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Nasal septal deviation and craniofacial asymmetries

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NASAL SEPTAL DEVIATION AND CRANIOFACIAL ASYMMETRIES

by

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CERTIFICATE OF APPROVAL

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MASTER'S THESIS

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ABSTRACT

Introduction: Nasal septal deviation may contribute to facial asymmetry. The purpose of this study was to assess the relationship between nasal septal deviation and facial asymmetry using three-dimensional geometric morphometric methods.

Methods: Computed tomographic scans were made of n=55 adult subjects, and septal deviation was calculated as a percentage of septal volume relative to the volume of a modeled non-deviated septum. Skeletal landmarks representing nasal, palatal, and lateral facial regions were recorded, and landmark data was superimposed using Procrustes analysis. ANOVA/MANOVA tests determined degree of overall fluctuating and directional asymmetry. Finally, correlation analysis and multivariate regression were used to examine relationship between septal deviation and asymmetry of the individual facial regions.

Results: Septal deviation was significantly correlation with lateral deviation of the nasal floor, vertical and lateral asymmetry of the anterior palate and width asymmetry of the posterior posterior palate and posterior alveolar thickness, but was uncorrelated with the overall magnitude of asymmetry. There was no correlation between septal deviation and lateral facial asymmetry.

Conclusion: Nasal septal morphology is linked to nasal and palatal asymmetry. Deviated growth of the septum may pre-dispose patients to dental and skeletal asymmetries that have important orthodontic considerations.

PUBLIC ABSTRACT

Asymmetries of the face, dentition and jaws are usually due to growth disturbances and are common occurrences in the general population. They are often recognized and treated by orthodontists. Many believe that the nose, and a midline structure called the nasal septum play an important role in the growth of the face and as such, deviated growth of the nasal septum may contribute to the development of facial asymmetries.

The aim of this study was to evaluate the correlation between asymmetry (deviation) of the nasal septum (a midline structure of the nose) and the presence of asymmetries in the jaws and face. Three-dimensional computed tomography (CT) scans of 55 adults were obtained and used for data collection. The amount of asymmetry of the nasal septum was calculated and landmarks representing nasal, palatal, and lateral facial regions were recorded. The data collected was statistically analyzed to determine the amount of asymmetry in each of the three regions as well as to determine the amount of correlation between asymmetry of the nasal septum and asymmetry of the three regions.

Our results indicate that there is significant correlation between nasal septal deviation and asymmetry in specific aspects of the nasal and palatal regions. Deviation of the nasal septum is correlated with specific asymmetries in nasal and palatal form and thus may predispose patients to dental and skeletal asymmetries, which are important to orthodontists and surgeons in diagnosis and developing a treatment plan to address facial asymmetries.

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INTRODUCTION

Dental and skeletal asymmetries occur in high frequency in orthodontic populations. In particular, patients often present with asymmetric sagittal molar relationships along with high frequencies of asymmetry in overbite, overjet, and skeletal deviations from the midline (Smith and Bailit 1979); (Sheats et al. 1998). Indeed, mandibular midline deviation occurs in approximately 62% of orthodontic patients while midline dental discordance occurs in 46% of patients. Sagittally, 22% of patients exhibit some form of molar classification (i.e., Angle class) asymmetry (Sheats et al. 1998)

The causes of dental and skeletal asymmetry are complex and can result from early loss of primary teeth, loss of permanent teeth, genetic or congentital malformations (e.g hemifacial microsomia and unilateral clefts), environmental factors (habits and trauma), and functional deviations (Bishara, Burkey, and Kharouf 1994, Burstone 1998). Asymmetry also results from aberrant or asymmetric growth of the maxilla or mandible (Sanders et al. 2010) as well as asymmetrical positioning of the maxillary and mandibular molars (Sanders et al. 2010, Janson et al. 2001). The magnitude and pattern of asymmetry often plays a large role in the treatment modality and the complexity of a case and while some asymmetries can be treated by orthodontic masking or extractions, others may require surgical or orthopedic treatment as well (Proffit and White 1991). Therefore, the proper diagnosis and understanding of the etiology for facial and dental asymmetries is critically important for treatment planning and successful correction of skeletal and occlusal disharmonies.

Another potentially important component of skeletal and dental asymmetry is deviated growth of the nasal septum. Though the morphogenetic capacity of the nasal septum is controversial (e.g., Moss 1954, Moss and Saletijn, 1969), there is considerable evidence to suggest that the nasal septal cartilage acts as a key facial growth center (Scott 1953, Wealthall and Herring 2006, Wexler and Sarnat 1961a, Sarnat and Wexler 1966). Following the nasal septal traction model, the mechanical forces produced by the expanding nasal septum (e.g., Copray, 1986) are thought to facilitate separation of facial sutures. In this regard, the nasal septum has been argued to act as a growth plate, in a manner similar to the cranial base synchondroses, with expansion resulting from both interstitial cartilage growth (i.e., cellular division, extracellular matrix production) and endochondral ossification along the perpendicular plate of the ethmoid (Wealthall and Herring 2006, Copray 1986).

The influence of the nasal septum on patterns of facial growth have been demonstrated by numerous studies that have experimentally modified the interaction between the growth of the nasal septum and surrounding skeletal tissues. For example, surgical extirpation or damage to the nasal septal cartilage results in a reduction of the anteroposterior snout growth in growing animals (Sarnat and Wexler 1969, 1967b, a, 1966, Wexler and Sarnat 1961a, Nordgaard and Kvinnsland 1979, Oyama 1969). In a similar manner, sutural growth restriction in the circum-maxillary sutures results in deviation of the nasal septum (Rönning and Kantomaa 1985) or compensatory growth at the premaxilla (Holton et al. 2011).

As in various animal models, the nasal septum likely plays an important role in normal and abnormal patterns of human facial growth. In pathological cases, for example, damage to the nasal septum during early growth and development, results in nasal saddling, a reduction in

midfacial growth, and alterations to the occlusal plane (Pirsig 1992, Pirsig 1984, Precious, Delaire, and Hoffman 1988, Verwoerd and Verwoerd-Verhoef 2010). The nasal septum may also have a significant influence on normal patterns of population variation in facial morphology. Holton et al. (2012) examined variation in nasal septal and facial form in European- and African-derived samples and found that individuals of European descent had significantly larger and more deviated septa when compared to individuals of African descent. Moreover, they documented that the size of the nasal septum was associated with population differences in nasal projection, facial prognathism, and cranial base morphology.

If the nasal septum acts as a facial growth center in humans, then deviated septal growth may contribute to the development of facial asymmetries. Indeed, various studies have documented that nasal septal deviation is correlated with asymmetries of the external nose (Gray 1983, 1978, Reitzen, Chung, and Shah 2011). Similarly, septal deviation is associated with internal nasal asymmetries such as unilateral nasal turbinate hypertrophy (Egeli et al. 2004). Similarly, there is evidence that nasal septal deviation is correlated with external facial (i.e., non-nasal) asymmetries. This is particularly evident in cases of cleft lip and palate, which, according to Hall and Precious (2013) results when the nasolabial muscles on the non-cleft side pull on the nasal septum causing lateral bending. This bending results in facial asymmetry due to the nasal septum pushing upon the anterior nasal spine via the septopremaxillary ligament and the nasolabial muscles during growth (Hall and Precious 2013). Without any intervention/treatment, the asymmetries may become worse as the child grows. However, by repositioning the nasal septum and muscles back to the midline, a more normal growth pattern can resume (Smahel, Mullerova, and Nejedly 1999). The influence of the septum in external facial asymmetries in subjects with non-craniofacial anomalies was studied by Kim et al. (2011) who reported that a

deviated septum was associated with horizontal facial asymmetries when comparing the right and left sides of the midface when viewing photographs of subjects. Similarly, research by Gray and colleagues on infants, adults, and human skulls found that septal deviations and palatal asymmetries were highly correlated with dental malocclusions (Gray and Brogan 1972, Gray 1977).

The results from previous studies suggest that there is a relationship between nasal septal deviation and facial asymmetries, however; these studies have been conducted using either two-dimensional photographs (Kim et al. 2011, Hafezi et al. 2010) or dental casts (Gray 1983, 1978, Pirsig 1992). Moreover, nasal septal deviation is often treated as a categorical variable (Gray 1978, Akbay et al. 2013) or is measured only in a single region of the nasal septum (e.g., Kim et al., 2011). As such, there is limited information regarding the relationship between the overall magnitude of septal deviation and three-dimensional patterns of facial skeletal asymmetry measured from computed tomography (CT) scans. Using three-dimensional CT images of subjects who exhibit a wide range of variation in nasal septal deviation, the goal of the present study is to assess the relationship between nasal septal deviation and asymmetries in the facial skeleton. First, we examine whether there are significant levels of shape asymmetry in multiple regions of the facial skeleton (i.e., nasal region, palatal region, and lateral facial region) using geometric morphometric methods. Next, we examine the presence or absence of correlation between facial asymmetries and nasal septal deviation.

LITERATURE REVIEW

Development of the Nasal Complex

There are three types of embryologic germ cells that develop into the tissues of the fetus: endoderm, mesoderm, and ectoderm. Most of the alimentary canal as well as the inner-most tissues of the embryo originate from the endoderm. The ectoderm is responsible for developing into the epidermis and the neural crest cells, while the mesoderm is responsible for developing into the connective tissue and the skeletal muscles. With respect to the face and nasal complex, the three main cell types are ectoderm, mesoderm and neural crest cells (BM 1998). At the start of 4 weeks gestation, there are five identifiable primordial structures surrounding the stomodeum. The stomodeum is the groove below the developing brain, which eventually becomes the face. The five identifiable structures are the frontonasal prominence, right and left maxillary prominences, and the right and left mandibular prominences. The nasal complex arises from the frontonasal prominence. At the end of the 4th week, a pair of thickenings on the frontonasal prominence develop, called placodes. These oval placodes develop into the nose and the nasal complex.

Beginning of the 5th week, the nasal placodes continue to thicken and form a horseshoe shape (Som and Naidich 2013). The depressions within the nasal placodes are called nasal pits and they later form into the nasal openings. These pits continue to depress. By 6 weeks, there is only a thin film between the nasal cavity and oral cavity. Soon the membrane disintegrates and an opening from the nasal cavity to the oral cavity is formed. During this time the palatal shelves fuse, the secondary palate forms, and the nasal cavity lengthens which eventually becomes the communication between the nasal cavity and the pharynx (Neskey, Eloy, and

Casiano 2009). Near the end of the 6th week of gestation the lateral nasal processes begin to fuse with the maxillary process to form the lateral nose, nasal ala and border of the nostril. The frontonasal process is pushed posteriorly as the nasomedial processes merge and form the intermaxillary segment. The posteriorly driven frontonasal process is responsible for forming the primary palate, crest of the nose, and a portion of the nasal septum. The incisive foramen of the palate is the point at which the primary and secondary palates fuse. From this initial fusion point, the palate continues to fuse anteriorly and posteriorly and displaces the mouth and tongue inferiorly and the nasal floor superiorly.

The embryonic midline cranial base tends to follow a posterior to anterior pattern of chondrification, as such, the nasal septum is one of the last parts of the chondrocranium to become cartilaginous. It is formed via the condensation of mesenchyme within the frontonasal process in the upper midline of the nasal cavity. By the middle of the sixth week, the cartilage from the body of the developing sphenoid extends forward into the nasal septum, which forms the primary cartilage of the nasal septum. The broad section between the choanae is the place where the nasal septum begins its growth. The nasal septum merges with the palate as the septum grows inferiorly from the nasofrontal process. By week nine, the fusion of the palate with the nasal septum is completed. Once fully formed, the nasal septum is comprised of membranous septum, vomer, quadrangular cartilage, perpendicular plate of the ethmoid, and the maxillary crest (Neskey, Eloy, and Casiano 2009).

By 8 weeks of gestation, 3 nasal turbinates are evident as invaginations into the nasal cavity from the outer nasal capsule. These will eventually divide the cavity into the superior, middle, and inferior meati. The outer nasal capsule is surrounded by a nasal cartilage, which is

continuous with the nasal septum and is responsible for the turbinate growth into the nasal cavity. Over the next 8-10 weeks, the nasal turbinates continue to develop and the nasal cavity continues to grow. Also during this time, the maxillary sinus has begun to form and will continue to do so over the course of infancy. By 24 weeks of gestation, the lateral nasal wall is at near completion of development. The nasal cartilages responsible for the turbinates have undergone ossification by this time and the nasal cavity continues to increase in size.

Nasal Septum as a Growth Plate

Defining the complicated process of facial growth has been a topic of great interest for many researchers. Previous research has helped to increase our understanding of facial growth, but as more is discovered, the complexity of the process becomes more apparent. In particular, the role of the nasal septum in facial growth has been a topic of great interest and debate amongst researchers. Scott (1953) argued that the nasal septum is an endochondral growth plate with its own intrinsic growth potential and serves as a growth center capable of producing forces required to influence anteroposterior and vertical craniofacial growth. This idea became part of the nasal traction model which hypothesizes that the nose is responsible for growth of the face downward and forward. The nasal septum is believed to influence facial growth until the age of seven when the fusion of the vomer and ethmoid occurs. This mitigates any future influence of the nasal septum on downward and forward facial growth. However, theoretically future growth of the nasal septum could potentially still influence nearby structures such as the palate and nasal cavities.

Nasal septal growth has often been studied in animal models to analyze its growth potential. Research by Wealthall and Herring, 2006 and Copray, 1986 demonstrated that the

nasal septum is capable of interstitial growth and placing pressure on surrounding structures due to its growth. In Wealthall and Herring's (2006) study they used length measurements and histological examination of mice nasal septa throughout growth to determine cell proliferation and growth within the nasal septum as well as the surrounding ossification of nearby bones. Their results showed that the nasal septum grew in length at a faster rate than the nearby ossification of its borders and that the interstitial growth outpaced the growth of the surrounding structures. They theorized that the interstitial forces produced by the nasal septal growth-plate were great enough to separate bony sutures of the face and thus facilitate cartilaginous apposition at sutural interfaces. These forces, if applied to a human model, could drive facial growth downward and forward (Wealthall and Herring 2006). Copray's investigation of rat nasal septa in serum free organ culture support Wealthall and Herring's findings. Using a Wistar rat model *in* vitro, the nasal septum was excised and placed in a culture medium for 10 days. When the growth of the septum was analyzed the results showed that overall the septum maintained its original shape. The areas of greatest cellular proliferation were in the center of the septum and the area adjacent to the septo-ethmoidal junction. The greatest increase in size was found in the anterior posterior direction, of which they calculated to have roughly 3.0-3.5 grams of force. The septum grew to a lesser extent in the vertical dimension and had a force level of 1.0-2.0 grams. These forces equated to 8.1-8.9 g/mm2 of pressure in the anterior posterior dimension and 6.0-6.6 g/mm2 in the vertical dimension. They hypothesized that this pressure should be enough to help drive facial growth and sutural opening (Copray 1986).

In contrast to the septal traction model, Moss et al, (1968) and Moss and Saletijn (1969) offered that the nasal septum is limited to only influencing nasal projection and nasal bone elevation. In their opinion the nose grows in relation to the need for respiration and soft tissue

expansion, and not by the nasal septum itself. In contrast to the nasal septum being a growth plate as Scott (1953) had described, the nasal septum merely grows incrementally to accommodate the demands of the soft tissues. They believed that although an individual with nasal septal deformities or missing septum will have deficiencies in nasal growth, they will more or less have normal facial growth outside of the nasal complex (Moss et al. 1968). This was supported by the fact that midfacial growth is normal except for lack of nasal projection and nasal bridge elevation in patients with holoporsencephaly and cyclopinia with arrhinencephaly—conditions where the nasal septum is missing. Later research by Holton et al (2012) supported this relationship in people of European and African descent. However, their research also showed that the size of the nasal septum was correlated with variation in upper facial height and the orientation of other midline cranial base structures, suggesting that its influence may extend beyond external nasal morphology.

Septal Excision Experiments in Animals

To test the nasal septum's role in craniofacial form and growth, researchers started surgically altering or extirpating the septum in animal models. In 1858, Fick published studies (cited in Wexler and Sarnat 1966) in which he removed part of the nasal septum in growing pigs, dogs, cats, and goats through a trephine opening. These are some of the earliest published studies on septal extirpation. He noted that the anteroposterior dimension of the palate was reduced in those undergoing septal extirpation and thus theorized that the nasal septum was responsible for growth of the palate. Fick's later works on dogs showed superior positioning of the floor of the anterior nose in those that underwent experimentally resected nasal septum. This further supported the idea that the nasal septum affects growth of surrounding structures. Nearly

100 years later, Wexler and Sarnat repeated these studies on rabbits. In their first nasal resection experiment, n=24 rabbits were divided into a control group of n=6 and an experimental group of n=18. The surgical procedure to remove the septum was conducted as follows:

> An approximately 1.5-2 cm transverse incision was made through the mucosa between the upper incisors and the lip. The tissues were elevated from the premaxilla, and entrance was gained into the nasal cavity. At this point, the caudal margin of the septum and the septovomeral joint were exposed. The cartilage of the nasal septum was mobilized by lifting the cartilage out of the vomerine groove inferiorly, incising the septal cartilage horizontally in the nasal vault as high as possible, and removing varying amounts of caudal portion and body of the septal cartilage by means of a grasping forceps. Varying amounts of vomer and premaxilla were likewise removed. No attempt was made to save mucoperichondrium. The mucosal wound margins were approximated and sutured with No. 4-0 black silk (Sarnat and Wexler, 1961).

The rabbits of the experimental group lived for another 7-118 days following surgery and then were terminated. Upon examination, the rabbits of the experimental group presented with shorter and wider snouts and a downward and anterior deflection. The nasal bones appeared to be shorter and have a more steep inclination downward as viewed from the lateral aspect. The incisive foramen and palatine processes appeared to be shorter and wider. Due to the shortening of the palate, the incisors were in crossbite, had elongated and grown laterally. Septal extirpation in rabbits had been shown to decrease the anteroposterior growth pattern of the midface to such an extent that the rabbits lacked a functional occlusion (Sarnat and Wexler 1966, Wexler and Sarnat 1961a). Repeat experiments on rabbits using different methods, such as sham surgical control groups, produced similar results (Sarnat and Wexler 1966). When repeated on adult rabbits, there was very little difference between adults and controls in facial form. These studies suggested that the nasal septum is more important in growing rabbits than adults, or rather that the nasal septum has a larger role in growth than support (Sarnat and Wexler 1967b).

Hartshorne et al., (1968) repeated a similar experiment as Sarnat and Wexler's experiments on canine pups. In their procedure, they removed the cartilaginous septum as well as the mucoperichondrium entirely. Their results showed that the canine pups had midfacial growth stunting similar to those shown in Sarnat and Wexler's rabbits (Kremenak, Hartshorn, and Dejmen 1968). However, several later studies attempted to explain that midfacial stunting was due to damage to the mucoperichondrium.

Bernstein (1973) performed a similar study to Kremenak et al, (1968) and Sarnat and Wexler's (1961, 1967, 1967) experiments on canine pups, except the experiment was carried out to simulate conditions similar to those that would be expected in human children who underwent septal surgery at a young age—the primary difference being that the mucoperichondrium was left intact. Their hypothesis was that since the mucoperichondrium contains the cells with inherent growth potential, if these cells are left intact, no changes in growth should occur. In this experiment the canine pups were split into 4 different groups: a surgical resection group in which the majority of the quadrilateral cartilage was removed with care to avoid removing any of the bony parts of the septum; a surgical autograft group in which a section of the septal cartilage was removed from the puppy and then replaced with no attempt at fixation; a surgical control group in which a mucoperichondral membrane was flapped back and then replaced; and lastly a sham surgical control where the nasal septum was exposed but no incisions or flaps of the mucoperichondral membrane were made. The results of this study showed no visible differences in midfacial growth in the dorsum of the nose or the mid-third of the face between experimental cartilaginous resections, experimental cartilaginous autografts, surgical controls, and sham surgical controls. Histologically the cartilage of the septum resorbed in many of the surgical experimental puppies. In a few of the resected nasal septums and those that were autografted,

there was regeneration of the cartilaginous tissue. However, in the majority of the group with resected nasal septums the septal cartilage was replaced by a fibrous tissue with large ingrowths of vascular tissues, which appeared to look like a cavernous angioma.

Nordgaard and Kvinnsland (1979) attempted a similar experiment as Bernstein, but with different results. They also removed portions of the nasal septum with care to keep the mucoperichondrium intact. However, they operated on Moll-Wistar strain of rats and varied the age at which the resections of the nasal septum took place. The ages at which the rats were operated on were as follows: newborn, 7 days, 14 days, and 21 days. Their results showed that in all groups the experimental group had a reduction in midfacial projection and developed a bull-dog like facial appearance. They noted that the severity of stunting of midfacial growth was correlated with the age at which the procedure was conducted. The rats operated on at birth showed the greatest blunting of the snout while those operated on at 3 weeks had a lesser degree of blunting. Although the mucoperichondrium was left intact during the surgical procedure, this did not appear to prevent stunting of midfacial growth and histologically no signs of cartilaginous regrowth was noted.

Other variations in surgical procedure on different animal subjects have been attempted to determine if surgical procedure affected growth of the face. Rhys Evans and Brain (1981) attempted to surgically mimic surgical procedures that are carried out on children with severe septal deviations in a rabbit sample. Their results showed that all types of septal extirpations stunted the anterior projection of the rabbit snout. No difference in degree of facial growth retardation was noted between those undergoing septal autographs or homographs. However, they found that osteotomies of the rabbit nasal bones did not affect the anterior growth of the

snout. A few experiements looked at the role of the vomer bone and its relationship to facial growth. Complete vomer resection in Beagles elicited a reduction of anteroposterior snout projection in those of the experimental group when compared to controls and sham animals (Wada, Kremenak, and Miyazaki 1980). Artificial clefts were created in dogs and the vomer was removed in an experiment conducted by Lathan, Deaton and Calabrese. Their results showed reduced growth of the maxillary complex in all artificially created clefts compared to those of dogs with congenital clefts and intact vomer bones (Latham, Deaton, and Calabrese 1975). Oyama believed that the rough resection methods of previous experiments could be to blame for why most septal resection treatments resulted in growth reduction. Using an electric knife, a careful resection of only a portion of the nasal septum was carried out on rats. After 20 days, the findings were similar to those of previous experiments—there was a reduction in anteroposterior growth and a downward projection of the snout when compared to controls (Oyama 1969). Gange and Johnson severed the septomaxillary ligament from the nasomaxillary complex in new-born rats by use of a precision electrocautery knife to determine if this would affect facial growth. Their results found that experimental rats had reduced anteroposterior dimensions than those of controls and sham surgical controls. There was, however, no difference in vertical dimension of the face (Gange and Johnston 1974).

Another approach to testing the growth potential of the nasal septum in animals is to restrict surrounding sutures of the face. This type of experiment would theoretically test growth potential of the nasal septum without surgically altering the septum itself. An experiment similar to this was conducted on *Sus scrofa* pigs. Holton et al. (2010 placed surgical fixation plates over the zygomaticomaxillary and frontomaxillary sutures in 30 pigs and divided them into experimental, sham and control groups. They tested the hypothesis that the nasal septum

would continue to grow to normal length (as measured by vomer length) despite sutural restriction as well as the hypothesis that reduction in facial length leads to compensatory lengthening of the premaxilla. The results of the experiment supported both hypotheses (Holton et al. 2010). Thus, this experiment is in agreement with the nasal traction model and indicates that nasal septal growth does not simply follow the growth of the facial bones encapsulating it.

Not all nasal septal extirpation experiments showed reduction in facial growth with removal of the nasal septum. Other extirpation studies on short snouted animals (guinea pigs, cats, and ferrets) performed by Stenström and Thilander, 1970; Freng, 1981; Cupero et al, 2001; did not see the changes in anteroposterior dimensions in their animal subjects as was noted in the studies performed on long snouted animals. They theorized that the shorter overall length of the nasal septum in these animals suggests a reduced role of the nasal septum in growth (Stenstrom and Thilander 1970, Freng 1981, Cupero, Middleton, and Silva 2001). Later experiments by Siegel and Sadler, 1981 on chimpanzees--which have a shorter snout than previous animal studies and more closely mimic human facial growth--showed that septal resection had minimal effect on facial growth when compared to controls (Siegel and Sadler 1981).

Effect of Septal Damage on Human Facial Growth

Studies looking at the effect of nasal septal resection, damage or dislocation reveal conflicting evidence as to the role of the nasal septum in the growth of the human facial skeleton. In 1984, a report by Pirsig reported on 3 patients who were 16 yrs old and had previous nasal trauma and subsequent loss of nasal septum. These individuals showed reduction in nasal prominence and reduction in the midfacial growth. However, they noted that in these individuals, the later the age of the loss of the nasal septum correlated with less prominent

negative effects on midfacial growth (Pirsig 1984). Brain and Rock (1983) came to similar conclusions when they studied children who needed to undergo nasal septoplasty due to previous nasal trauma leading to septal deviation. They reported that there was a reduction in the downward and forward growth of the midface with those suffering septal trauma at an early age (Brain and Rock 1983).

In contrast to studies assessing the effects of septal damage on facial growth, several studies looking at septoplasty on young children appear to show little difference in facial growth from those of un-operated children. Freng and Kvam evaluated the effect of subtotal resection of the vomero-palatal junction on children with choanal atresia on facial growth compared to those of untreated children. Their results showed no significant difference in facial growth of those undergoing septal surgery and those without. However, they did note that those children with continued impeded nasal respiration developed shorter maxillas and retroganthic facial appearances (Freng and Kvam 1979). In another study by El-Hakim et al (2001), the effects of an external approach to nasal septal surgery, a procedure where the quadrilateral cartilage is removed, remodeled and re-inserted, was evaluated. Their results showed that although nasal dorsum length and nasal tip protrusion were mildly decreased, overall facial growth was not significantly altered in those undergoing septoplasty in early childhood (El-Hakim et al. 2001). A very similar study by Bejar et al evaluated facial and nasal growth after external septoplasty in children and followed up for an average of 3.4 yrs. Only the nasal dorsum length was decreased slightly in 57% of patients. All other parameters were similar with respects to growth when comparing those undergoing septoplasty and controls (Béjar et al. 1996).

Nasal Septal Deviation

Elucidating the role of the nasal septum in facial growth is further complicated by the presence of deviations of the nasal septum itself. A deviation of the nasal septum occurs when it is displaced laterally—either to one side, or both. This displacement would suggest that there is a growth disturbance or abnormal growth pattern with respect to the nasal septum and the surrounding structures, which ultimately further complicates the understanding of facial growth.

Septal deviation can develop during fetal development, birth, and even later during development. A failure in proper development during any stage of embryological development can lead to septal deviation. Genetics and environment both play an important role in the development of septal deviations. Several researchers have suggested that trauma during childbirth can contribute to nasal septal deviations. Gray was the first to discuss this idea and is known as the Birth Moulding Theory (Gray 1965). High, prolonged pressures during the intrauterine stage are believed to cause compression of the anterior maxilla, as well as buckling of the anterior palate and vomer which lead to deviation of the anterior nasal septum. This theory is supported by the fact that infants delivered via spontaneous labor have a higher rate of anterior nasal septal deviation than those birthed via caesarean section. Kawalski and Spiewak (1998) found that in newborns evaluated within 12 hours of birthing, 22.2% of those undergoing live birthing had nasal septal deviations verus on 3.9% in those undergoing caesarean section. However, spontaneous straightening was found in the majority of infants after a few days. Very few posterior nasal deviations were noted and there was no difference in birthing process. Therefore, nasal septal deviations caused by birthing trauma are unlikely to necessitate surgical repositioning (Kawalski and Śpiewak 1998). Other causes of septal deviation have been

accounted to genetic influences and mechanical injuries. Rarely congenital malformations, infections and neoplasia have also been reported as causes of septal deviation (Pirsig 1992). Kim et al (2011) found that the presence and size of sphenoidal process of the nasal septal cartilage was correlated with a greater amount of septal deviation and thus suggested that a decrease in septal cartilage ossification leads to a longer and more deviated septum (Kim et al. 2011).

Many researchers have attempted to determine the incidence of septal deviations amongst children and adults. For both populations, no one protocol has been established to define the degree of nasal septal deviation and record its incidence. One of the largest population studies to determine incidence was conducted by Gray and colleagues on 2,380 Caucasian infants. They evaluated infants 3 days after birth and 6 months later for anterior cartilage deviation (asymmetry of the external bony pyramid and dislocation of the cartilage off the anterior nasal spine) and combined septal deformity (kinking or spur formation of the vomer, perpendicular plate of ethmoid and quadrilateral cartilage). Their results showed that 58% of children under the age of 6 months were found to have kinked septa, while 10% of newborns had anterior cartilage deviation, but most of these disappeared over the course of 6 months (Gray 1978). As previously mentioned, Kawalski and Spiewak (1998) found 22.2% of infants were born with anterior nasal septal deviations, while Podoshin et al, (1991) found this rate to be only 0.93% (Kawalski and Śpiewak 1998, Podoshin et al. 1991). As one can see, the range of nasal septal deviation in newborns varies, which most likely is due to differences in nasal septal deviation criterion and measuring techniques (Vig 1998).

In adult populations, incidence of nasal septal deviation was first evaluated looking at skulls. In 1880 Mackenzie evaluated over 2000 skulls of varied races and found that 23% of

individuals had straight septa, 67% with kinked and 10% with deviated (Mackenzie 1880). Similarly, Gray evaluated 2,112 adult skulls of 5 ethnicities and found that 21% were straight, 42% were kinked, and 37% were deviated. Furthermore, Gray found that the septal deviations were correlated with dental malocclusions (Gray 1978). Recently the use of magnetic resonance imaging (MRI) and CT imaging has improved the ability to analyze the nasal septum. However, using this technology the incidence rates still remain varied as defining septal deviation and method of measuring deviation varies. Mladina et al found the incidence of septal deviation to be as high as 89.2% in adults, however this population involved patients from an ENT office seeking care for nasal complaints (Mladina et al. 2008). Although Reitzen Chung and Shah did not report statistical percentages, their results showed that as patients age, the incidence of nasal septal deviation increases from childhood to teenage and adult years (Reitzen, Chung, and Shah 2011).

Nasal Septal Deviation as it Relates to Respiration and Facial Form

A significant amount of research on nasal septal deviation has been dedicated to studying its effects on the ability to respire air through the nose. It has long been documented that a severely deviated nasal septum impedes the ability to respire. However, not everyone who has nasal septal deviation has an obstructed nasal cavity. Thus, several research studies have been conducted to evaluate what amount of deviation of the nasal septum is required to cause clinically significant changes in ability to respire. Cole et al simulated nasal septal deviations at different areas of the nasal septum in human subjects and used rhinomanometry to evaluate the amount of respiratory resistance. Different sizes of fiberfoam were adhered to the nasal septum at 4 different sites and airway resistance was calculated for both the untreated and decongested

nose. Their results showed that nasal septal deviations at the upper lateral cartilage produced the most resistance. They demonstrated that a 3mm deviation in the untreated nose produced significant resistance, while, in the decongested nose, no significant change in resistance was noted. However a 4mm deviation in both untreated and decongested patients had significant airflow resistance. In contrast, no matter the status of decongested or untreated nasal passage, the size of the deviation in the nasal cavum did not affect the nasal resistance, and thus posterior nasal septal deviations up to 5mm are not considered to affect nasal resistance. This study concluded that the anterior nasal septum is more susceptible to cause nasal resistance and that differences of up to 1mm can be significant (Cole et al. 1988).

A more recent study by Garcia et al used different techniques for simulating septal deviations, but came up with similar results. Using CT scans of a healthy nose with a relatively straight septum, simulated nasal septal deviations were produced using geometry-deforming software. Nasal airflow and resistance was calculated using computational fluid dynamics. Their results showed that the posterior nasal cavity can accommodate significant nasal septal deviations without a substantial increase in airflow resistance. However, in the nasal valve regions, small deviations produced large increases in nasal resistance. For instance, a 30 mm^2 reduction of anterior inferior nasal cavity space due to septal deviation increased resistance by 124% (Garcia et al. 2010). They concluded that septal surgeries to correct nasal septal deviations should be limited to anterior displacements that significantly reduce the ability to respire air through the nose (Garcia et al. 2010).

From a clinical standpoint, nasal septal deviation can have numerous implications. Septal deviations that inhibit the ability to respire in infants can lead to difficulties with feeding,

choking, natural breathing, hypoxia and increases the risk for sudden infant death syndrome (SIDS) (Kawalski and Śpiewak 1998). Amongst children and adults, the incidence of upper respiratory infections, cough, earache, ear discharge, and fever are increased with nasal septal deviations. Thus, early interventional management of deviated nasal septum at birth appears to be a safe procedure and may prevent future need for septoplasty surgery later. (Sooknundun et al. 1986).

In 1988, Freng, Kvam and Kramer were some of the first researchers to evaluate the relationship between a deviated nasal septum and facial form. In their study, they evaluated 34 individuals with stenosing deviated nasal septa with no previous history of allergies, nasal trauma or infectious disease that would account for their nasal obstruction and a control group of 44 randomly drawn nasally unaffected students of similar ethinc backgrounds as the experimental sample. Using lateral cephalograms, they found that patients with a deviated nasal septum had a 30% increase in airflow resistance based upon structural size. The patients with nasal septal deviation also had significantly smaller posterior facial height, posterior rotation of the mandible, smaller height of the anterior nasal aperture and shorter nasal ceiling (Freng, Kvam, and Kramer 1988). Thus, this was the first study to show that nasal septal deviation may have the ability to affect facial form in humans.

Another clinical manifestation of nasal septal deviation can be chronic mouth breathing due to nasal obstruction. Nasal obstruction can be caused by multiple reasons. In a cross sectional study of 370 Brazilian children, Abreu et al found that the incidence and etiologies of nasal obstruction were allergic rhinitis (81.4%), enlarged adenoids (79.2%), enlarged tonsils (12.6%), and obstructive deviation of the nasal septum (1.0%) (Abreu et al. 2008). In order to

adapt to nasal obstruction, patients breathe through their mouth chronically. This leads to a condition that was first coined as “adenoid facies” by Meyer in 1868 in which patients exhibit an elongated lower anterior facial height, retrognathic jaw and posterior rotation of the lower jaw (Meyer 1870). Although “adenoid facies” is still a commonly used term, it has recently been changed to being called “long face syndrome” as the adenoids are not always the primary etiology to the facial form. Long face syndrome is characterized by increased lower facial height, interlabial gap, narrow alar base, narrow maxillary arch, high palatal vault, posterior crossbite and class II dental occlusion (Vig 1998). A recent study by Harari et al, found similar results when analyzing mouth breathing children versus normal nasal breathers. They also noted that the lack of lip to tongue anterior oral seal was significantly more frequent in mouth breathers and thus had a greater propensity for anterior dental openbites (Harari et al. 2010).

The age at which a long face syndrome patient presents to the orthodontist often determines treatment route. In a non-growing patient, a combination of orthodontics and surgery will be needed in order to correct dental and skeletal problems (Vig 1998). In a growing patient, a combination of orthodontics and orthopedics are often needed. However, for both adult and adolescent patients, the etiology of mouth breathing must be addressed or unwanted growth and relapse are potential problems. For instance, if the etiology of the long face syndrome is believed to be due to enlarged adenoids and tonsils, the removal of the tonsils and adenoids may help to improve nasal breathing and mitigate the negative effects of mouth breathing on dental and facial form. (Shapiro and Shapiro 1984).

<u>Incidence and Etiology of Facial and Dental Asymmetries</u>

Facial symmetry has been recognized as a marker of facial beauty and evolutionarily a trait of superior genetic mate selection (Scheib, Gangestad, and Thornhill 1999, Udry and Eckland 1984). Individuals with greater facial symmetry are often viewed as more attractive and have been reported to have better prospects for happier social and professional lives (Perrett et al. 1999, Dion, Berscheid, and Walster 1972). However, perfect facial symmetry is rarely found in humans and asymmetries of facial and occlusal relationships are common occurrences, especially for those seeking orthodontic care.

There are several studies that have looked at the incidence of facial and dental asymmetries. Initial studies of craniofacial asymmetries were conducted on skulls. The anthropologist Woo was one of the first to carry out direct chordal and arcual measurements on a large number of skulls to determine the presence of craniofacial asymmetries. He noted that there were differences in size and shape of the left and right sides of the skull. Particularly he noted that in his Egyptian population, the right side of the cranium was larger, while the left side Maxilla and Zygoma were larger (Woo 1931). Vig and Hewitt (1975) noted similar findings when reviewing cephalometric tracings. More recently, Sheats et al studied the incidence of dental and facial asymmetries in a large retrospective cross sectional sample of treated and non-treated patients through a series of screenings. Amongst the non-treated patients, sagittal molar asymmetry was found in 30% of children, while only 23% at a second screening, an average of 4 years later. They recorded that 12% had facial asymmetries and 21% had non-coincident midlines. Amongst patients receiving orthodontic care, 62% had mandibular midline asymmetry to the facial midline, 46% lacked coincident dental midlines, 39% had maxillary midline deviation from the facial midline, molar classification differed in 22% of patients, 6% had facial asymmetries, 4% with chin deviations, and 3% had nose deviations (Sheats et al. 1998).

The etiology for facial and dental asymmetries are numerous. The causes of dental and facial asymmetries may be genetic, environmental, or a combination genetic and environmental factors. Genetics clearly plays a role in affecting facial growth and the presence of asymmetries. Differences in growth and development of the right and left sides of the face and dental arches often can lead to asymmetries. This is most notably seen in patients with hemifacial microsomia. Also, the fact that in cleft lip/palate patients the left side of the face is nearly twice as likely to be affected than the right seems to indicate that there is a genetic role in the formation of asymmetries of the two halves of the body (Lundström 1961). Environmental pressures also play a role in the development of asymmetries. Some infants are born with facial asymmetries due to parturition pressures, but most studies have shown that asymmetries caused by birthing pressure only last for a few weeks to months before normal relationships of the facial and skull bones are restored (Boder 1953).

Habits and trauma have also been shown to cause development of facial and dental asymmetries. Trauma causing fracture of the mandible during growth, infections and trauma of the temporomandibular joint with ankyloses of the condyle, are a few examples of traumatic events that can lead to asymmetries. Osteochondromas and neurofibromatosis have also been shown to cause facial asymmetries (Bishara 1994). Lundstrom demonstrated that asymmetries of the oral cavity may be caused by sucking habits and asymmetrical chewing habits due to caries, extractions and trauma. (Lundstrom 1961). He characterized dental asymmetries as quantitative or qualitative based upon number of teeth on one side of the arch versus the other as well as the size and orientation of the teeth on one side of the arch versus the other. In a review of the literature, Bishara reported, in addition to the previous genetic and environmental factors mentioned, abnormal dental eruption, early loss of primary teeth, functional deviations, and

aberrant growth of the maxilla and mandible can cause facial and dental asymmetries. The etiology and severity of these asymmetries are often interrelated. Some dental and facial asymmetries are simple differences of a few millimeters from one side of the arch to another, while others are more significant and can be centimeters in difference. The magnitude of asymmetry often plays a large role in the treatment modality and the complexity of a case—some asymmetries can be treated by orthodontic camouflage with extractions, while others cannot be treated with orthodontics alone and may require surgical or orthopedic treatment as well (Bishara, Burkey, and Kharouf 1994, Burstone 1998). This underlines that proper diagnosis and understanding the etiology of facial and dental asymmetries is crucial for eliminating asymmetries via orthodontic care.

Dental and Facial Asymmetries and Nasal Septal Deviation

If the nasal septum plays an important role in facial growth, deviations or asymmetries in the nasal septum may produce asymmetries in the mouth and craniofacial complex as well. In regards to the external nose, severe traumatic injury to the nasal septum causes deviations that have been well documented and correlated with external nasal asymmetries (Gray 1983, 1978, Reitzen, Chung, and Shah 2011). Internal nasal asymmetries have also been shown to correlate with septal deviations. In the lower meatus, turbinate hypertrophy on the contralateral side of septal deviations has been noted (Egeli et al. 2004). This hypertrophy increases nasal resistance and may affect ability for nasal respiration. However, there have been relatively few studies that have attempted to correlate nasal septal deviation with craniofacial asymmetries outside of the nasal complex.

The results and techniques of quantifying deviation and asymmetry have varied throughout the literature. Previous studies have quantified facial asymmetry using bilateral comparisons of linear and angular measurements (Janson et al. 2001, Sanders et al. 2010), as well as other studies that have used triangulation methods on posterior-anterior cephalograms to determine asymmetry across the facial midline (Vig and Hewitt 1975, SHAH and Joshi 1978). Similarly, septal deviation has been evaluated differently amongst studies. Many have evaluated the degree of deviation of the septum based upon the most angulated point of the septum using posterior anterior cephalometrics or CT scans (Kim et al. 2011, Akbay et al. 2013), while others have used clinical exam of patients or analysis of photographs (Hafezi et al. 2010, Gray 1965, Gray and Brogan 1972, Gray 1983, 1978). A more recent technique by Holton et al (2012) used CT scans to evaluate the volume of the septum along its entire length and compared this to a volume of the septum if it were to be non-deviated to describe the nasal septal deviation as a percentage. The value of this technique is that it represents deviation of the septum as a whole along its entire length.

Some of the earliest studies to evaluate nasal septal deviation and facial asymmetry/abnormalities were conducted by Gray and colleagues during the 1970's and 80's. In early research they looked at incidence of septal deviations in infants, adults, and on a compilation of human skulls. Although these studies were looking at the effects of palatal expansion, one of their principle findings was that septal deviations were highly correlated with dental malocclusions (Gray and Brogan 1972, Gray 1977). Later studies focused more on the incidence of septal deformities and followed infants from birth to 8 years to determine if asymmetries and deviations at birth were prevalent from birth to 8 years. Using alginate impressions at birth, 5 years, and 8 years, their data suggested that palatal asymmetries and

dental malocclusions were highly correlated with septal deviations and these findings generally did not correct from birth to 8 years old. Specifically type B (unidirectional deviation) and type C (bidirectional deviation) deviations had the greatest changes of the presence of palatal asymmetry. However, their findings did not indicate a significant correlation between palatal height and septal deviation (Gray 1983).

In 2010 Hafezi et al attempted to directly correlate the deviated nose with asymmetric facial growth. In their study a total of 5,822 pre- and post-rhinoplasty photographs were taken on 547 individuals. This population was split into 3 groups: group A included gross nose and face asymmetry; group B included nose asymmetry with no facial deformity; group C included facial asymmetry with straight nose. Selected measurements were performed on the pre- and post- photographs which were used to determine differences in right and left side anatomical asymmetry. The two main measurements were lateral canthi to the lateral mouth corners (D1) and from the midface to the most lateral part of the zygomatic arch (D2). The results of their study showed that there was significant difference in the nose and face deformity group (Group A) when comparing left and right side of the face D1 and D2. They found that growth retardation of the midface and orbit appeared to occur on the concave side of the nose. In addition, it was noted that dystopic orbits, elevated lip corners, asymmetric zygomatic arches, asymmetric misplaced nasal alae, and lack of parallel growth on both sides of the nose was present in those with a deviated nose (Hafezi et al. 2010). Although this study has compelling results to suggest that the nose may play an important role in facial asymmetries, the authors do point out that there is a possible bias when reviewing photographs. Also, it must be noted that because the study was performed on two-dimensional photographs, the presence/absence of asymmetries in an anteroposterior dimension cannot be quantified.

Later, work by Kim et al 2011attempted to correlate visual facial asymmetries with internal nasal septal deviations. In their study 25 individuals with deviated nasal septa who underwent facial esthetic surgery were selected. CT scans and facial photos of each patient were collected for analyses. Deviation of the nasal septum was quantified from a coronal slice of the CT scan at the most deviated segment of the nasal septum. At this segment, the angle of septal deviation was calculated as well as angle of lateral nasal wall, angle of the inferior turbinate, and width of nasal cavity. Asymmetry of the face was determined by analysis of facial photographs using distances between selected landmarks: midsagittal plane to zygion, glabella to exocanthion, exocanthion to cheilion, and zygion to cheilion. The results of the study seemed to indicate that nasal septal deviation was associated with facial asymmetry. Specifically they found that the left to right distances of mid sagittal plane to zygion distance, glabella to exocanthion, and chelion to zygion were correlated with direction of septal deviation. Thus their study concluded that nasal septal deviation may contribute to differences in left to right growth creating facial asymmetry (Kim et al. 2011).

MATERIALS AND METHODS

In order to assess the relationship between facial asymmetry and nasal septal deviation we used CT scans of a sample of 55 adult subjects. Previous research by Holton et al (2012) documented that there is significant population variation in nasal septal deviation with subjects of European-derived subjects exhibiting a significantly greater magnitude of nasal septal deviation when compared to African-derived individuals. Given the wide range of variation in nasal septal deviation (i.e., slight deviation to highly deviated) used by Holton et al. (2012), this geographically diverse sample is well suited to assess the association between nasal septal deviation and facial asymmetries. Our European-derived subsample (n= 45) consisted of 30 male and 15 female European-Americans ranging in age from 19 to 70 years. Our African derived subsample (n=10) was composed of 3 male and 7 female African-American and native South Africans ranging in age from 20 to 67 years old.

In contrast to previous studies that have relied on qualitative (Gray 1978, Akbay et al. 2013) or simpler two-dimensional approaches (Kim et al. 2011, Hafezi et al. 2010) in measuring nasal septal deviation, we utilize a three-dimensional quantitative method that accounts for the overall morphology of the nasal septum. This results in a more accurate assessment of the magnitude of nasal septal deviation across the entire septum and gives us finer resolution for assessing the relationship between septal deviation and facial asymmetry. The magnitude of septal deviation was quantified by first manually segmenting the nasal septum from anterior tip of the external nasal septal cartilage to the posterior aspect of the vomer at hormion (Fig. 1a and 1b). We then and measured the overall size of the nasal septum by calculating the volume of the resulting three-dimensional septal reconstruction (Fig 2). Next, we calculated the volume of a

modeled non-deviated septum following the borders of the nasal septum (Fig. 1c). Both nasal septal volume and the non-deviated volume were segmented at constant thickness of 1.0mm to control for potential variation in mucosal and cartilage thickness.

As such, a value of 100% indicates the absence of nasal septal deviation while a percentage >100% is indicative of septal deviation (Holton, Yokley, and Figueroa 2012).

In order to evaluate the relationship between nasal septal deviation and craniofacial form, we collected a total of k=41 three-dimensional coordinate landmarks from the facial skeleton (Table 1). Coordinate landmark data was collected twice for all subjects as to facilitate analyses of asymmetry and minimize measurement error. Coordinate landmarks were separated into three discrete facial regions. First, the nasal region was represented by unilateral midline and bilateral landmarks representing the external nasal aperture, nasal bones (red landmarks in Fig. 3) and the internal nasal cavity. Internal nasal cavity landmarks were collected along two coronally oriented planes. The first plane (Fig. 4a and 4b) was located at the midpoint of nasal floor length (i.e., 50% of anterior nasal spine-posterior nasal spine length) while the second plane (Fig. 4a and 4c) was located at the level of the posterior nasal spine (i.e., 100% of nasal floor length). Next, the palatal region was represented by unilateral midline and bilateral landmarks representing anterior midline of the maxilla (i.e., subnasal region) and buccal crest of the external alveolar process of the maxilla (green landmarks in Fig. 3), as well as the roof of the palate. Palatal landmarks were collected along four coronally oriented planes selected relative to the length of the nasal floor. The first plane (Fig. 3) was located at 25% of palate length while the second plane was located at the midpoint. The third plane was located at three quarters of the palatal length and the fourth plane was located at the posterior nasal spine. Finally, the lateral facial region was represented by bilateral landmarks along the lateral surface of the zygomatic

bone and floor of the orbit (blue landmarks in Fig. 3) All nasal septal and coordinate landmark data were collected using Osirix DICOM imaging software (Rosset, Spadola, and Ratib 2004). We examined patterns of facial asymmetry in the nasal, palatal and facial regions using a three dimensional landmark-based geometric morphometric approach.

This method contrasts with previous studies that have quantified facial asymmetry using bilateral comparisons of linear and angular measurements (Janson et al. 2001, Sanders et al. 2010), as well as other studies that have used triangulation methods on posterior-anterior cephalograms to determine asymmetry across the facial midline (Vig and Hewitt 1975, SHAH and Joshi 1978). Here, our coordinate landmark data was submitted to a Procrustes analysis, which superimposes the coordinate landmarks by eliminating the effects of translation, rotation, and scale among individuals. Using a Procrustes-based approach, landmark configurations with object symmetry (e.g., the skull) can be distilled into symmetric and asymmetric components of shape variation. The asymmetric component of shape is obtained by first determining an averaged symmetric shape for each landmark configuration. A symmetric configuration is determined by averaging mirrored landmark configurations for each subject. The asymmetric component of variation is then quantified as the deviation between the original and symmetric configurations (e.g., (Klingenberg, Barluenga, and Meyer 2002)).

Using the asymmetric component of variation, we first assessed overall patterns of asymmetry in the nasal, palatal and lateral facial regions by examining the effects of directional (side) and fluctuating asymmetry (side x individual) using Procrustes ANOVA. Directional asymmetry would indicate a consistent difference in shape between the left and right sides of a region of the facial skeleton (i.e., a non-random deviation from symmetry). Fluctuating asymmetry on the other hand is a measure of an individual's asymmetry relative to mean shape

asymmetry (i.e., random deviations from symmetry among individuals) (Klingenberg and McIntyre 1998, Klingenberg, Barluenga, and Meyer 2002). While Procrustes ANOVA is useful for measuring the effects of asymmetry, it assumes isotropic variation (random, non-biased variation) at each landmark. As such, we additionally examined the effects of asymmetry using MANOVA, which does not require isotropic variation at each landmark (Klingenberg, Barluenga, and Meyer 2002). To ensure that variation in the asymmetric component of variation wasn't being driven by left-right landmark placement error, the error term for each test was assessed by collecting landmark data for all individuals twice.

Next, we examined whether there was a significant correlation between nasal septal deviation and fluctuating asymmetry (i.e., does a highly deviated septum correspond to greater overall fluctuating asymmetry). Here, the magnitude of overall fluctuating asymmetry for each individual was calculated as the distance between the individual asymmetric shape configurations and the mean symmetric configuration. Distances were calculated using both raw Procrustes and scaled Mahalanobis distance values. Additionally, we used multivariate regression to determine the morphological relationship between the asymmetric component of shape for each region (dependent variables) and nasal septal deviation (independent variable). Using the regression coefficient vectors we visualized asymmetric shape changes via wireframe models. To assess the bivariate relationship between the asymmetric component of shape and nasal septal deviation, we plotted individual dependent shape scores, which are a combination of shape changes predicted by the regression and the residual (i.e., non-predicted) shape variation, against independent septal deviation values. To test for statistical significance in the relationship between region asymmetry and nasal septal deviation we used resampling procedures, i.e.,

10,000 randomizations of dependent and independent variables. All analyses were conducted using MorphoJ (Klingenberg, Barluenga, and Meyer 2002).

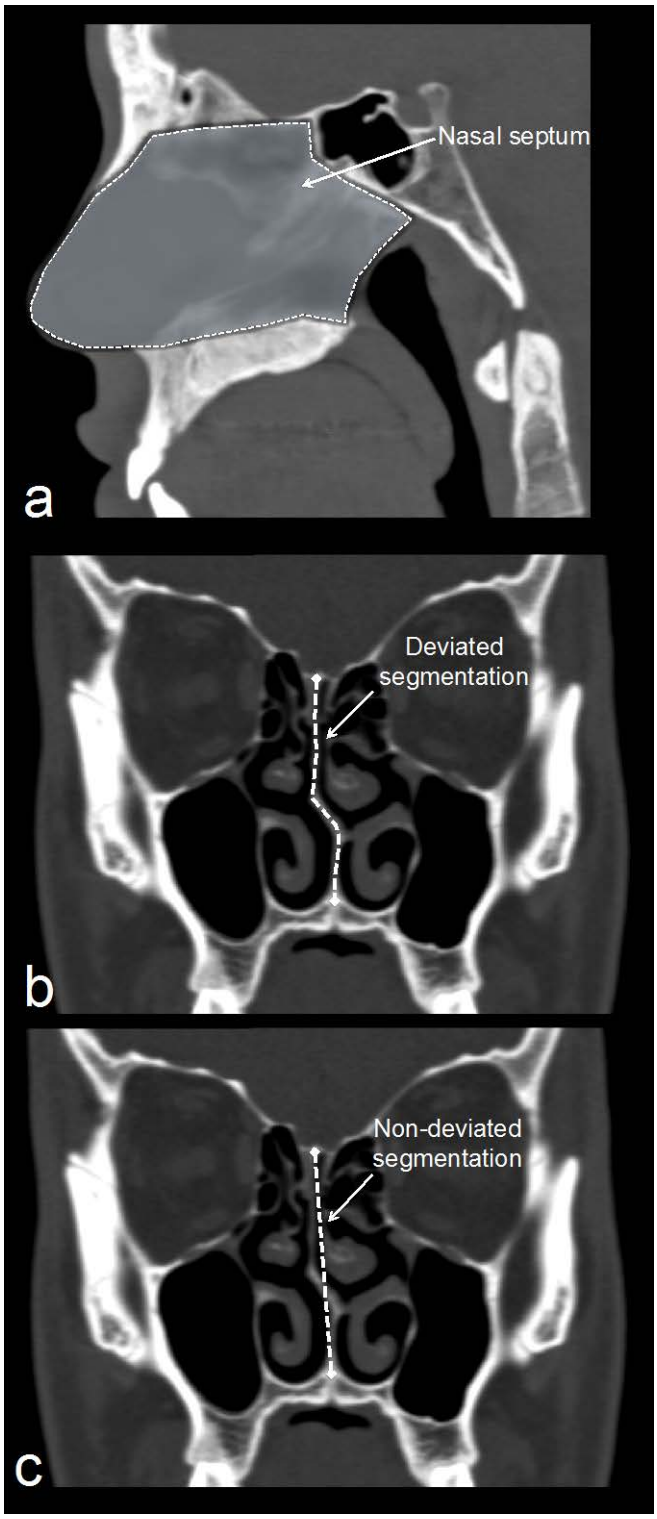

Figure 1. Nasal septal deviation was quantified by segmenting the nasal septum (a) using coronal sections (b) from the anterior to the posterior extent of the septum. Next, a midsagittal non-deviated volume that followed the borders of the nasal septum was segmented (c). Septal deviation was calculated as [(nasal septal volume/midsagittal volume) x 100].

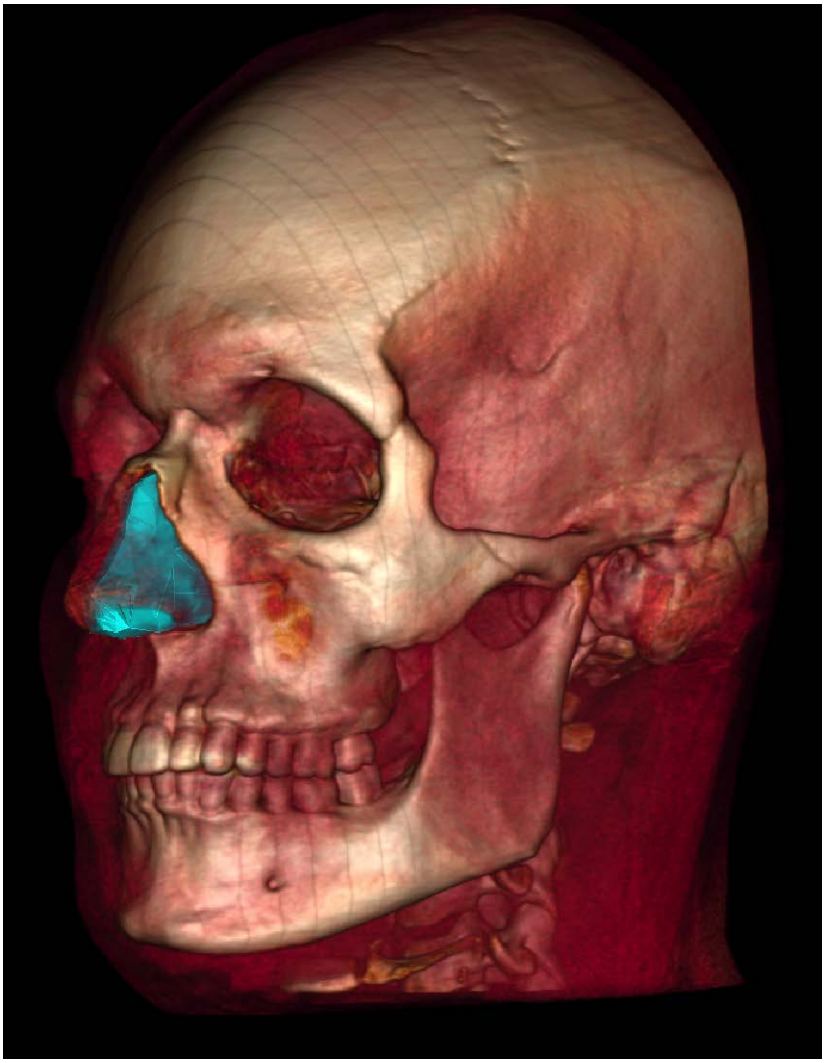

Figure 2. Three dimensional rendering of subject with reconstructed nasal septal volume (in blue).
Individual nasal septal deviation values were calculated as a percentage of nasal septal volume relative to the volume of the modeled 'non-deviated' septal volume [(nasal septal volume/midsagittal volume) x 100].

Table 1. Landmarks used to assess patterns of asymmetry in the nasal, palatal and lateral facial regions.

Landmark number	Landmark name/description	Region
1	nasion	nasal
2	rhinion	nasal
3	alare (Right)	nasal
4	alare (Left)	nasal
5	anterior nasal spine	nasal/palatal
6	A point	palatal
7	prosthion	palatal
8	lateral incisor/canine septum (right)	palatal
9	lateral incisor/canine septum (right)	palatal
10	ectomolare (right)	palatal
11	ectomolare (left)	palatal
12	zygomaxillare (right)	lateral facial
13	zygomaxillare (left)	lateral facial
14	orbitale (right)	lateral facial
15	orbitale (left)	lateral facial
16	frontomalare obitale (right)	lateral facial
17	frontomalare orbitale (left)	lateral facial
18	frontomalare temporale (right)	lateral facial
19	frontomalare temporale (left)	lateral facial
20	jugale (right)	lateral facial
21	jugale (left)	lateral facial
22	superior zygomaticotemporal suture (right)	lateral facial
23	superior zygomaticotemporal suture (left)	lateral facial
24	alveolar/palatal process junction at 25% cross-section (right)	palatal
25	intermaxillary suture at 25% cross-section	palatal
26	alveolar/palatal process junction at 25% cross-section (left)	palatal
27	alveolar/palatal process junction at 50% cross-section (right)	palatal
28	intermaxillary suture at 50% cross-section	palatal

29	alveolar/palatal process junction at 50% cross-section (left)	palatal
30	alveolar/palatal process junction at 75% cross-section (right)	palatal
31	intermaxillary suture at 75% cross-section	palatal
32	alveolar/palatal process junction at 75% cross-section (left)	palatal
33	posterior nasal spine	palatal
34	intersection between nasal septum and cribiform plate at 50% cross section	nasal
35	lateral most aspect of nasal cavity at 50% cross section (right)	nasal
36	lateral most aspect of nasal cavity at 50% cross section (left)	nasal
37	lateral aspect of nasal floor at 50% cross section (right)	nasal
38	lateral aspect of nasal floor at 50% cross section (left)	nasal
39	superior aspect of nasal septum at 100% cross section	nasal
40	lateral most aspect of nasal cavity at 100% cross section (right)	nasal
41	lateral most aspect of nasal cavity at 100% cross section (left)	nasal

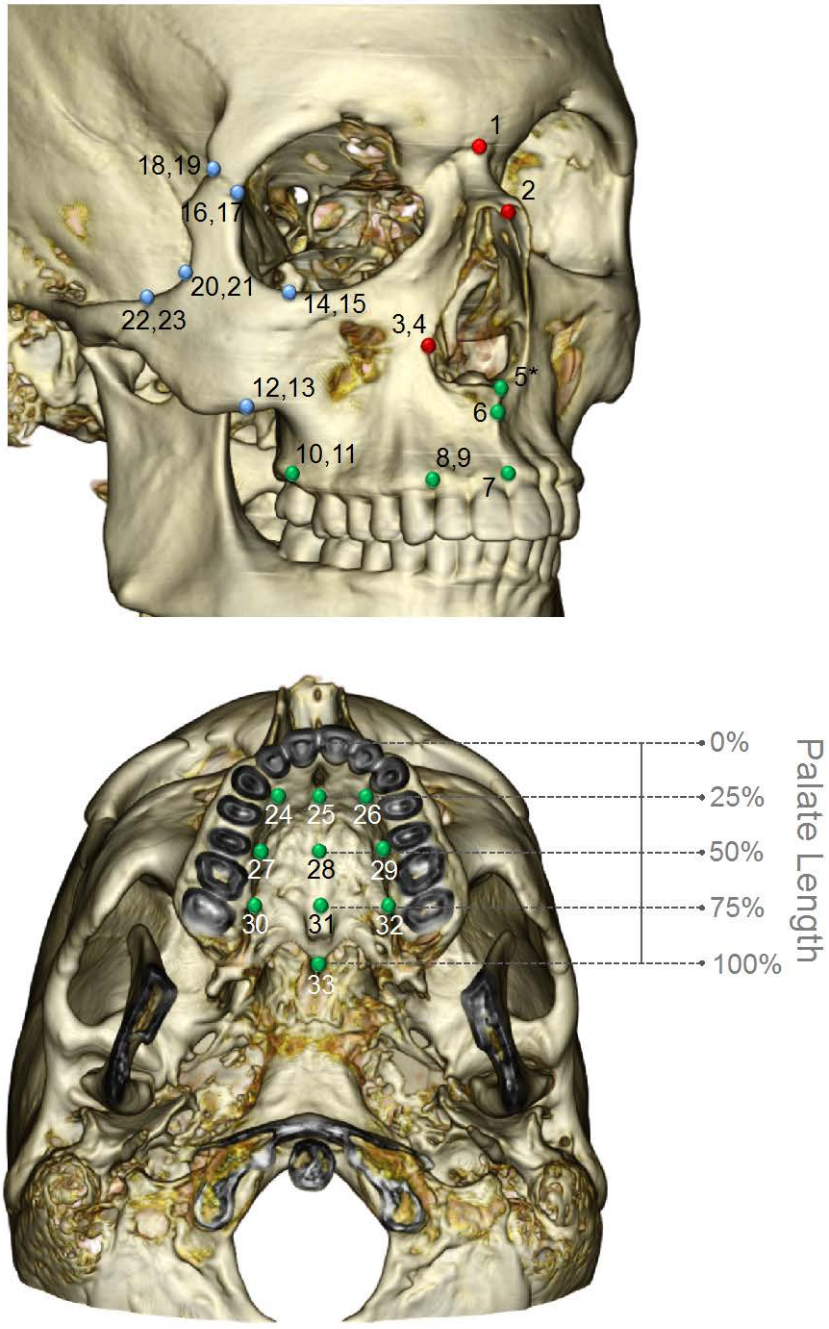

Figure 3. External skeletal coordinate landmarks used to assess asymmetries in the nasal region (red), palatal region (green) and lateral facial region (blue). See Table 1 for landmark descriptions.

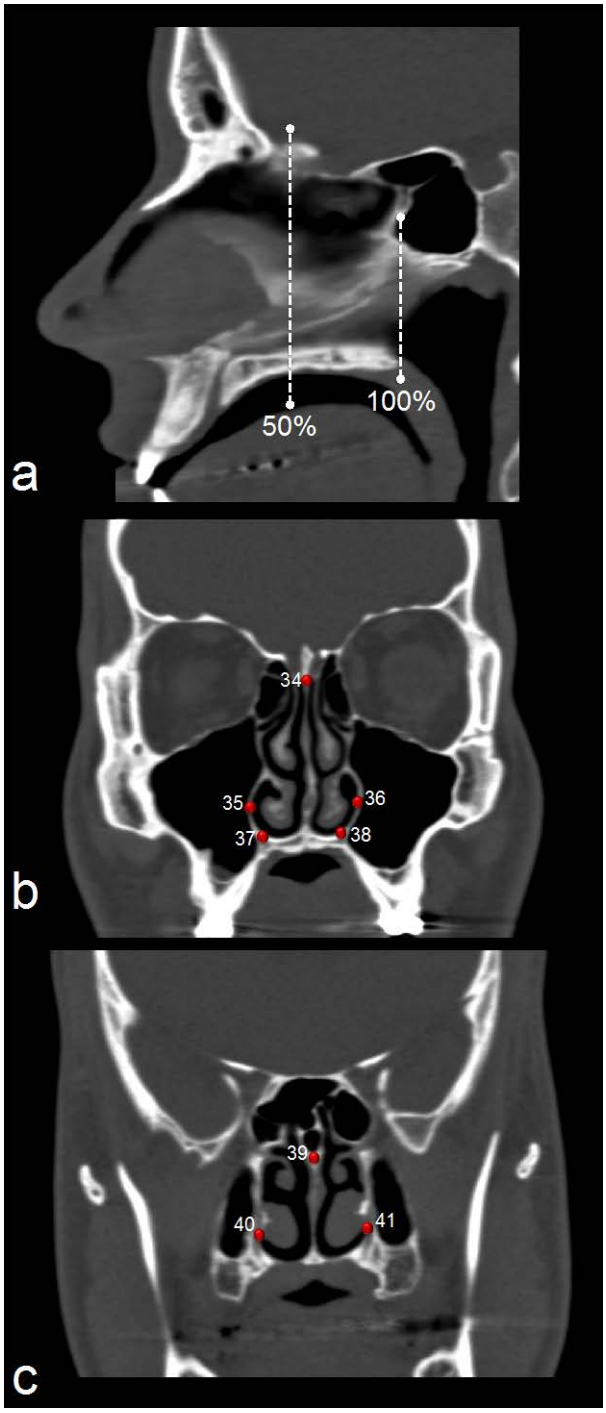
a
50%
100%
b
34
35
36
37
38
c
39
40
41

Figure 4. Internal nasal landmarks used to assess asymmetries in the nasal region. Landmarks were collected from two internal planes (a). The first plane was located at the midpoint of the nasal floor, i.e., 50% the length between the anterior nasal spine and the posterior nasal spine (b). The second plane was located at the posterior nasal spine, i.e., 100% the length of the nasal floor (c).

RESULTS

The results of our analysis indicate that there are significant levels of asymmetry in the nasal, palatal, and lateral facial regions as evidenced by the results of the ANOVA/MANOVA tests (Tables 2 and 3). It is important to note that the residual values are low indicating that error in left-right landmark placement has only a minor effect on the ANOVA/MANOVA results for fluctuating and directional asymmetry. Both tests reveal significant "side" and "individual x side" interactions indicating significant levels of directional and fluctuating asymmetry respectively for all three regions of the facial skeleton. Nevertheless, sum of squares (ANOVA) and Pillai's Trace (MANOVA) values for fluctuating asymmetry were greater for all comparisons. Thus, while directional asymmetry explains a significant amount of sample variation, fluctuating asymmetry explains more of the variation in the sample.

The correlation between fluctuating asymmetry distance values and nasal septal deviation are found in Table 4. Fluctuating asymmetry distance values are measures of deviation from perfect symmetry. As such, a greater distance value corresponds to a greater magnitude of total asymmetry for the given region (i.e., nasal, palatal and lateral facial). With regard to both Procrustes and Mahalanobis distance values, there were no significant correlations with nasal septal deviation. As such, when examining overall asymmetry in a region, an increase in the magnitude of fluctuating asymmetry for the nasal, palatal and lateral facial regions does not predictably correspond to an increase in the magnitude of nasal septal deviation.

Using multivariate regression, we were able to assess whether there were localized aspects of the overall pattern of nasal, palatal and lateral facial asymmetry that were significantly

correlated with nasal septal deviation. The results of our multivariate regression of septal deviation values and the asymmetric component of variation for the different regions of the facial skeleton indicate that in spite of the lack of correlation between deviation and distance values, deviation of the nasal septum is significantly correlated with certain aspects of asymmetry in the nasal (p=0.0484) and palatal (p =0.0138) regions (Fig. 5a and 5b). There was, however, no correlation between nasal septal deviation and the asymmetric component of the lateral facial region (p =0.6861; Fig. 5c).

Patterns of correlated asymmetry between nasal septal deviation and the nasal region are illustrated in Fig. 6 using wireframe models (see Figs. 3 and 4 for landmark reference). In all wireframe models, asymmetry is magnified. Note that magnification does not have an effect on the results of the analysis but is used to aide in the visualization of often-subtle albeit significant levels of asymmetry. The correlation between nasal septal deviation and the asymmetry of the nasal region is evident in the spatial relationship between the anterior nasal aperture, the plane of the internal nasal cavity (i.e., 50%) and the posterior nasal aperture (i.e., 100%). In particular, a deviated nasal septum was associated with asymmetries along the region of the posterior nasal floor such that there is a relative lateral deviation of the posterior nasal floor (landmark #'s 40 and 41) when compared to the position of the floor of the internal nasal cavity (landmark #'s 37 and 38).

In addition to the nasal floor, there is evidence of nasal asymmetry along the lateral walls of the external and internal aspects of the nasal region. With regard to the external nasal region asymmetry is evident in the relationship between the midline nasal aperture landmarks (landmark #2 rhinion, landmark #5 anterior nasal spine) and the alar landmarks (landmark #'s 3 and 4).

Similarly, the lateral aspects of the internal nasal cavity (landmark #'s 35 and 36) exhibit both lateral and vertical asymmetry relative to the midline.

Patterns of correlated asymmetry between nasal septal deviation and the palatal region are illustrated in Figs. 7 and 8. With regard to the anterior palatal region, the midline landmarks, i.e., ANS, A point and prosthion (landmark #s 5-7 respectively) exhibited a medial-lateral deviation from the midline. Additionally, relative to the anterior palatal midline, the incisor-canine septal landmarks (#'s 8 and 9) exhibited both anterior-posterior (Fig. 7) and superior-inferior (Fig. 8) asymmetries which affect the relative orientation of the anterior palate. Midline asymmetry is also present in posterior to prosthion in the anterior region of the midpalatal suture (landmark #25). In the more posterior aspects of the palate, there are clear asymmetries in the mediolateral position of ectomolare (landmarks #11 and 12) relative to the palatal midline. Further, there are medial-lateral and superior-inferior asymmetries in along the superior border of the lingual alveolar ridges (dashed lines in Figs. 7 and 8).

Table 2. Procrustes ANOVA results for the nasal, palatal and lateral facial regions.

	Effect	SS	MS	df	F	P
Nasal region	Individual	1.06093	1.091E-03	972	7.04	<0.0001
	Side	0.00433	3.093E-04	14	1.99	0.0159
	Individual x Side	0.11719	1.550E-04	756	9.3	<0.0001
	Residual	0.02933	1.667E-05	1760		
Palatal region	Individual	1.50517	1.115E-03	1350	10.06	<0.0001
	Side	0.00507	2.667E-04	19	2.41	0.0007
	Individual x Side	0.11371	1.108E-04	1026	5.78	<0.0001
	Residual	0.04637	1.916E-05	2420		
Lateral facial region	Individual	0.25915	3.428E-04	756	4.64	<0.0001
	Side	0.00268	1.786E-04	15	2.42	0.0019
	Individual x Side	0.05988	7.393E-05	810	24.69	<0.0001
	Residual	0.00477	2.995E-06	1595		

Table 3. MANOVA results for the nasal, palatal and lateral facial regions.

	Effect	Pillai's Trace	P
Nasal region	Side	0.42	0.0306
	Individual x Side	11.83	<0.0001
Palatal region	Side	0.61	0.0021
	Individual x Side	15.26	<0.0001
Lateral facial region	Side	0.54	0.0023
	Individual x Side	13.77	<0.0001

Table 4. Correlations (and *p* values) between fluctuating asymmetry scores and deviation for the palatal, nasal and facial regions.

	Procrustes distance	Mahalanobis distance
Nasal region	-0.010 (0.944)	-0.007 (0.958)
Palatal region	0.120 (0.381)	0.140 (0.307)
Lateral Facial region	-0.154 (0.261)	-0.129 (0.346)

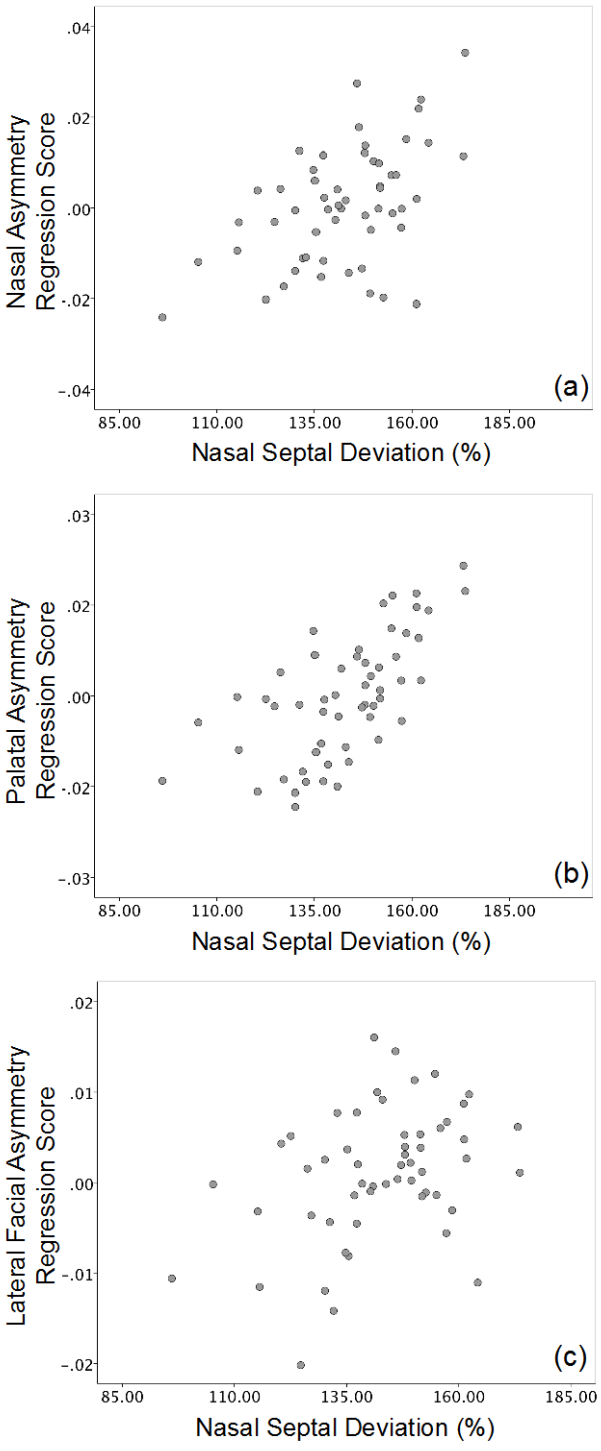

Figure 5. Scatter plot of shape scores of the asymmetrical component of variation against nasal septal deviation for the nasal region (a), palatal region (b) and lateral facial region (c).

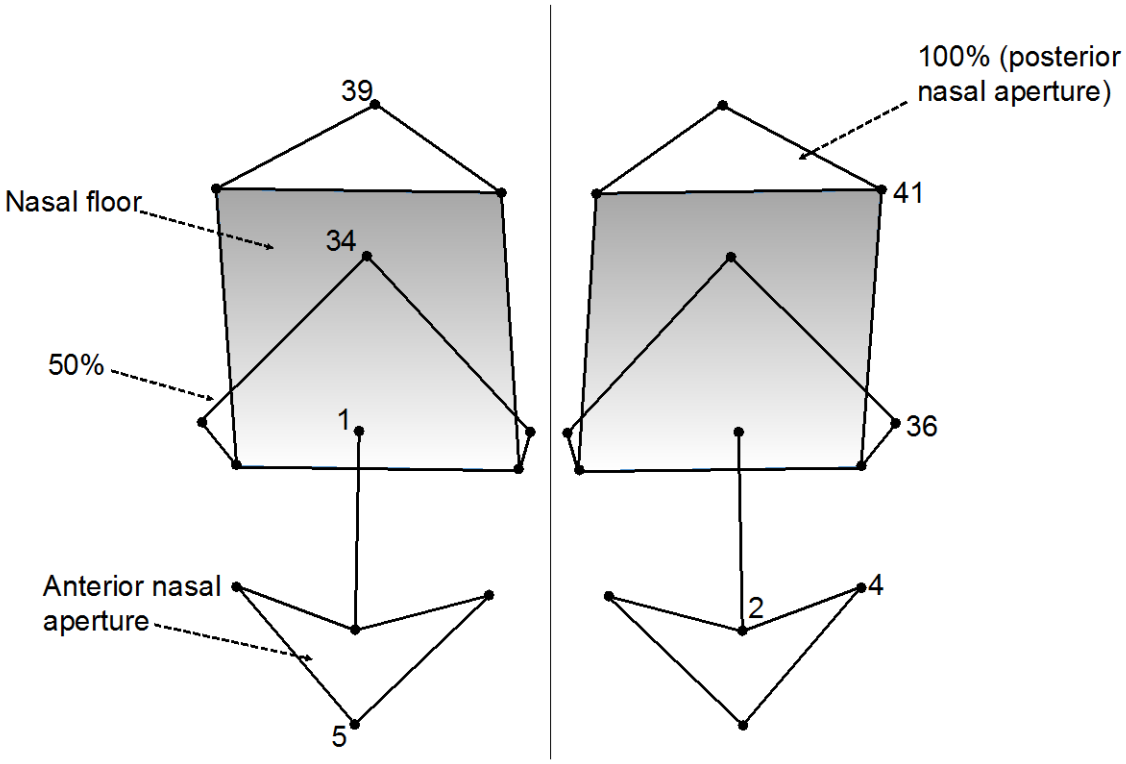

Figure 6. Mirrored wireframe models illustrating the pattern of asymmetry in the nasal region that is correlated with nasal septal deviation. Landmarks for the anterior nasal aperture are illustrated in Fig. 3 while internal nasal landmarks (i.e., 50% and posterior nasal aperture) are illustrated in Fig. 4. Landmarks are described in Table 1.

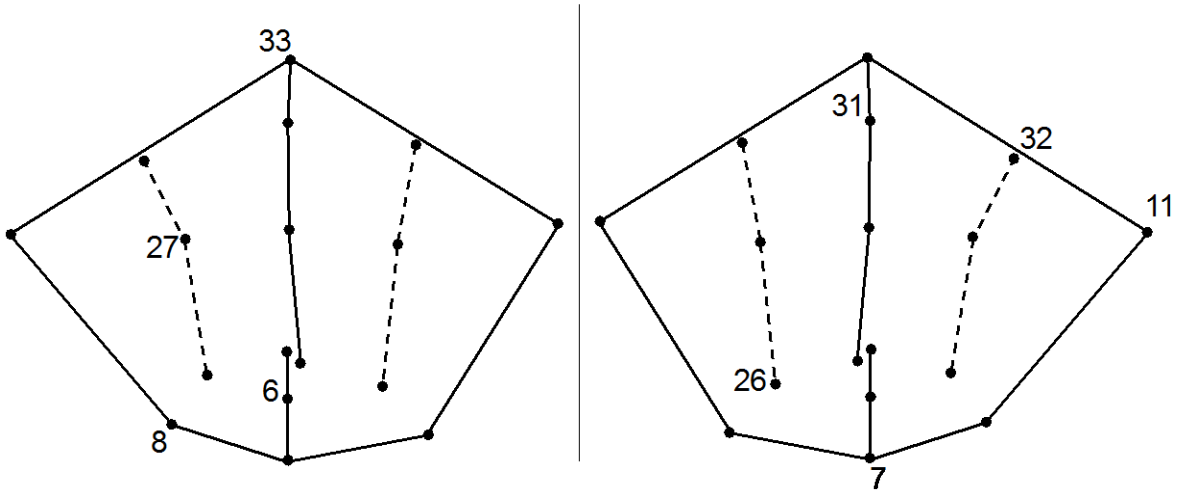

Figure 7. Superior view of mirrored wireframe models illustrating the pattern of asymmetry in the palatal region that is correlated with nasal septal deviation. Landmark numbers correspond to those illustrated in Figs. 3 and 4 and described in Table 1.

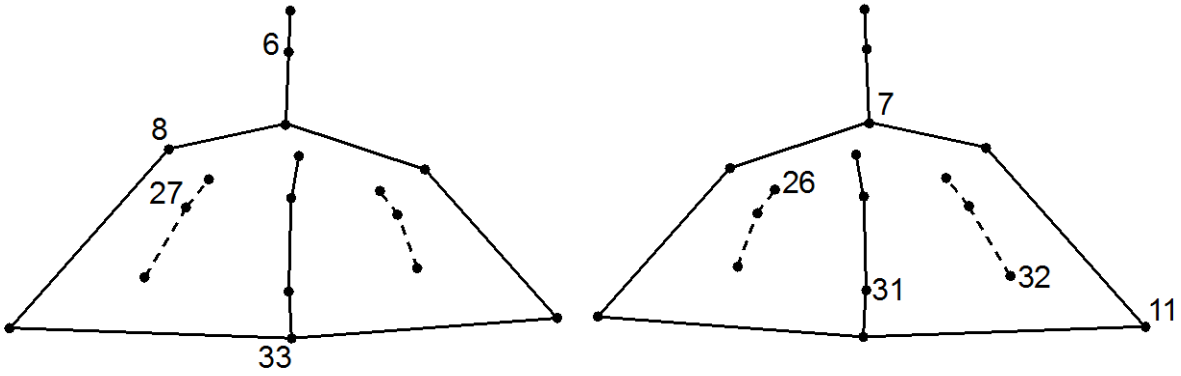

Figure 8. Anterior-inferior view of mirrored wireframe models illustrating the pattern of asymmetry in the palatal region that is correlated with nasal septal deviation. Landmark numbers correspond to those illustrated in Figs. 3 and 4 and described in Table 1.

DISCUSSION

The precise role of the nasal septum in facial growth is still an unresolved issue. While some researchers have offered evidence that the nasal septum acts as a key growth center (Scott 1953, Copray 1986, Sarnat and Wexler 1969, 1967b, 1966, WEXLER and SARNAT 1961b, Wealthall and Herring 2006, Nordgaard and Kvinnsland 1979), others suggest that septal growth plays more of a supportive role in facial development (Moss et al. 1968, Moss and Salentijn 1969, Siegel and Sadler 1981, Stenstrom and Thilander 1970, Cupero, Middleton, and Silva 2001). To further our understanding of the potential developmental influence of the nasal septum, we assessed the morphological relationship between nasal septal deviation and asymmetries of the facial skeleton. An association between septal deviation and facial asymmetry would be consistent with the nasal septal traction model, which posits that the nasal septum exerts a morphogenetic influence on surrounding skeletal tissues. While this relationship has been assessed using traditional morphometric methods of asymmetries measured from photographs and dental casts (Gray 1978, Pirsig 1992, Hafezi et al. 2010, Kim et al. 2011) to date there has been no study examining septal deviation and facial asymmetry using a geometetric morphometric analysis of three-dimensional data collected from CT scans. A lack of association between septal deviation and asymmetries of the facial skeleton would weaken thenasal septal traction model as akey player in facial development.

The results of our Procrustes ANOVA and MANOVA indicate that all three regions of the facial skeleton (i.e., nasal, palatal, and lateral facial) exhibited significant levels of fluctuating and directional asymmetry. Importantly, this asymmetry was not due to asymmetrical placement of the bilateral coordinate landmarks (i.e., observer error) as evidenced by the low error term for

Procrustes ANOVA models. Moreover, the results of our multivariate regression analysis indicated that there was a significant relationship between nasal septal deviation and localized asymmetries in the nasal and palatal regions. In contrast, there was no correlation between septal deviation and lateral facial asymmetries.

With regard to the nasal region, we found that nasal septal deviation was associated with nasal floor asymmetry. Particularly evident was the lateral deviation of the nasal floor in the posterior region when compared to the internal nasal floor. Asymmetry in height and width were not found. This result is most likely due to the close anatomical and developmental relationship between the nasal septum and the nasal floor. Following the nasal septal traction model, as the growing nasal septum places a mechanical force on the surrounding tissues (e.g., Copray, 1986), a deviation from normal midline growth may alter the direction of force of the expanding septum.

Interestingly, while our results suggest that septal deviation was associated with lateral nasal wall asymmetry, the degree of asymmetry is relatively minor when compared to the results of other studies. For instance, Hafezi et al., (2010) and Kim et al., (2011) found that lateral facial asymmetries correlated with nasal septal deviation in their samples. However, subjects used in these studies were selected from pools of patients who were undergoing corrective rhinoplasty/facial esthetic surgery in order to correct external and internal nasal septal asymmetries and therefore most likely exhibited a large magnitude of deviation. Unfortunately, given that we measured septal deviation by reconstructing three-dimensional septal volumes from CT scan data, rather than from photographs (Hafezi et al. 2010) or two-dimensional coronal CT images (Kim et al. 2011), we are unable to directly compare the range of variation in nasal septal deviation across studies. However, given that our study sample was selected to represent a

wide range of morphological variation in the septum (i.e., from no deviation to highly deviated), it is likely that our sample, on average, was less deviated when compared to other studies.

When compared with other septal deviation studies, our result may suggest that in samples with less deviation on average, the nasal airway and associated turbinates may act as a zone of accommodation, which buffers against the development of nasal wall asymmetries. It is possible, for example, that at reduced levels of nasal septal deviation, asymmetrical development of the turbinates (Egeli et al. 2004, Berger et al. 2000) may be sufficient to compensate for lower magnitudes of nasal septal deviation. In a similar fashion, this dynamic may also account for the lack of a significant relationship between septal deviation and lateral facial asymmetries documented by our multivariate analysis. Indeed, a recent study by Holton et al. (2013) found that the maxillary sinuses may also act as a buffer between morphological variation in the nasal region and the lateral facial skeleton.

It is also important to underscore that our inability to document a significant correlation between nasal septal deviation and asymmetries of the lateral facial region, in contrast to Kim et al. (2011) may be due differences in the quantitative methods between studies. In their analysis, Kim et al. (2011) found that nasal septal deviation was significantly correlated with asymmetry in the distance from the midsagittal plane to the zygomatic. This would indicate, in contrast to our results, that nasal septal deviation does have an influence on lateral facial asymmetries. However, based on their methodology, it is impossible to determine whether the asymmetry was being driven by deviations in the facial midline, or by asymmetry in the zygomatic region. In our study, we individually assessed the nasal, palatal, and lateral facial regions, using geometric morphometric techniques. This allows us to better isolate aspects of facial skeletal asymmetry

associated with nasal septal deviation suggesting that the lateral facial deviations documented by Kim et al. (2011) may be due to midline deviations rather than asymmetry in the zygomatic region.

The results of our analysis indicate that nasal septal deviation was further associated with aspects of palatal asymmetry. This result perhaps isn't too surprising given the relationship between septal deviation and nasal floor asymmetries. Specifically, asymmetry was present with regard to the width of the palate from midline to ectomolare as well as the width of the palate from midline to lateral palatal shelf—thus total width and alveolar process width are asymmetric. The greatest degree of correlated palatal asymmetry was in the anterior premaxillary region of the palate where there was both mediolateral and vertical asymmetry. Previous studies have underscored the close developmental relationship between the nasal septum and the anterior premaxillary region during early ontogeny as the growing nasal septal cartilage places tension on the premaxillary suture via attachment of the septopremaxillary ligament (Latham, Deaton, and Calabrese 1975, Gange and Johnston 1974, Mooney and Siegel 1986, 1991, Siegel et al. 1990). Moreover, Precious and Hall (2013) have emphasized that surgically repositioning the nasal septum to the midline during cleft palate repair is paramount to facilitating symmetrical facial growth. When the nasal septum is allowed to deviate from the midline asymmetries of the palate, lip, and nose develop (Precious, Delaire, and Hoffman 1988). While our analysis was conducted on adult subjects, and thus we cannot speak to the development of septal deviation and facial asymmetries in our sample, our results nonetheless indicate that nasal septal asymmetries are associated with premaxillary asymmetries after the cessation of facial skeletal growth.

In spite of the results of our multivariate regression, there was a lack of a correlation between septal deviation and asymmetry in Procrustes and Mahalanobis distance scores. Combined, these results suggest that while nasal septal deviation is correlated with aspects of nasal and palatal asymmetry, it is uncorrelated with the overall pattern of nasal and palatal asymmetry. This is due to other factors, independent of nasal septal deviation, that are likely influencing patterns of facial asymmetry in our sample. For example, bilateral asymmetry in tooth dimensions (Lundström 1961, Garn, Lewis, and Kerewsky 1966, Harris and Bodford 2007) likely affects asymmetric variation in dental arches. Similarly, asymmetry in the palatal and lateral facial regions are likely affects by jaw function and asymmetry in chewing side during unilateral mastication (Christensen and Radue 1985, Mc Donnell, Hector, and Hannigan 2004, Rovira-Lastra et al. 2014). Thus, while there is a significant relationship between nasal septal deviation and facial asymmetry, it is only one of many potential factors affecting variation in our sample.

While our analyses suggest that nasal septal deviation is just one contributing factor to facial asymmetries, our results nevertheless have orthodontic implications for understanding the etiology of certain malocclusions. The presence of anterior palatal asymmetries in the vertical and horizontal dimension near the incisor region may suggest that patients with nasal septal deviation are likely to have midline discrepancies and/or anterior incisor cants. More posteriorly, the asymmetry in palatal width might suggest these patients are inclined to have asymmetric arch forms and possibly be more inclined to have posterior crossbites or greater buccolingual dental compensations. Since our CT scans did not capture the lower arch, the presence of crossbites cannot be determined—however, this could be assessed in future studies with CT scans that include both the upper and lower arches. It should also be noted that previous

studies have shown that nasal septal deviation is associated with a dolichofacial morphology (Freng, Kvam, and Kramer 1988, Vig 1998, D'Ascanio et al. 2010, Harari et al. 2010). This suggests that the correlated patterns of asymmetry and septal deviation may be more common in vertical growers—thus a clinician should be aware of this correlation when considering treatment planning on a growing individual.

CONCLUSION

This study evaluated the correlation between nasal septal deviation and craniofacial asymmetries. We specifically looked at the correlation between nasal, palatal and lateral facial asymmetries with the presence of nasal septal deviation. Nasal septal deviation was correlated with asymmetries in the nasal region (e.g., nasal floor) and palatal region (e.g., vertical and lateral asymmetries in the anterior palate) but was uncorrelated with asymmetries of the lateral facial region. Our results indicated that nasal septal deviation did not show correlation with overall asymmetries in nasal, palatal, and lateral facial regions as a whole. The degree to which septal deviation can be viewed as a causal determinant of septal deviation, our results suggest its influence is significant however, it is only one of many likely causative factors. While the results of our study might suggest that patients with nasal septal deviation have palatal asymmetries that may predispose them to anterior midline discrepancies, incisor cants, asymmetric archforms, and posterior crossbites, further research is needed.

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