of cerebral signaling factors on facial morphogenesis [23-29]. The brain regulates cranial skeletons through the dura mater, brain, meninges and skull in an integrated system [28]. In addition, the brain and facial tissues interact in a covariant complex through the following mechanisms:

1) The brain affects the facial morphology directly by influencing the facial structures. For example, with an enlarged brain, the human face can become atypical when it is below rather than in front of the frontal lobe. A three-dimensional spatial packing model has been verified by comparative data of primates, revealing the ratio of brain size to cranial base length and thus explaining the majority of consecutive changes of the cranial base angle [25].

2) The forebrain tends to regulate the facial shape by establishing a signal center in the frontonasal ectodermal zone (FEZ) via signaling pathways. Genes involved in regulation include Hedgehog, fibroblast growth factor, Wnt, Notch, and transforming growth factor-β, etc. [30-32].

Modularized development and evolvability

The "Mosaic", namely modularized development, is a key mechanism in improving evolvability and stability (**Figure 1**) [33]. The anterior cranial base with the mid-upper face, and the posterior cranium with the lower jaw, respectively, form two craniofacial skeletal modules. Whereas the upper face above the eyebrows forms a single musculoskeletal module. The cranial skeletons are derived from different germ layers. For instance, the neural crest cells (ectoderm) are in the anterior part of the skull, whereas the mesoderm is in the posterior part. The boundary of both layers is located in the sagittal suture at the dorsal side near the pituitary fossa at the ventral side. The occipital bone is present as an enlarged spine that supports the whole brain [34, 35]. Simultaneously, the anterior and posterior skulls are regulated by different genes [36]. Similarly, meninges covering the brain have two tissue sources,

where meninges covering the cerebral hemisphere (forebrain) originates from the neural crest, while that covering the midbrain and hindbrain is derived from the mesoderm [28]. Numerous studies [37, 38] have demonstrated that the cranial base plays a key role in covariance of other craniofacial components. Development of the cranial base can be considered as a dynamic complex process including double sources. The anterior cranial base growth pattern differs from the posterior cranial base growth pattern. In addition, the linear growth of the anterior cranial base is approximately twice that of the posterior cranial base and is regulated by different genes [38].

According to the "New Head Hypothesis" proposed by Gans and Northcutt, the rostral head of vertebrates is a neomorphic unit. The "New Head" is derived from the neural crest, allowing a shift from filter feeding to active predation. Therefore, the neural crest-mesoderm boundary should correlate with the rostral-most tip of the notochord, thereby creating a coincident boundary with the prechordal-chordal boundary in the cranium [39]. Trigeminal crest cells give rise to the premandibular and mandibular components of the cranium [40]. However, there is a controversy about the location of the boundary between the premandibular and mandibular components. Historically, the maxillary prominence has been considered part of the mandibular arch; however, recent embryological and molecular genetics studies suggest that specification of the maxillary domain is mechanistically different from the dorsal-ventral patterning of the arches. This has led to speculation that the maxillary domain may not be an extension of the mandibular arch but rather a distinct structure analogous to the frontonasal prominence [41]. Now, this speculation has been well documented by anatomical networks [33] and molecular morphological markers [42].

The tracking of neural crest-derived mesenchymal cells by staining did not advocate classifying maxillary and mandibular diseases derived from the first pharyngeal arch in human and mouse phenotypes. Their data favored the opinion that the maxillary process is not derived from the first pharyngeal arch. Furthermore, since the first pharyngeal arch mainly constitutes the mandible and joints, it is totally appropriate to describe the pharyngeal arch as a mandibular arch [43]. Numerous animal experiments have proven that the pharyngeal epithelium influences the growth velocity and patterns of the mandible. On the other hand, the maxillary process and lateral nasal processes from the lateral part of the maxilla as well as their morphology are affected by the epithelium and mesenchyme interactions. Meanwhile, the middle part of the maxilla is derived from the frontonasal process, and its morphology is affected by the nasofrontal epithelium [44]. Differences of the maxilla and mandible can also be reflected in the congenital midline cervical cleft. The mandibular cleft often coexists with the midline cervical cleft, while the maxillary cleft is rarely accompanied by mandibular clefts. In addition, the cervical cleft is considered as the result of fusion failure of the pharyngeal arch at the midline and represents a defect in the ventral midline of the cervical skin at birth [45].

The anterior cranial base and mid-upper face are significantly integrated, forming a developmental module that can promote and inhibit changes in the craniofacial morphology. This has been confirmed by many studies of paleontology and molecular signaling [33, 46, 47]. The lower jaw forms a joint with the posterior cranial base and is therefore more likely to be influenced by the posterior cranial base. A study conducted by Esteve-Altava *et al*. [33] has shown that the lower jaw and posterior cranial base also form an anatomical and functional module. Posterior cranial base bending is human-specific, and its length as well as inclination affect the location of the lower jaw. Facial muscles above the eyebrow form a single neuromuscular module, while those in the middle and lower face are divided into the left and right muscular modules [33, 38, 47].

The regulation of the forebrain, anterior cranial base, and mid-upper facial midline

The forebrain, anterior cranial base, and mid-upper facial midline are regulated by the same signaling factors; thus, the three components are highly consistent. The midline is a developmental axis of a vertebrate embryo. The high consistency of the forebrain, anterior cranial base, and mid-upper facial midline has been fully reflected in both physiological and pathological conditions [48-51]. The midline is the first determined structural boundary formed

during early nerve plate development in rat embryos before the 0 body segment. In vertebrates, their cranial cartilage is formed by the middle part together with other paired structures, including the eyes and nose. The frontonasal prominence is the midline structure of mid-upper face and the anterior cranial base.

At the third week of embryonic life, the original tissues of the trilaminar embryo produce the notochord and prechordal mesoderm. The prechordal plate cells appear to be a basic regulation center for the differentiation of the midline structures of the brain, face, and mouth. The facial midline structures include the following: ethmoid bone, crista galli, nasal bone, vomer, nasal septum, premaxilla including incisors, triangular part of primary palate, and philtrum [52]. The prechordal plate defines the facial midline by signaling factors such as sonic hedgehog (SHH) and induces the forebrain to develop into two hemispheres, thus dividing the orbital area into two. The forebrain, anterior cranial base, and mid-upper facial midline are regulated by the same signaling molecules, thus the three are highly consistent. The midline is the developmental axis of the vertebrate embryo [53]. The above theory supports the "New Head Hypothesis", which suggests that the prechordal plate functions as the midline of the prechordal cranium to set the midline of the forebrain and mid-upper face. Brugmann *et al*. [54] have suggested that the width of the human facial midline (frontonasal prominence) may vary. When pathological conditions are superimposed on normal variations, a nearly unbroken series of facial morphologies is produced. When viewed in full, this spectrum ranges from cyclopia and hypotelorism to hypertelorism and facial duplications. In addition, the abnormal facial midlines often coincide with abnormalities in the cerebral midline. The severity of the facial deformity is influenced by that of the brain deformity. For example, patients with holoprosencephaly are often combined with cyclopia and other facial midline damage [54].

A strong correlation of the forebrain, anterior cranial base, and mid-upper facial midline structure has been fully reflected in other pathological conditions [55-58]. For instance, intracranial lipoma (ICL) is a rare disorder. However, approximately 45% of ICL cases occur along the midline axis between the two hemispheres. A new mouse mutant (called tuft) has been detected that manifests the forebrain and intracranial lipoma with abnormalities of craniofacial midline structures. Severe holoprosencephaly is usually accompanied by defects of facial midline structures, such as cyclopia and arrhinia. Hedgehog signals may lead to excessive duplication of neural crest cells, resulting in ocular hypertelorism and even frontonasal dysplasia (FND). FND includes a bifid nasal septum, cleft palate, cranium occultum, and agenesis of the corpus callosum [59-61]. Similar to FND, the mouse mutant tuft provides a model to illustrate the formation of the anterior cranial encephalocele following neural tube closure failure as well as its relationship with the subsequent craniofacial morphology.

Integrated and modularized human head and the consistency between the brain and facial midline provide new insights and methods for three-dimensional analysis of craniofacial asymmetry

Based on the studies reviewed, we suggested a framework of craniofacial structures according to evolutionary development and molecular biology evidence. We suggested that the brain, cranium, and face interact to be an integrated and modularized developmental system. The cerebral midline is consistent with the facial midline. Inspired by this, the authors proposed to use the anterior cerebral falx as the reference plane for studying craniofacial symmetry. We suggested to use the cerebral falx part anterior to the hypophysial foramen as the accurate reference plane. The anterior and posterior dura have different sources of tissues as the cranium, hence they may differ from each other [62]. In addition, a number of studies have revealed a deviation of the cerebral falx from the midline adjacent to the occiput [63]. The cranial skeletons anterior to the pituitary fossa are derived from neural crest cells, whereas the posterior is derived from the mesoderm [28]. The cerebral falx is a dura mater boundary formed between the two cerebral hemispheres, and it can be viewed clearly on CT and ultrasound images. The gold standard for brain midline shift suggests to use the falx as a reference midline and to measure the deviation of the septum pellucidum from the falx cerebrum [17]. Although a large-field CBCT

is capable of scanning the whole brain, it has yet to be popularized in the clinic. However, the method of determining the median sagittal plane based on the head symmetry axis is a new idea for three-dimensional analysis of craniofacial asymmetry. Also, the authors have introduced the modularization viewpoint for the first time to explain the aggravated asymmetry from the upper to the lower face. The authors suggested that the most functional and inherent craniofacial asymmetry is derived from the lower jaw-posterior cranium skeleton module and is transferred to the upper face via an asymmetric contraction of muscle modules on both sides and occlusal compensation. Additionally, the bilateral upper-lower jaw muscle modules may experience functional asymmetric contractions that further cause lower jaw skeleton asymmetry. The anterior cranial base and mid-upper facial module are relatively stable, especially the upper third of the face. This further confirms the conclusions made in the human head anatomical network analysis that the upper face is a single module of nerves, bones, and muscles; therefore, it has the best symmetry [33, 64].

We have proposed a new method to determine the three-dimensional analysis of craniofacial asymmetry using the midline of the brain (anterior falx cerberi) as a reference plane. The integrated and modularized human head and the consistency between the brain and facial midline provide new insights and methods for the three-dimensional analysis of craniofacial asymmetry.

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Disclosure of conflict of interest

None.

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