DEFINITION OF TOPOGRAPHIC ORGANIZATION OF SKULL PROFILE IN NORMAL POPULATION AND ITS IMPLICATION ON THE ROLE OF SUTURES IN SKULL MORPHOLOGY

A Thesis Submitted to the College of

Graduate Studies and Research

In Partial Fulfillment of the Requirements

For the the Degree of Master in the Department of Community Health and Epidemiology

University of Saskatchewan

Saskatoon

By

FARHAD PIROUZMAND, M.D., FRCSC

Keywords: skull shape, skull topography, cranial suture, factor analysis

Permission to Use

In presenting this thesis in partial fulfilment of the requirements for a Postgraduate degree from the University of Saskatchewan, I agree that the Libraries of this University may make it freely available for inspection. I further agree that permission for copying of this thesis in any manner, in whole or in part, for scholarly purposes may be granted by the professor or professors who supervised my thesis work or, in their absence, by the Head of the Department or the Dean of the College in which my thesis work was done. It is understood that any copying or publication or use of this thesis or parts thereof for financial gain shall not be allowed without my written permission. It is also understood that due recognition shall be given to me and to the University of Saskatchewan in any scholarly use which may be made of any material in my thesis.

Requests for permission to copy or to make other use of material in this thesis in whole or part should be addressed to:

Department Head, Community Health and Epidemiology

University of Saskatchewan

Saskatoon, Saskatchewan S7N 5E5

Canada

ABSTRACT

Objectives

The geometric configuration of skull is complex and unique to each individual. The main objectives of this study are two fold: 1) to provide a new technique to define the outline of skull profile and 2) to find the common factors defining the ultimate skull configuration in adult population. The secondary objective was to explore the effect of age and sex on skull shape formation.

Materials & Methods

Ninety-three lateral skull x-ray from the CT scan films were selected and digitized. The lateral skull surface was divided into 3 regions based on the presumed location of coronal and lambdoid sutures. A software program (Canvas 7) was used to match the outer surface of lateral skull with circular curves. Three main curvatures (frontal, parietal, occipital) were consistently identified to overlap the skull periphery. The radius, cord length and inclination of each curvature were measured.. Factor analysis technique was also used to reduce the number of variables explaining the overall shape of skull. Student t-test and regression analysis was also used to explore the effect of sex and age on skull shape.

Results

There were total of 93 patients in this study (54% male). The average values for three defined curvatures of the skull profile were recorded. Factor analysis produced 3 factors**.** The first factor explained 32% of total variance and was related to the overall size of the head as represented by total length and the radius of the curvature in vertex and back of the head. The second factor covered 26% of the variance representing the inverse correlation between the angle of the frontal and parietal curves. The third factor revealed the direct correlation of occipital and parietal angle. In all of these factors, the frontal zone variation was independent or opposite of the parieto-occipital zone. A strong direct association between the total length of skull, occipital curve radius and length with the sex was shown. No age related variable was identified.

Conclusions

There is a large variation in the values of different part of the skull. The skull profile topography can be defined mathematically by two distinct territories: frontal and

parieto-occipital zones. These territories hinge on the coronal suture. Therefore, coronal suture may play a dominant role in final skull configuration.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Abbreviation

BOG: Biorthogonal grids

CCA: Conventional Cephalometric Analysis

CT scan: Computerized Tomographic scan

EDMA: Euclidean distance matrix analysis

EFF: elliptical Fourier functions

FEM/FESA: finite element morphometry/ finite element scaling analysis

KMO: Kaiser-Meyer-Olkin

MAA: Medial axis analysis (or transformation)

MRI: Magnetic Resonance Imaging

MSA: Measures of sampling adequacy

TPS: thin-plate spline analysis

CHAPTER 1

INTRODUCTION

1.1 Background

The shape of skull is an integral part of our identity and important determinant of the esthetic balance in the face. This complex geometric shape is unique to each individual. Detailed study of the skull shape allows better quantitative definition of its curvature changes. To define these morphology quantitatively, one need reliable reference anthropometric data on the skull. These data serve two important purposes. The first is definition of the normal range of values in the population. The second purpose is provision of numerical data that can be analyzed mathematically for various comparative and analytic researches on the skull shape and growth. This potentially includes studies on the environmental factors and more fundamental forces affecting the ultimate shape of skull. There are obvious variations in the skull size and shape among people in the population. The variations in these surface parameters or measurements can provide potential clues to the factors affecting the differences in skull formation and growth. Deviation of these “normal surface values” in the disease state can be quantified and potentially helps to understand some of the mechanics of the underlying pathological processes.

Ideally, these data on skull morphology should be simple enough to have practical applications such as guiding skull defect reconstruction. This simplification also allows easier mathematical modeling for the research purposes. Traditionally the morphology of craniofacial structures is measured by cephalometric techniques. Cephalometry is defined as a radiographic technique for abstracting the human head into a measurable geometric scheme. The main application of cephalometrics is as a shape descriptor. Cephalometric radiography is used to describe the morphology and growth of the craniofacial skeleton, predict growth, plan orthodontic treatment, and evaluate treatment results. Most of these tasks require identifying specific landmarks and calculating various angular and linear variables.

The lateral view particularly the midsagittal vault profile has been frequently considered in evolutionary studies because of its recognized availability, usefulness, and evolutionary meaning. [1]

There have been many cephalometric measurements devised to allow accurate, reliable and valid measures of different facial and skull parameters. These however fail to define the 3-dimensional (3D) surface morphology of the skull.[2] In recent years with advancement in computer technology, the skull surface has been reconstructed using computed tomographic scan data. This technique has been used to fabricate the full-size implant models of skull defect with high precision. The size, shape, and curvature of the implants can be matched using computed tomographic data. These techniques require complex software with preoperative planning, prefabrication of skull surface (i.e. defect) and high costs, which hampers its widespread use. Currently, there are no simple normative values defining the geometric morphology of the skull surface in the literature.

1.2 Purpose of study

There were two primary objectives and one secondary objective for this study.

1.2.1 Primary objectives

I. The first objective of this study was to provide a new simple technique to define the skull profile based on the measurements of a group of people with no skull deformity. The resulting dimensions and coordinates should be easily digitalized to allow mathematical and geometric modeling of skull shape and its changes in health (e.g. normal variations, effect of age, sex, ethnicity, etc.) and disease states (e.g. Craniosynostosis).

II. The second main objective of this study was to find the common factors defining the ultimate skull configuration in adult population. Based on the obtained normative data, the main hypothesis in this study was that there are predictable forces (e.g. brain growth and suture fusion) affecting the skull growth and its final configuration. The detail analysis of the morphological diversity of skull size and shape in this study using factor analysis provides a system of the traits or common factors. These can simplify the definition the skull surface topography using only few factors.

These findings allow classification of the skull shapes or phenotypic variations as measured in this study into independent components. This helps to recognize the potential unique fundamental genetic forces regulating these complex components as biological systems.

1.2.2 Secondary objective

The secondary objective was to further explore the effect of ubiquitous and inherently influential biological factors of sex and age on the skull profile shape. This was done using independent statistical assessment.

1.3 Rational/Relevance

This study provides accurate and reproducible reference parameters of normative data in the studied population. The implications of these results are many fold. It allows longitudinal study of these parameters in the population. It also facilitates reconstruction of the skull defects and establishes a range of measures against which the abnormal skull shape (i.e. deformity) can be assessed.

Cranial defects resulting from congenital deformities, ablative resection of osseous tumors, traumatic injury, and destructive infectious lesions are often severe enough to warrant surgical reconstruction. In particular cases, satisfactory cosmetic results may be difficult to achieve because of the extent and location of the lesion. It should be noted that both severe congenital deformities and large cranial defect reconstruction are epidemiologically uncommon. There is no reliable figure on large (i.e.> 3cm in diameter) cranial defect in the literature. Currently at the author's hospital (Sunnybrook HSC, Toronto), there are about two to three major cranial defects per month is reconstructed. Similarly the figures at Sick Children Hospital at Toronto which is a major tertiary referral center for complex pediatric disorders are comparable to this adult hospital and relatively infrequent.

The other aspect of this study can provide insight into the more fundamental aspect of skull growth and its ultimate configuration using factor analysis. These data can guide further study for understanding the final pathways through interaction of multiple factors affecting various aspects of skull growth and shape formation.

CHAPTER 2
LITERATURE REVIEW

2.1 An overview of skull formation

The mammalian skull vault consists mainly of five' flat' bones, the paired frontals and parietals, and the unpaired interparietal; the lateral walls have contributions from the squamous part of the temporal bone (squamosal) and the greater wing of the sphenoid bone (alisphenoid). All of these bones are formed by intramembranous ossification within a layer of mesenchyme, the skeletogenic membrane, between the dermal mesenchyme and the meninges surrounding the brain. Between the interparietal bone and the foramen magnum (outlet for the spinal cord), cartilage derived from the sclerotomal components of the occipital somites ossifies to form the supraoccipital bone, which fuses with the membranous interparietal to complete the skull vault posteriorly. These bones are initially separated by the fibrous tissue of sutures, which are gradually filled up through sutural growth at the bony edges.[3]

Growth in the sutures is perpendicular to the orientation of the suture, and is normally maintained throughout the period of growth of the brain. Synostosis of one or more sutures is accompanied by compensatory growth, both in other sutures and by remodeling (appositional growth) of other parts of the skull. Bony fusion does not normally occur until an advanced age in the human skull, except for the metopic suture, which begins to fuse at around 18 months of age. In the mouse, only the posterior frontal suture (equivalent to the posterior part of the human metopic suture) undergoes fusion; the other sutures remain open throughout the short life (2–3 years) of the animal.[4] Appositional growth (remodeling) involves osteoclastinduced bone breakdown on the inner surface of the skull and osteoblast-mediated thickening on the outer surface. In the normal human skull this mechanism is important for adapting the degree of curvature of the calvarial bones to the changing circumference of the brain; in craniosynostosis it is an important compensatory mechanism for the premature loss of sutural growth centres.

Suture formation

Three of the calvarial sutures, the sagittal, metopic and lambdoid, are formed by the narrowing of membranous gaps between bones that are initially widely separate. Their positions overlie areas in which brain tissue does not lie close to the surface, i.e. the midline between the cerebral hemispheres and olfactory lobes (sagittal and metopic) and the area between the cerebral hemispheres and the cerebellum (lambdoid). The coronal suture does not form in the same way, and the parietal bone can be seen to overlap the frontal bone from the outset. This is a flexible joint and in newborn babies with very little hair, the overlapping bones can be seen to slide over each other to widen the suture when the baby cries and intracranial pressure rises. The coronal suture does not form over an anatomical landmark of the brain: the original position of the neural crest–mesoderm boundary over the telencephalon–diencephalon border is maintained as each cerebral hemisphere expands, extending caudally beneath the suture to attain the final anatomical relationship in which the suture lies over the cerebral hemisphere. The expanding cerebral hemispheres carry with them a covering of neural crest cells that form the meninges, which can be seen beneath the mesodermal parietal bone.

Insights into the molecular basis of suture formation and function have largely come from identification of the mutations underlying craniosynostosis syndromes. This knowledge of the genes involved in abnormal human development has been applied to experimental investigations in the mouse, so that we now have a growing understanding of the mechanisms of both normal skull growth and the biology of craniosynostosis.

Craniosynostosis: genes and syndromes

Until just over a decade ago, little was known about the causes of craniosynostosis. Since then, the identification of mutations in both syndromic and non-syndromic cases has led to considerable insights into the etiology, classification and developmental pathology of these disorders. The first mutation to be identified was a heterozygous missense mutation within MSX2, in patients with Boston-type craniosynostosis.[5] This is a rare syndrome, being confined to a single large family. MSX2 encodes a homeobox-containing transcription factor, and the mutation, which is within the homeodomain, acts by stabilizing DNA binding.[6] The majority of known genetic causes of craniosynostosis are mutations in the genes encoding fibroblast growth factor receptor types 1–3 (FGFR1, 2 and 3); other significant genes are TWIST1 and EFNB1.

The most common mutations in FGFR1, 2 and 3 that cause craniosynostosis and other skeletal growth disorders are dominantly acting and affect specific regions of the proteins. Most of the known mutations in FGFR3 are associated with growth disorders of the long bones (dwarfism), ranging from the relatively mild hypochondroplasia through the most common form, achondroplasia, to the perinatal lethal thanatophoric dysplasia.[7] FGFR3 also harbours the mutation underlying Muenke syndrome, the most common syndromic form of craniosynostosis, and a rare variant of Crouzon syndrome associated with the skin disorder acanthosis nigricans.

In early postnatal life the bones of cranial vault consist of single cortical plate. Later, they become thickened by endocranial and ectocranial deposition of bone with concomitant resorption of endosteal surface forming the middle diploic layer. The volume of brain is about 50% of the adult value at 1 year of age, 75% at 3 years, and 90% at 7 years. The growth in the cranial vault length and width follows the rapid gradient of neural tissue expansion. The size and shape of delicate human calvarium is mainly determined by underlying neural mass.[8] The dura mater is the inner periosteal lining of the calvarium. This layer is known to play the central role in regulating the growth of sutures in skull.[9-11]

There are many know factors that influence the skull morphology. The head form is one of the typical racial expressions. A long (dolichocephalic) head predominate amongst Europeans, Middle East and North America whereas Asian have a tendency toward flattened (brachycephalic) head. Males typically have a larger head circumference (approximately 0.9cm) than female. They also have more frontal bossing and occipital prominence.[12] Nutrition has also been implicated in skull growth. In rats, malnutrition leads to shortened neurocranial length, width and height.[13]

It is generally agreed that the morphogenesis and growth of bones of cranial vault is dependent upon brain growth. Bone is responsive to forces imposed on the skull, such as those due to contracting muscles and the expansion of the brain.[14] When dynamically loaded, bone cells undergo a cascade of responses, although the initial stage is not yet understood; the experimentally ascertained sequence of reactions involves an increase in intracellular osteoblast calcium and then an increase in protein kinase C activation, followed by expression of genes (including transforming growth factor b and insulin-like growth factor I) that is succeeded by osteoblast proliferation and matrix synthesis, resulting in mineralization.[15]

Resorption is also a critical part of the process as documented by the pathologies of skulls developing without functional osteoclasts. From what is known about the response of bone to physical forces, it is likely that these play a role in shaping and remodeling the skull. But it is unlikely that these directly canalize skull shape; according to one model, which is still admittedly controversial, it is not the bony phenotype but rather strain, measured by a ratio between the deformations induced by a force relative to the original dimension, which is regulated. Although strains vary across bones and ages, as do responses to strain [16], strains for particular bones appear to be maintained at nearly constant levels by the balance between deposition and resorption.[17]

After early deposition of bone on all the surface of cranial vault, the growth become more localized and occurs primarily by bone deposition at the sutures. The bone deposition will however, continue on both the endocranial and ectocranial sufaces[18-20] and continue through adulthood. These processes seem to be complementary findings at different biological developmental stages. The calvarial bones are passively displaced outwards, floating, as it were, on the expanding neurocranial content. At the same time individual bones are expanded by peripherally by osteogenesis at the margin.

At our present state of knowledge the growth function of sutures are regarded as independent from each other, and adaptive or restrictive to external influences depending on the circumstances such as age, their structure and location. Most of these studies are based on animal studies with different and sometimes conflicting results regarding the role of sutures in skull growth and formation.

2.2 Literature on skull normal values

Form can be considered as an aspect of fundamental importance in morphological investigations. Studies as diverse as classification of species or diagnosis in pathology are based on the analysis of form. All biological forms consist of a large number of shared aspects that include size, shape, colour, structure, patterning, etc. However, the numerical characterization of such forms has been more of a challenge than may be at first realized. This is especially the case in morphological studies of biological organisms, which tend to be irregular in form. Moreover, even such concepts as size, shape, and form have not been without controversy. For example, form and shape has been used interchangeably. According to Webster[21] form is defined as “shape or outline of anything; figure; image; structure, excluding colour, texture and density”. Upon looking up “shape” things become more confusing with shape defined as ‘… outline or external surface” or ‘the form characteristic of a particular person or thing”. According to these definitions, “shape” and “form” are interchangeable, to be viewed as identical. Clearly, this unsatisfactory state of affairs is in need of re-definition. To alleviate some of these problems, a simple linear formulation has been proposed[22] as: Form = Size + Shape.

Size can be defined as a quantity that depends upon dimensional space. In a one-dimensional world, difference in size can be viewed as a difference in vector length. In two dimensions, linear measurements in combination (such as ratio) have proved to be inadequate, and area becomes one definition of size. In three dimensions, volume would be the appropriate size quantity. Shape, on the contrary, is a quantity that is difficult to adequately define, but has been characterized as ‘residual’, or what is left after controlling for size. A more technical definition for shape has been proposed as that which remains invariant under scaling, translation, rotation and reflection.[23]

The methods currently available to evaluate craniofacial form include anthropometry, (stereo)photogrammetry, cephalometry, ultrasound, computed tomographic (CT) scanning, magnetic resonance imaging (MRI), and optical surface scanning. Arguably, cephalometry continues to be the most versatile technique in the investigation of the craniofacial skeleton because of its validity and practicality. Despite the inherent cephalometric distortion and differential magnification of the craniofacial complex, in comparison with newer imaging techniques, the cephalogram produces a high diagnostic yield at a low physiological cost.[24]

Nevertheless, there are problems in deriving a numerical representation of craniofacial form using cephalometry.[25] This is because ‘form’ is the combination of ‘size’ and ‘shape’ and separating shape from size is complex.[26] Perhaps the most important limitation of cephalometry relates to the errors inherent with the identification and recording of the structures therein. Because each cephalogram involves the exposure to a small, but not insignificant dose of ionizing radiation, they must be appropriately analyzed in order to obtain the maximum clinical information. The traditional method of analyzing cephalograms (conventional cephalometric analysis, CCA) has, in recent years, been supplemented with a variety of sophisticated morphometric methods.[24]

Analysis of the cephalogram

There are two distinct groups of scientifically valid analytical methods used in cephalometry: landmark-based techniques and boundary outline methods.

Landmark-based techniques are dependent on cephalometric landmarks: discrete points defined intrinsically in terms of the surrounding anatomy to represent the craniofacial form. As such, landmarks do not define the form of the object they represent; they lie upon it.[27] Landmarks convey information relating only to their location, providing no information either about the interlandmark or surrounding anatomy. In particular, landmarks cannot represent curving anatomy, and all are not equally valid and reproducible.

Landmark-based techniques include CCA, Procrustes superimposition techniques, Euclidean distance matrix analysis (EDMA), thin-plate spline analysis (TPS), biorthogonal grids (BOG), and finite element morphometry/ finite element scaling analysis (FEM/FESA). BOG has been superseded by FEM and is effectively redundant.

Boundary outline techniques do not require cephalometric landmarks to represent the craniofacial form. As their generic term suggests, they only investigate the shape of the perimeter of a structure. Medial axis analysis (MAA), resistant-fit theta rho analysis, eigen shape analysis, and elliptical Fourier functions (EFF) are considered under the boundary outline technique umbrella. MAA and EFF are both of relevance in cephalometry and are described in some detail below.

Conventional cephalometric analyses (CCA)

The use of algebraic measurements in traditional cephalometric analyses is now known as conventional cephalometric analysis. The simplicity of CCA ensures its universal clinical and research use. This method consists of linear measurements of distances, angles, and ratios. The four parameters employed in CCA are:

1. Linear distance measurements between two landmarks, such as articulare–gnathion, measuring mandibular length on the lateral cephalogram.
2. Angles, calculated from triplicate measurement of landmarks, e.g. SNA. Importantly, the size of angles varies with the relative spatial location of the landmarks (e.g. changes in the location of nasion).
3. Areas of triangles can be measured and summed, e.g. maxillary area on lateral cephalograms.
4. Ratios: usually of linear distance measurements.

These can be compared between images obtained at different magnification factors. Spurious correlation can arise when several ratios are calculated using the same denominator.

Limitations of CCA

CCA relies on the use of a reference structure for orientation and superimposition: the anterior cranial base (sella–nasion) in lateral cephalometry. This is assumed to be biologically constant. Apparent changes occur only in relation to this plane.[28] Even small changes in the anterior cranial base diminish its validity as a reference structure, rendering the localization of form differences between cephalograms difficult. Importantly, the use of a reference plane for the comparison of forms may be biologically meaningless. CCA is an excellent method of describing a regular object; however the craniofacial complex is an irregular biological structure. Although angles are size independent and have been coveted with having some relevance to shape, they cover large aspects of the craniofacial complex, failing to describe the information within the included angle.[29] As a result, CCA cannot adequately produce the shape detail demonstrated by the cephalogram, and is therefore not capable of fully evaluating craniofacial form.

Some landmarks used in CCA (e.g. menton) are neither 'co-ordinate-free' nor invariant[29], being dependent on a method of registration and superimposition. The location of many landmarks, e.g. Downs's points 'A' and 'B' on the lateral cephalogram, is related to the subject's head posture during recording of the image.

One of the most significant limitations of CCA is the lack of objectivity. Thus investigators can choose the landmarks to be recorded and select the variables to be measured. On occasion, these may be selected to demonstrate the results desired by the investigator.

Despite the numerous drawbacks associated with CCA, this user-friendly simple technique is likely to continue in routine clinical use to determine an individual patient's response to treatment or the effect of growth. Above all, the comparison of cephalometric data of individual patients to referent data can only be conducted using CCA

Geometric morphometrics

The term 'Morphometrics' is derived from the Greek words 'morph', shape, and 'mentron', measurement, used in contemporary investigations to define *size and shap.*[30] Size change refers to a proportional increase or decrease in all dimensions of the form under examination, often accompanied by a change in shape. Changes in shape require a change in the outline of the form under examination, often resulting from localized size changes.

The use of geometric morphometric tools in the analysis of form is also known as statistical shape analysis. The sophisticated morphometric techniques of Procrustes superimposition, EDMA, TPS analysis, FEM/FESA, and EFF produce unambiguous shape information *if the forms under comparison are scaled to an equivalent size beforehand*. The mathematical elegance and rigor of these techniques avoids the necessity for registration and superimposition— a prerequisite when using CCA. Therefore, any changes in the relative spatial relationship of the landmarks are solely due to shape changes. Furthermore, morphometric techniques allow the integration of the distinct information present in cephalometry: geometric *location* and biological *homology*[31], regardless of whether the information is collected using landmarks or outlines.

EFF and MAA are techniques that are particularly useful for analyzing the shape of outlines of structures, especially where viable landmarks do not fully represent the curving biological form, such as the lateral cephalometric mandibular outline. Because they do not rely on individual landmarks, they are not limited by the inherent error of landmark identification.

The EFF technique was developed originally for military aircraft identification[24] and like conventional Fourier functions is a curve-fitting procedure. The basic principle involves embedding a set of closely spaced observed measurements on an object's boundary into a mathematical function.

MAA is a geometric transformation of an outline identifying a branching set of points constituting the middle of a form[24]. The medial axis can be considered as conjoined centers of circles maximally contacting the shape boundary. Where a circle contacts more than two points on the shape boundary, a branch point is identified for the medial axis. This axis, in addition to the expression of its distance from the peripheral boundary, provides shape information, independent of size. A series of measurements can also be derived from the medial axes and statistically tested using univariate and multivariate techniques. The complexities of medial axes and the measurements derived from them mean that MAA is not useful for the clinical management of individual patients.

All the above techniques require intense mathematical analysis and multiple point registration of specific shape outline.

Normal cephalometric data have been traditionally used to define geometric characteristics of the face and skull.[32-34] This standard information has been instrumental in orthodontic diagnosis and treatment.[35-42] These data also need to be standardized for age, sex and ethnic groups which can influence the skull morphology. The reference points for skull definition are usually on the skull base or surface, sometimes difficult to accurately define and only provide linear (i.e. distance) or angular measurements. To our knowledge, there is no reliable curvature measurement of the skull surface published in the past. The described method in this study can obviate some of the sources of error in the measurement even for linear skull values by using digitized tracing method for different cephalometric reference points and curvatures.

2.3 Literature on skull reconstruction

Bony reconstruction of the skull defects especially for the large ones remains challenging.[43;44] Current reconstructive surgery techniques include a combination of autogenous, allogenic, and prosthetic materials.[45-48] With new advancement in the field of tissue engineering, the recombinant proteins, gene transfer, and cell-based strategies are being developed to augment the skull reconstruction.[49] In recent years with the aid of complicated computer software and high-resolution three-dimensional computed tomographic scan, these defects can be fabricated using various alloplastic materials.[50;51]

A major problem in craniofacial reconstruction has been the complex patient-specific geometry of the skull, which has posed problems in both preoperative planning and postsurgical rehabilitation, often with poor aesthetic and functional results due to intraoperative modeling of implants. Computed tomography data have been used since the 1980s, first for visualization and later for prefabrication of customized prostheses. Three-dimensional reconstruction of computed tomography images was first described in the mid-1980s, with various groups describing its utility in preoperative planning for craniofacial surgery, in the form of a surgical simulation program before craniofacial surgery and for fabrication of life-size skull models. There are generally two methods in preparation of computer-designed prosthesis: Indirect and direct methods.[52]

A) Indirect Methods

Implants were first manufactured using an indirect method, with computer-based models first assembled from three-dimensional reconstruction of computed tomography images; these were then used to create individual physical models or molds, which in turn were used to fabricate the prosthesis. Toth et al.[53] used a computer-controlled milling device to fabricate prostheses, which were then demonstrated in a six-patient case series where they were used as alloplastic implants, templates to fashion autogenous bone grafts, or models for tissue removal. The use of life-size models to manufacture craniofacial implants has also been described for titanium. More recently, computed tomography–guided stereolithography has been described in the manufacture of models for preoperative planning and prosthesis fabrication. Briefly, complex anatomical models can be fabricated by polymerization of ultraviolet light–sensitive liquid resin using a laser beam, from computed tomography data. Stereolithography models were used to manufacture ceramic implants for orbital reconstruction as well as to fabricate customized cranial titanium plates, carbon fiber–reinforced polymer implants for cranioplasty, and hydroxyapatite implants for reconstruction of very large and complex cranial bone defects.

B) Direct Methods

The use of solid freeform fabrication technologies for the direct manufacture of implants, not requiring a model or mold, is a more recent innovation. The accuracy, ease, and fit of these implants, which do not require indirect modeling based on life-size models, allow for even more precise prostheses. The accuracy of methylmethacrylate prostheses fabricated by Toth et al.[53] using an indirect method were about 2 percent. Eufinger and Wehmoller[54] described the prefabrication of titanium implants using a direct method, achieving a precision of 0.25 mm with implants of up to 18 cm (about 0.1 percent). In all case, the duration of surgery was reduced dramatically and predictable and constant clinical and radiological results were obtained. Costs were high (up to $7000 per implant), however, and wound healing was uneventful in all but one case.

There are several limitations with these techniques such as the preparatory stage of alloplast fabrication prior to the plan reconstruction, finding the suitable alloplast materials for shaping, sterilization and durability, inability for intraoperative modification of the defect size and the cost. These are among some of the limiting factors hampering their generalized use. One of the best materials for the graft is autogenous material which is not amenable to preoperative molding based on 3D CT scan. By having general guidelines for the size and shape of different regions of the skull as provided partly in this study one can approximate the skull shape with either autogenous or alloplastic materials intraoperatively. This becomes more manifest in reconstructing large cranial vault defects.

CHAPTER 3
METHODS

3.1 Study design

This is an exploratory-analytic study based on the cross-sectional collection of skull profile data over a 3-month period. The source for the collected data on this case series was almost equally divided between two different centers (Sunnybrook Health Sciences Centre, Toronto and Royal University hospital, Saskatoon). The selection process of study subjects was based on haphazard selection of CT scans in each study day. The retrieval of any patient's CT scan was essentially based on picking every other 10 consecutive CT images of the brain in either institute for the day of image collection.

3.2 Sample size

The main determinant of the sampling size in this study was the requirements for the analytic portion of the study (i.e. factor analysis). It is generally recommended that the required variable to subject ratio lies between 1:5 and 1:10, with the former being absolute minimum and the latter being sufficient[55]. There are several measures of sampling adequacy that can be used to confirm the adequacy of sampling size in a specific study. One of the initial requirements for factorability of a data matrix is presence of several sizable correlations in the correlation matrix, quantitatively with coefficient of .3 or greater.

The diagonals of anti-image correlation matrix are another way to assess sampling adequacy of each variable hence called measures of sampling adequacy (MSA**).** This range 0 to 1 where 1 indicates each variable is perfectly predictable from others. The MSAs should be a coefficient of .5 or more for each of the variables and variables with an MSA of less than .5 should be excluded from the analysis.

Kaiser-Meyer-Olkin (KMO) measure of sampling adequacy and Bartlett's test of sphericity are also tests used to determine the factorability of the factor matrix as a whole. The KMO measure provides a value between 0 and 1. Small values for the KMO indicate that a factor analysis of the variables may not be appropriate, since the correlations between variables cannot be explained by the other variables. The values above 0.5 are considered satisfactory for factor analysis.

Bartlett's test of sphericity is a test statistic used to examine the hypothesis that the variables are uncorrelated in the population. In other words, the population correlation matrix is an identity matrix; each variable correlates perfectly with itself (r = 1) but has no correlation with the other variables (r = 0). The Barlett's test should be statistically significant (i.e. p value < .05).

The number of subject needed to allow meaningful factor analysis was set as about 10-15 subjects per selected items in this study (total subjects=93). There were many significant correlations (i.e. greater coefficients of.3) in the descriptive correlation matrix. The MSA coefficient was more than .6 for all the diagonal measures. The measure of sampling adequacy for this factor analysis with Kaiser-Meyer-Olkin measure was 0.6. The Bartlett's test of sphericity was also significant (P<.000). These are supportive value indicating adequacy of sample size.

3.3 Population

Ninety-three lateral skull x-rays from the CT scan films were (see above under section 3.1 for the procedure) selected from the radiology department pool in these two hospitals over three months (based on the availability of the researcher) for radiographic assessment. The reasons for radiological investigation were generally either trauma or suspect brain lesions (without any known effect on the skull shape). Exclusion criteria were as follow: Poor visualization of skull landmark for accurate measurement, known craniosynostosis or skull deformity, hydrocephalus, age less than 10 years. The final number of selected cases in each day of data collection was about 5% of the all brain CT scans done in that day.

3.4 Measurement procedures and instruments

Lateral scout skull x-rays from the CT scan with appropriate printed scale were collected. These were either photographed in an standardized fashion with digital camera (Olympus , model C3040) parallel to and 30 cm from the CT scan film or imported directly as digitalized image from the radiology department. The image data were then imported and saved into a secure central computer. The lateral skull surface was artificially divided into 3 regions based on the presumed location of coronal and lambdoid sutures. In these areas there were consistent changes in the degree of surface skull curvature. Using a graphic software program (Canvas 7, Denebra system Inc., Miami, Florida), the best possible circular curvature fit for each 3 parts of the calvarium outlines were drawn and overlapped on the skull margins. The criterion for matching curvatures was to fall within 5 mm of skull outer margin. The most anterior portion of skull just over supraorbital region and frontal sinuses were not included in the measurements due to local variation in the size of the sinus. Overalls, 3 main curvatures (frontal, parietal, occipital) were consistently identified to overlap the majority of skull periphery in each patient (Fig. 3.1). These curvatures were called “zone” one to three respectively. To allow the measurement of different orientation (i.e. angle) of these three curvatures in relation to the skull base, a reference line was drawn from the inferior orbital margin to external auditory canal (i.e. Frankfort line). For each curvature three parameters were measured and recorded as follow: radius, cord length and inclination of each curvature (angle between the cord length line and Frankfort horizontal line). The largest distance between the frontal and occipital bones was also measured to represent the overall length of skull and to allow proportional comparison of the length of each curvature in the study population based on the overall skull length. The Canvas 7 program was used to record all of the skull measurements. All the data were stored in the computer hard drive and final measures on each skull were printed on the paper for permanent storage. The process of selection and retrieval of x rays, digitization, curve match, various measurements and storage was somewhat labor intensive and required average of 1-2 hour time for each case. The above described procedure for curve definition, selection and measurement techniques were not previously described in the literature. Therefore, appropriate analysis for reliability of this technique was included in this study.

3.5 Analysis

3.5.1 Descriptive (first primary objective)

The measurements from corresponding parts of the skull (i.e. different zone values) were averaged together and SD, maximum and minimum for each measure was calculated. Pearson correlation coefficient was used to assess the relationship between different measured components of each curvature. The p value of less than 0.05 was considered significant

3.5.2 Factor analysis (second primary objective)

Factor analysis technique was used to explore more fundamental variables explaining the overall shape of skull.[56;57] In general, the purpose of the factor analysis is to describe and explain a large set of independent variables by a few underlying new (hypothetical) variables, called factors. Factor Analysis can be conceived of as a method of examining a matrix of correlations in search of clusters of highly correlated variables. A major purpose of factor analysis is data reduction, i.e., to reduce complexity in the data, by identifying underlying (latent) clusters of association.[58]

If a variable correlate well with the factor, it is perceived to "load" meaningfully on that factor. By studying the degree of factor loading, which is interpreted as a correlation coefficient, one can determine how well the factors explain the data. A group of items in an outcome scale may represent any number of underlying factors, from single factor to the total number of items. In the latter case, each item represents a unique factor, which is an undesirable property for outcome scales. In general, an ideal scale represents a small number of underlying factors.

There are many steps in performing factor analysis. The issue of factorability and sampling adequacy is described in above section (3.2). An acceptable factor analysis provides factors which explain majority of the variance in each independent variable. The communality is the proportion of explained variance for each variable. Mathematically, it is sum of the squared loadings for a given variable across factors. It ranges between 0 and 1. Low communalities mean there is considerable variance unexplained by factors extracted and may need to extract more factors. A good factor solution is one that explains the most variance with the fewest factors. The result is typically acceptable when 50-75% of the variance explained.[59]

The ideal number of factors is a subjective process but one usually consider the theory behind the study, eigen values, scree plot result and interpretability of last factor. One usually seeks to explain maximum variance with few factors and aim for 50-75% of variance explained with one-quarter to one-third as many factors as variables/items. The extracting factors should stop when they no longer represent useful characteristics of the variables being analyzed.

The eigen value is the sum of squared correlations for each factor and demonstrate the overall strength of relationship between a factor and the variables. Each successive eigen values have lower values and the values over 1 are stable and used as selection criterion for factor derivation. Scree plot is a graphic representation of eigen values. It depicts the percent of variance explained by each factor. In this graph one look for the point where an additional factor fails to add appreciably to the cumulative explained variance. The first factor explains the most variance and last factor explains the least amount of variance. The “elbow” in the curve - point where additional factors don’t add much to explained variance is usually the cut-off point for selection of factors.

Interpretability of the obtained factor is the ultimate goal of this technique. Unless we can determine what characteristics or trait a given factor measures it is seldom wise to study that factor. Factor loadings in the ‘unrotated’ matrix are difficult to interpret. To find a more easily interpretable factor structure it is usually necessary to ‘rotate’ the factor loading matrix. Two basic types of factor rotation are orthogonal and oblique. The underlying assumption in orthogonal rotation is that the subscale formed from the factors are independent of each other (i.e. they are uncorrelated). The oblique variation allows factors to covary and probably more realistic in health sciences.

Factor loadings tell us about relative importance of each item to each factor. Usually there should be at least 3 items per factor. The more items per factor provide more reliability.

In this study data reduction using factor analysis with varimax rotation (a form of orthogonal rotation) was used to explore the potential correlation among different measurements of each curve (i.e. angle, radius, cord length). This provides more easily interpretable results. Absolute loading of more than .4 and single loading were considered for factor analysis.

It is clear that these obtained factors are subject to measurement error. The reliability of these factors refers to the extent to which they are free of measurement error. To assess the reliability of the obtained factors, two techniques were used. First, the internal consistencies of each produced factors were assessed. This refers to how well the items that make up each factor fit together. If a given set of items that make up a factor are homogeneous, it would be expected that the correlation among these items would be high hence having high internal consistency. In this study, the Cronbach's alpha method was used to evaluate the internal consistency of each obtained factors. Second, the temporal stability of the raw data was assessed by repeat measurement of the original variables of the skull shape (all ten) using the same technique (as described in measurement section above) by the same individual (F.P.). This re-measuring technique called test-retest reliability assesses the random error inherent in the observed values. To establish test-retest reliability 10 patients were selected randomly from the overall pool of patients in a blinded fashion by the same investigator. The corresponding Pearson correlation coefficient in each measurement group (curvature radius, cord length or angle) was recorded to provide an objective tool for reliability of the raw measurements.

3.5.3 Secondary analysis (secondary objective)

The sex and age are two inherently strong biological factors affecting the phenotype of every individual Therefore in this study the effect of sex and age on the skull profile shape was independently assessed. They were not included in the factor analysis due to the fundamental difference of these types of variables (i.e. anatomical values defining a single shape versus non-anatomical variables such as sex and age). Regression analysis provides a powerful statistical approach for explaining and predicting quantifiable outcome measures such as skull shape. Multiple regression analysis can examine multifaceted relationship of several factors in predicting the skull shape. This technique was used to look at the possible effect of age on the overall skull length and also forehead characteristics.[60] The front al angle was selected as the representation for the forehead prominence and the total length of skull as overall index of skull volume.

The stepwise procedure was used to maximize the consistency of prediction with the smallest number of predictors. Typically backwards elimination has an advantage over forward selection and stepwise regression because it is possible for a set of variables to have considerable predictive capability even though any subset of them does not. Backwards elimination starts with everything in the model, so their joint predictive capability will be seen.

The univariate analysis using Student's T-Test was chosen to assess the possible association between any of the studied skull shape variables and gender. This technique was selected mainly due its simplicity of calculation and interpretation. The P value of less than 0.05 (2-tailed) was considered significant for all the above statistical analysis.

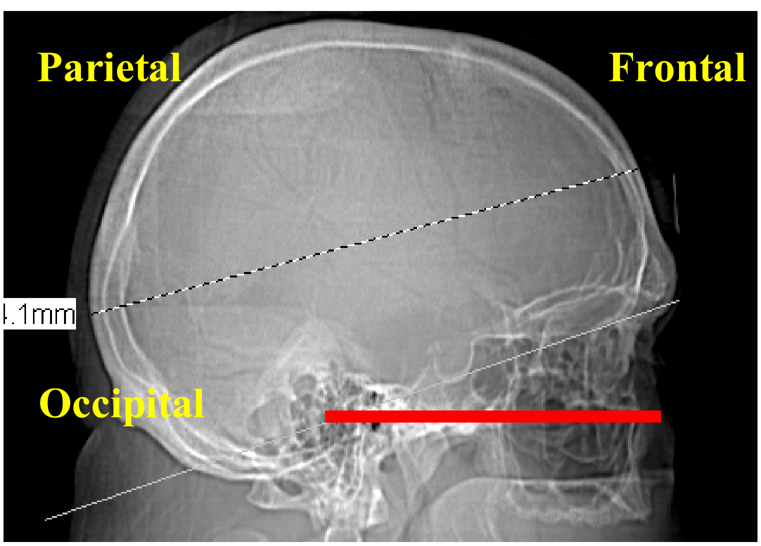

Figure 3.1 The 3 main curvatures of skull (i.e. frontal, parietal, occipital), fronto-occipital distance and Frankfort line (red thick color) are shown.

CHAPTER 4

RESULTS

The results are presented in three subsections corresponding to the two primary objectives and one secondary objective. The first section examines univariate measurements of skull shape in the studied population while the second looks at the evidence for more basic and fundamental factors that explain the variable skull shape in the populations. The last section describes the effect of sex and age on skull shape.

4.1 Developing average values for three different defined curvatures of the skull profile

There were total of 93 patients in this study. Most were male (50/93). Their age was ranging between 11 and 92 years (mean = 54 years). Table 4.1 demonstrates quantitative values for different curvatures of the skull profile.

Table 4.1. Descriptive data on the characteristics of individual measures (all linear measurements are in mm).

	N	Range	Minimum	Maximum	Mean		Std. Deviation
					Male	Female	
Radius Frontal Curve	93	53.1	43.8	96.9	69.2	66.8	9.4
Radius Parietal Curve	93	43	54.2	97.2	76.9	75	8.2
Radius Occipital Curve	93	27.4	46.9	74.3	59.9	57.7	4.9
Length Frontal	93	45.4	57.8	103.2	89.1	86.4	8.8
Length Parietal	93	59.5	98.1	148.6	114.7	110.4	11.6
Length Occipital	93	41.9	80.4	122.3	105.9	100.5	7.9
Length Total	93	52.9	152.5	205.4	185.5	177.4	11.5
Angle Frontal (degree)	93	27.4	32.5	59.9	45.3	45.7	4.4
Angle Parietal(degree)	93	25.7	7.2	32.9	23.6	22.8	5.5
Angle occipital(degree)	93	30	99.8	129.8	118.3	118.3	5.4

4.2 Identifying the common factors determining formation of defined skull curvatures

The main analytic results were through the exploratory factor analysis. Before proceeding to factor analysis, we chose seven most relevant values (i.e. variables) among all the ten collected values to allow more accurate estimation of different factors by reducing the number of variables. The removed variables were the cord length of each curvature. The rational for this omission was that these measures are highly correlated with the radius size for each curve and therefore mostly reflected by radius values (This data is clear in the correlation matrix and is not shown in here).

The first step in factor analysis is the creation of a correlation matrix for all the relevant test items as shown in Table 4.2. This reveals sufficient number of significant correlations above .3 among items to justify undertaking the factor analysis on these data.

Table 4.2. The correlation matrix summarizes the association among 7 selected independent variables in skull profile.

	Radius frontal	Radius parietal	Radius occipital	Length total	Angle frontal	Angle parietal	Angle occipital
Radius frontal				.3	-.4	.4	
Radius parietal			.3	.6			.3
Radius occipital		.3		.6	.3		
Length total	.3	.6	.6		-.4		
Angle frontal	-.4		.3	-.4		-.3	-.3
Angle parietal	.4				-.3		.6
Angle occipital		.3			-.3	.6	

Only the Pearson's r values at or above absolute .3 with significant correlation (i.e. $p<.05$) are shown.

In this study to estimate how many factors may explain the skull profile's different values, we examined the scree plot (Fig. 4.1) and also select factors with eigen values over 1 (Table 4.3). The plot scree breakage point is between the factor 3 and 4. The eigen value is above 1 for the first three extracted factors. Therefore, these three factors were selected for the analysis.

Table 4.3. The eigen values for the extracted factors are shown.

Component	Initial Eigenvalues	% of Variance Explained	Cumulative % Explained
1	**2.268**	**32.406**	**32.406**
2	**1.826**	**26.088**	**58.494**
3	**1.089**	**15.560**	**74.054**
4	.788	11.250	85.304
5	.444	6.341	91.645
6	.303	4.334	95.979
7	.281	4.021	100.000

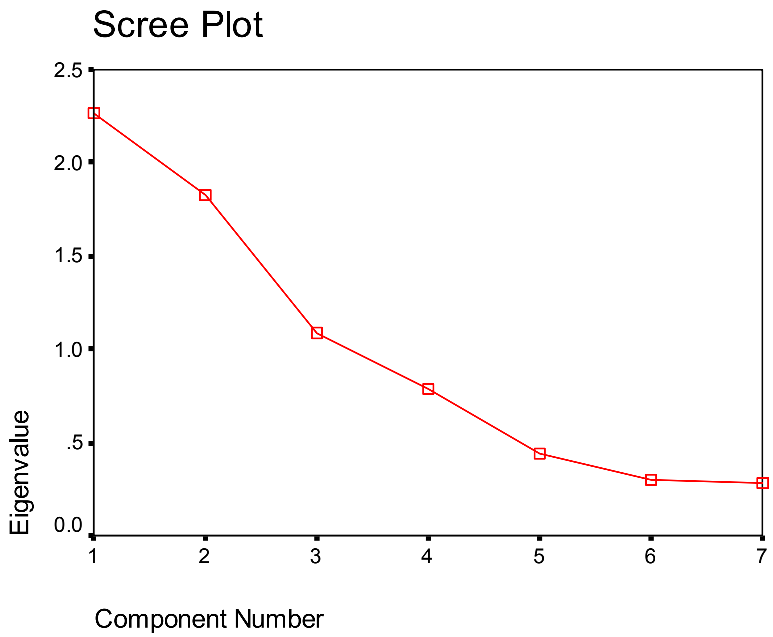

Figure 4.1 The scree plot representing the amount of variance explained by each variable. Note that the "breakage point is between 3^{rd} and 4^{th} points.

The scree plot shows percent of variance in original variables accounted for by each factor. We look for the "elbow" in the curve - point where additional factors don't add much to the explained variance. The eigen values measure the amount of variation in the total sample accounted for by each factor. In this study only variables with loading of more than 0.4 were selected in each factor.

In factorization of these seven values for the skull profile, the test produced 3 factors based on the above criteria. We used varimax rotation of the factor loading matrix to find more easily interpretable factors (Table 4.4).

Table 4.4 Factor analysis of skull profile curvature measures reveals 3 factors.

Items	Factor 1	Factor 2	Factor 3
Radius Frontal		.850	
Radius Parietal	.662		.433
Radius Occipital	.826		
Length Total	.862		
Angle Frontal		-.672	
Angle Parietal		.513	.597
Angle Occipital			.916

Note: Varimax rotation is used to obtain the results. The significant loadings of variables on each factor (i.e. above .4) are shown.

The cumulative percent of variance extracted by these 3 factors reaches 75% which shows reasonable explanation of total variation with practically significant factors (Table 4.3).

The first factor explains 32% of total variance in all the variables and is related to the overall size of the head as represented by total length and the radius of the curvature in vertex and back of the head. The second factor which covers 26% of the variance represents the inverse correlation between the angle of the frontal and parietal curves. It also reflects direct correlation between the frontal angle and radius. The third factor presents the direct correlation of the occipital angle with the parietal angle and radius. This factor explains 16% of total variance in the variables defining the skull profile.

The communality is the degree of variance in each independent variable (or surface attribute) that is accounted for by the common factors. The result for communality is more than 60% for all variables (data not shown). This also reveals a high degree of variance explained by the proposed common factors in this model.

To assess the reliability of this instrument in explaining the skull shape two aspects were analyzed. The internal consistency of elements of each factor was calculated. This measure of reliability represents the proportion of total variance in a given scale that can be attributed to a common source. These ranged from 70% for the first factor to 50% for the third factor. It has been suggested that a high Cronbach's alpha coefficient may represent a very narrow focus and some of the items constituting that factor could be deleted. This was not the case in our result although factor 3 had relatively low alpha value. To assess the temporal stability of the collected data test-retest reliability was calculated based on 10 subject repeated measurements. The correlation coefficient was high enough (ρ=89%) to support this aspect of reliability in the proposed technique. The result for reliability testing of the obtained factors is shown in Table 4.5.

Table 4.5. Reliability Statistics for internal consistency of each factor is shown.

	Cronbach's Alpha	Cronbach's Alpha Based on Standardized Items
Factor 1	.69	.72
Factor 2	.57	.62
Factor 3	.46	.53

Note that all of the factors have the value above 0.5 supporting the reliability of these factors.

The Pearson correlation coefficient for all the variables (i.e. curvature radius, cord length and angle) in the ten re-measured patients was more than 89% (data not shown).

4.3 Secondary analysis on data exploring the effect of sex and age

The student t-test results on the effect of sex on all the variables revealed strong association between the total length of skull, occipital curve radius and length with sex (Table 4.6). Typically males have longer heads (i.e. total length) with more flat occipital (i.e. higher occipital curvature radius).

Table 4.6. The t-test results for the effect of sex on different skull variables.

	Mean (mm)		Sig. (2-tailed)
	Male (n=50)	Female (n=43)	
Length Total	185	177	***.001***
Radius Frontal	69	67	.22
Radius Parietal	77	75	.26
Radius Occipital	60	58	***.028***
Length Frontal	89	86	.14
Length Parietal	115	110	.07
Length Occipital	106	100	***.001***
Angle Frontal	45	46	.65
Angle Parietal	24	23	.48
Angle Occipital	118	118	.95

Significant values are shown in bold.

To investigate the effect of age on some of the variables measured in this study, the frontal angle was selected as the representation for the forehead prominence and the total length of skull as overall index of skull volume. Multivariate regression analysis (using backward elimination for variable selection and using all defined 10 variables in the methods section and age as covariables) showed no affect of age on frontal curve angle (Table 4.7_a) and total length of skull (Table 4.7_b).

Table 4.7 Relationship of various skull shape measures to (a) the frontal angle and (b) total length in a multivariate analysis after backward elimination of different measures.

Independent variables	Frontal angle (a) P value	Total length (b) P value
Age	NS	NS
Total length	NS	-
Frontal angle	-	.00
Parietal angle	.00	NS
Occipital angle	.00	.00
Frontal length	.00	.00
Parietal length	.00	.00
Occipital length	.00	.00
Frontal curve	.00	NS
Parietal curve	NS	.00
Occipital curve	NS	NS

NS = not significant.

CHAPTER 5

DISCUSSION

5.1 Introduction

The shape of skull profile especially in the forehead has a significant importance in the general balance of the face and overall constitution of individual anatomical identity. There has been very few simple quantification of the skull shape based on the surface curvature definition in the literature. This study to our knowledge is one of the first to provide such data for the lateral skull measures. The result of this study provides two sets of information: descriptive data and analytic results.

5.2 The average values for three different defined curvatures of the skull profile (i.e. first primary objective)

The result of this study provides a useful database for quantitative description of human skull surface morphology. This is based on the description of three different zones (i.e. curvatures) and their described indices. This information is based only on two dimensions (i.e. lateral view of skull) and establishes a standard against which the abnormal morphology of the head in various syndromes can be assessed. There has been growing interest in the study of human neurocranial growth. This has been sparkled further by the large body of research knowledge on the fundamental role of sutures in both normal and abnormal skull growth and formation.[61-64] The study of cranial dysmorphology such as in craniosynostosis has also shed more light on these basic growth pathways.[65-75] Knowledge of the normal values is obviously essential to quantitatively describe these pathologies and assess their effect on the skull morphology. The collected data in this study is an attempt to provide a simple and reproducible way of describing these noramative data. The main premise of this study was that the lateral skull surface can be matched with three circular curvatures. This idea was originated from the fact that there are two breakage points on the surface of skull at the coronal and lambdoid sutures which divide the lateral surface into three different “zones” of frontal, parietal and occipital. This criterion was used in all the studied patients and we were able to match the skull surface within 5 mm of its surface boundaries in every patient. All the measurements were performed by one investigator (F.P.) to assure more homogenous recording technique. The mathematical software used for surface matching and other curvature measurements allowed necessary versatility to achieve the “best match” for the skull surface. This provided a reliable test result for each patient. Furthermore, internal validity was confirmed by high correlation coefficient between the random samples of 10 patients from the study. Therefore collected data has the potential for digitized quantification and recording of skull surface morphology. It also allows comparison of different values in normal and pathological states.

Craniosynostosis is a rare anomaly with incidence varying between 3 to 14 per 10,000 live birth.[76] In this anomaly one or more of the cranial sutures undergoes premature fusion either prenatally or postnatally. It is described as either primary, where there is a defect within a suture, or secondary, where the premature closure of the sutures is secondary to an underlying disorder such as mucopolysaccharidoses and rickets.

In primary craniosynostosis, premature fusion of a cranial suture results in abnormal calvarial development as compensation for the rapid growth of the brain during the first year of life. The clinical presentation and severity of deformity depend on the suture involved. Surgical treatment should be performed early to prevent the further progression of the deformity and possible complications associated with increased intracranial pressure. The principles of surgical intervention are not only to excise the fused suture but also to attempt to normalize the calvarial shape.[77]

Nomograms for cephalic indices are available and are one way to evaluate the severity of the craniosynostosis. The cephalic index measures only linear two dimensional values of the skull and does not allow assessment of either frontal bossing or occipital protuberance. Our technique provides simple descriptive values that can define the deformity and allow better quantification of its severity. It can also theoretically help restoration of skull shape closer to “norm”.

Cranial defects resulting from congenital deformities, ablative resection of osseous tumors, traumatic injury, and destructive infectious lesions are often severe enough to warrant surgical reconstruction. In particular cases, satisfactory cosmetic results may be difficult to achieve because of the extent and location of the lesion. Although neuronavigation has emerged as an adjunct tool in cranial reconstruction, its use is limited in large midline defects due to lack of reliable landmarks.

These normative values can potentially allow more accurate and standardized measurements that can be used for reconstructive purposes. This problem becomes more obvious in large cranial defects (e.g. due to trauma, tumor, infection, etc.) with no easily identifiable surrounding landmarks. Theoretically, having an approximation of the curvature especially around the forehead region can assist more anatomical reconstruction in these difficult cases.

One of the important quantitative finding of this study is that measurement on the various “zones” of skull surface have wide ranges. This variability amongst individuals potentially limits the usage of “mean” values for reconstruction toward the “average” skull. In other word, the “average skull” values based on the rigid use of the mean values for different described zones are not very common occurrence in the population. Each normal person has its own unique composition of measures in different zones, which does not necessarily closely approximate the average value for any particular segment of skull surface. Therefore these data only provide a template upon which other surface landmarks information should be integrated. For example in restoring a large skull defect to normal, one can use the remaining bone edges of the defect to help orienting and shaping the graft material.

Another potential usage of the collected data is in studying the temporal changes of skull surface geometry during normal growth process or their variation in different sexes. In this study various bivariate comparisons of different surface measurements and age did not reveal any significant effect for different ages. It must be stressed that the data presented here are cross-sectional and therefore do not represent the true growth changes over time. The other limiting issue is the number of studied subjects which can reduce the power of this conclusion as described in the limitation section below.

5.3 Identifying the common factors determining formation of defined skull curvatures (i.e. second primary objective)

Factor analysis is a statistical tool for reduction of multiple variables to a less number of the underlying new variables which can still explain most of the variance in these variables. It essentially studies the order and structure in multivariate data. In this study the population of interest is skull surface shape in a sample of normal population. The various measurements of skull curvatures are called "surface attributes". Factor analysis involves a set of techniques designed to identify order and structure in these surface attributes by providing a parsimonious and meaningful explanation for the observed variation and covariation in surface attributes. The cornerstone of factor analytic theory is the postulate that there exist "internal attributes" or "factors" which are essentially hypothetical. These constructed internal attributes affecting the surface attributes in a systematic fashion. Given the principle that the factors influence the surface attributes, it can be understood that the combination of factors account for an individual's degree or level on a surface attribute. This means that in this study each individual's measure of skull curvature value arise from individual's level on the relevant factor(s). There are essentially two different factors, common and specific. Common factors are internal attribute which affect more than one of the surface attributes and specific factors are influencing only one of the surface attributes. Variation in surface attribute is attributable, in part, to the variation on the specific factors but covariation of surface attributes is attributable mainly to the dependence on some of the same common factors. The main advantage of this statistical analysis is explanation of covariation of the large number of skull curvature measurements in terms of few of common internal attributes or factors.

At the first stage of this study the skull shape was defined by 3 curves and it was shown to be reproducibly measurable by the above described technique (see methods). In the next stage, seven items were selected for analytic testing based on their relative apparent independence. This was based on the hypothetical assumption of the primary investigator and confirmatory correlation matrix table (data not shown but available upon request). The exploratory factor analysis produced 3 factors which explained the majority of variance in the surface topography of examined skull.

In this study the relationship between surface attributes (seven) and the three identified (common) factors are illustrated in Figure 5.1.

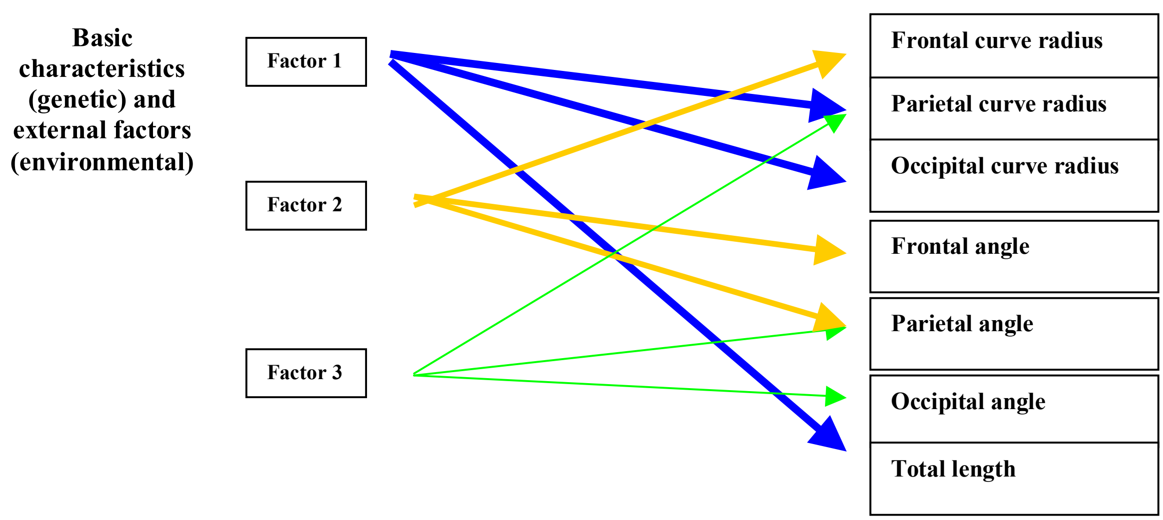

Figure 5.1 Relationship between surface attributes and factors

It is important to emphasize that factor analysis does not tell us what substantive labels or meaning to attach to the factors. This decision must be made by the researcher. Factor analysis is purely a statistical technique indicating, which, and to what degree, variables relate to an underlying and undefined factor. The substantive meaning given to a factor is typically based on our careful examination of what the high loading variables measure.

In the present factor analysis model, there are 3 factors which essentially represent the final balance between the effect of expansile of brain (i.e. brain growth, possible skull de novo active growth) and skull restrictive forces (i.e. permissive/restrictive effect of the sutures).

Factor 1 shows the high loading for the representative of skull and brain volume (i.e. total length of the skull and expansion of supero-posterior curvature of the skull). The values for the factor I highlight two important points: a) Antero-posterior total length of skull as a measure of the overall size and volume of the skull is mainly governed by the forces with supero-posterior vector orientation. b) The curvature of parietal and occipital bones respond congruently to these expansile forces. Lack of simultaneous frontal region curvature expansion is either because of the absence of brain expansion in the frontal lobe (which is not likely the case) or more restrictive control steps on the frontal skull expansion. These inhibitory mechanisms act most likely through the control on suture growth and closure. The lambdoid suture region is more responsive to these expansile forces almost in a direct and passive way. It is interesting that the posterior fontanel closes much earlier than the frontal one (6 months versus 18 months on average, respectively). Despite this tendency for early suture closure, the restrictive effect of the lambdoid suture is not shown in this series. This highlights the fundamental differences in the influence of skull sutures on the calvarial growth. The two embryologically separate osteogenic centers of the parietal and occipital bones respond similarly to the elongation of the skull by expanding their curvatures (i.e. increasing the radius). Therefore, factor 1 predicts a dominant postero-superior growth force affecting the elongation of the skull and expanding the curvature of the parieto-occipital bones. The timing of lambdoid suture closure does not seem to have any major effect on the final emerging skull configuration.

Factor 2 reveals reciprocal and opposite relationship between the angle of frontal and parietal region as well as frontal curvature. The values for the factor 2 highlights two important points: a) there is an inverse relationship between the frontal and parietal curvatures angle (i.e. interzonal relationship), and b) there is an opposite relationship between the curvature angle and radius in the frontal region (i.e. intrazonal relationship). This means that the more acute angle in frontal zone is associated with a flatter curvature. The inverse relationship of frontal and parietal angles suggests a pivotal function for the coronal suture. One explanation for this relationship is that the enlarging uncompressible brain volume acting as the expansile force against the restrictive effect of the coronal suture. Therefore, with the restrictive effect due to the closure of coronal suture at an earlier stages of growth, one can expect flatter (i.e. more acute angled and less curved) frontal zone and more obtuse angled and curved posterior parietal brain region (Figure 5.2). The other finding is the fact that presumed coronal suture restrictive effect occurs predominantly on the frontal zone side of the suture (i.e. flattening of forehead with more acute angle of frontal zone) than the parietal zone side. This suggests asymmetric effect of this suture closure on the frontal versus parietal sides. In this study the flattening occur over most of the frontal region and not just in a narrow strip parallel to the suture. This implies a broad restrictive effect on the growth of the frontal side of the coronal suture. The restrictive effect also acts in the vertical dimension (contrary to the popular belief). Another explanation for this asymmetric finding is that the nature of bone formation and remodeling is different in frontal zone comparing to more posterior aspect of the skull. This implies that with the restrictive effect of coronal suture the frontal bone becomes more flat and angled in relation to the skull base mainly because of vertical growth restriction. Recent analysis of tissue origin in the developing skull of murine has revealed two different sources for skull formation. The frontal bone is derived from the neural crest cells in contrast to parietal bone which has mesodermal origin [40]. The coronal suture could therefore function with different growth capacity on either side (i.e. frontal and parietal sides).

The last factor (i.e.3rd factor) essentially represents parietal and occipital zones angles which for the most part move in congruent directions. This fact again suggest that despite having two separate osteogenic centers for these bones intervened by lambdoid suture, they act as one mechanical unit in response to the growth forces of the skull. It is clear from the above description that in all the defined factors, frontal zone variations are independent or opposite of the changes in parieto-occipital zones.

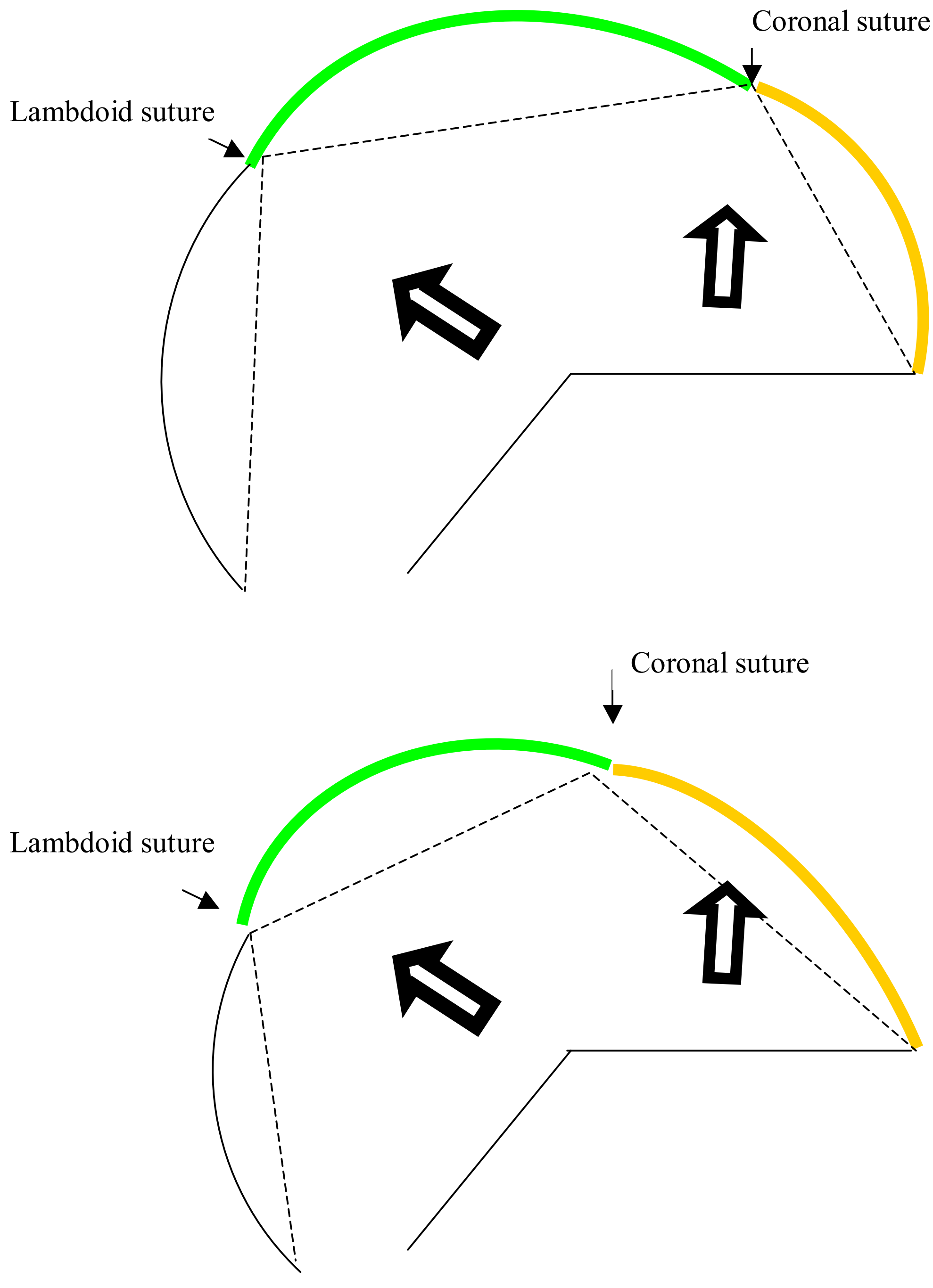

Figure 5.2 The two end of the spectrum in skull shape as suggested by factor 2. This is presumably the result of restrictive effect of the coronal suture against the expansile forces of brain growth (perpendicular to the skull base).

There has been a large body of data on the morphogenesis of skull and its growth as the result of sutural growth and subsequent bony remodeling.[78] The role of suture in normal development currently remains under intense study. One of the reasons is the known effect of suture role in formation of pathological skull dysmorphism. The factors governing the appropriate signals for growth had become partially deciphered.[79]

The normal postnatal morphogenesis of cranial vault is clearly a multifactorial and complex process that relies on the permissive accommodation of cerebral expansion at the cranial sutures. The most rapid expansion is permitted in the areas of suture patency, and final shape of the mature skull is generally dictated by the pattern by which these sutures naturally fuse with aging. This pattern is the result of delicate balance between cellular proliferation and cellular differentiation at the suture osteogenic fronts. Both the genetic and environmental factors govern the balance between the proliferation and differentiation at the sutures level. Any imbalance in this delicate process results in a spectrum of changes in the skull. The effect of environment on skull plasticity however, has been questioned by Spark et al.[80] In his view most factors affecting the final shape of skull are inherent to the individuals based on their genes.

Dura is also known to affect and possibly govern the osteogenesis process of overlying skull at these suture lines.[81-85] Most of the experimental studies are done in the non-primate animals in this regard. It has been suggested that FGF-2 (fibroblast growth factor 2) signaling from regional dura matter play an important role in regulation of murine cranial suture fate.[86-90] The exact mechanism through which FGF-2 receptor activation is translated into osteoblast differentiation and bone formation is largely unknown. These data suggest that in the murine model, the dura mater directs overlying cranial suture biology through paracrine signaling between dural cells and calvarial osteoblasts in the cranial suture.[91]

In abnormal skull formation classically seen in craniosynostosis deformities, suture closure has been implicated as one of the key pathophysiological factors resulting in ultimate skull deformity. In the syndromic craniosynostosis several unique genetic abnormalities (possibly causal for the disease) have been identified. For example in Apert syndrome FGF2 receptors are mutated.[92;93] This implies a central role for the FGF2 receptors in the dura as major determinant of the suture closure time.

One of the important biological issues in ultimate skull topography is the relationship between the skull geometric morphology and its function. The cranium houses the brain and vital sensory organs and that skull bones function as struts and levers that must be properly placed to function effectively (e.g. to align occluding teeth). However, skull shape is molded by complex interactions that might be differently coordinated across individuals. These interactions ensure that the calvarium is just large enough to enclose the brain, for example, and that bones are strong enough to resist being deformed when loaded by muscles. Whether the currently proposed three zone description of the skull and especially the hypothetically suggested "common factors" have a relevant biological meaning need to be evaluated in future studies.

There is a general tendency to form ultimately similar morphology in each species during development. Canalization refers to this buffering of developmental systems so that the same phenotype is produced despite genetic environmental variation in the population. In many cases, canalization might prevent variation from being generated in the first place and thus represents generative constraint or could restore deviants toward the mean, as in the case of targeted growth.[94] Our result although preliminary and based on relatively small sample sizes, indicates that there is overall basic phenotypic skull shape yet with considerable diversity among populations in skull morphology. It also suggests that geographically confined population could be more heterogeneous than previously thought. These results generate a template for future research on ethnic and geographic diversity of human being and even open the horizon for the same analysis in anthropological studies of Homo sapiens evolution. The main objectives in physical anthropology are to document the vast range of human variation of past and present populations and to investigate the evolutionary and environmental forces responsible for phenotypic variation. The patterns of human variation among different geographic populations have been examined using genetic markers, linguistic and anthropometrics.
The result of this research can help quantifying these human variations and compliment the armamentarium of investigational tool to explore these above goals in anthropology.

5.4 Exploring the effect of sex and age (i.e. secondary objective)

Further analysis of the results confirms the expected gender effect on the length of skull (i.e. male have longer heads). Overall, males have larger brain size and volume on average comparing to females. This translates to larger heads for males. Flattening of the occipital curvature suggests that the increased rate of growth in volume is disproportionably accommodated in the posterior aspect of the skull. This suggests potential restrictive effect of anterior skull growth centers (i.e. around Coronal suture) on the final cumulative skull expansion. There were no significant association between the forehead angle, which represents the forehead slope, and the gender. This is contrary to the common expectation assuming more prominent or vertically oriented forehead in males. Multivariate analysis also didn’t show any important role for the age in adult skull length and forehead angle. Hence, there is no need for age-specific cephalometric reference data on the forehead shape.

5.5 Study Limitations

5.5.1 Reliability of the results

The consistency and reproducibility (i.e. reliability) of different measurements which are the essential variables in this study (curvature radius, angle and cord length) can potentially be affected during several stages of raw data collection as follow:

a. Orbitomeatal line orientation based on radiographic landmarks (sometimes not very clear on original copy with only approximate overlapping of this line and bony landmarks).
b. Subjective nature of the best fitted curve on the skull surface. This was approximated to +/- 5mm of the overlapping zone to increase the objectivity of this task.

c. Definition of the boundaries between different curvatures (i.e. frontal, parietal, and occipital regions) was at time not very sharp due to gradual curvature change in the actual skull. This was not a determining factor in finding the appropriate curvature matches as all of the studied subjects had three previously described match curves.
d. Poor definition of the inferior part of occipital curvature due to bony overlap.

All these categories can be grouped under “Fuzzy landmarks’’. This have been defined as ‘‘the position of a biological structure that is precisely delineated, but occupies an area that is larger than a single point in the observer’s reference system’’. However, a within-observer error test proved that the uncertainty of fuzzy landmarks is limited and can be reduced by the experience.

5.5.2 Validity of the results

a. Method of radiograph selection which was essentially a “sporadic pick up” of patients rather than true random selection and the limited number of subjects has limited the generalizability of the result of this study to general population. We suspect that the current quantitative results are closely resembles the North American population. **.**
b. Hypothetical construct (i.e. identified common factors) based on the above factor analysis need to be verified with larger population and inclusion of more variables. This study is to our knowledge is one of the first principal components analyses attempting to elucidate common factors (i.e. internal attribute) governing the skull shape. Further successive studies building on the knowledge gained from the preceding studies are needed. The battery of newly measured variables should add new variables based on the prediction of the composition of the above factors. These further confirmatory studies with different mixture of relevant variables lead to better understanding of the studied domain of skull shape and improve the interpretation of the resulting factors.

c. Assumptions for the factor analysis in the study:

i. No selection bias/proper specification. The process of variable inclusion is described in the body of discussion. The exclusion of relevant variables and the inclusion of irrelevant variables in the correlation matrix being factored will affect, often substantially, the factors which are uncovered. Although factor analysis is used as a way of exploring data whose structure is unknown, knowing the factorial structure in advance helps select the variables to be included and yields the best analysis of factors. This dilemma creates a chicken-and-egg problem. This is not just a matter of including all relevant variables. Also, if one deletes variables arbitrarily in order to have a "cleaner" factorial solution, erroneous conclusions about the factor structure could result.

ii. Linearity. Principal components factor analysis is a linear procedure and this was assumed for our data.

iii. Moderate to moderate-high intercorrelations of variables are desired for factor analysis. Applying factor analysis to a correlation matrix with only low intercorrelations will require for solution nearly as many principal components as there are original variables, thereby defeating the data reduction purposes of factor analysis. In this study the reliability testing for the internal consistency of the elements of each factor revealed acceptable correlation (see results)

iv. Factor interpretations and labels must have face validity and/or be rooted in theory. It is sometimes difficult to assign valid meanings to factors. A recommended practice is to have a panel not otherwise part of the research project assign one's items to one's factor labels. This can be done as complimentary part of this project in future.

5.5.3 Other shortcomings

a. This study focuses on the midline sagittal information (i.e. two-dimensional) to describe the topography of the skull surface. In reality the skull surface is three-dimensional and therefore further studies including more lateral landmarks such as in lateral frontal or temporal bone can clarify, strengthen or weaken the result of this study.
b. Another potential shortcoming is lack of inclusion of skull base landmarks as important variables affecting the ultimate skull shape. The skull base has different ossification process (i.e. endochondral) with known effect on skull shape.
c. This study is a cross-sectional series of measurements on multiple individuals in different stage of skull maturity. Therefore, this study analyzes the variation in skull shape within a cross-sectional sample and does not take into account the longitudinal growth changes in the skull of individual cases. However, this factor was not shown to be significant in univariate analysis of the effect of age on different skull surface variables (see supra in the results). This is probably due to the selection of relatively mature age in this study (i.e. >10 years age) which as a group has already completed most of their skull growth.

5.6 Study strengths

5.6.1 Measurement of boundary outline

This study provides an innovative approach to quantify the outline shape of skull profile. It also creates an avenue for other creative thinking in describing the shape in other parts of body and allows analytic assessment of the results.

5.6.2 Relative simplicity

The technique for measurement in this study is somewhat time consuming but is practical for individual patients. Specific software can be devised for these measurers to make this approach more users friendly without large amount of mathematical calculation.

5.6.3 Fusion of form and biology of skull growth

This approach divides the skull profile into three zones corresponding to the anatomical location of sutures. It considers biological forces in skull formation and likely simplifies the study on pathophysiological forces ultimately responsible for skull outline configuration.

5.6.4 Future applications of the technique

This innovative approach allows further descriptive and analytic approach to study skull shape formation in future.

5.7 Future research directions

The choice of the individual morphometric technique used can be likened to the holistic principle (Anekàntvàda) of Jain logic: if six blind men each touch a different part of an elephant, they come to a differing opinion. In consequence, the elephant should be looked at from all sides. Thus, the use of only one morphometric technique in the evaluation of cephalometric craniofacial form may only, in part, describe overall form. The particular technique selected will depend on the type of information that is required to be derived, be that size, shape, or overall morphology. Moreover, where any doubt exists as to the best analytical method to use it may be preferable to use more than one technique. With such an approach to the evaluation of craniofacial form, the corroboration of results from different techniques would be ideal.

Non-corroborative results (including contradictory results) could be explained by the limitations of the individual techniques. The computer age continues to provide tremendous opportunities for the development of morphometric techniques. Nevertheless, because of the practical difficulties in interpreting morphometric data and the graphical display of results, it is likely that the morphometric toolkit will remain within the realm of craniofacial topography research. Although CCA will continue to be widely utilized by clinical orthodontists, univariate statistics are overused and future clinical research should instead make greater use of more appropriate multivariate techniques. Furthermore, the opportunity exists for future cephalometric studies to utilize the symbiosis of CCA and sophisticated morphometric techniques. This is of particular relevance where shape and size changes characterize a form difference such as that which occurs with growth.

Three-dimensional (3D) analysis is ideal for precisely assessing craniofacial morphology. With the advent of more powerful computer tools and proliferation of 3D software[51], it is conceivable that this information become more readily available for both research and everyday clinical usage.

The shape changes have been poorly investigated. This is, in part, due to lack of user-friendly methods satisfactorily demonstrating the overall outline and its changes. More user friendly techniques are going to be the solution for more practical application of any of these tools in future.

CHAPTER 6
CONCLUSIONS

In summary, the skull surface configuration is the end-result of intricate interaction of genetics and environmental factors. This study reveals certain common factors explaining the topographic organization of skull with reasonable accuracy. These factors suggest an important role for the coronal suture region (not the lambdoid suture) in the formation of final skull shape. It seems that the timing and speed with which this area contributes to the osteogenesis and subsequently halting of the growth by fusion of coronal suture is an important determinant of the skull configuration. The final shape is determined mainly by the overall brain size (as represented in factor 1 with the skull length representing the overall volume) acting as the expansile force and the Coronal region final inhibitory force (as shown by factor 2 with reverse relationship of the frontal and parietal angle/curvature radius). Future sophisticated 3D surface computer modeling of the skull can expand these concepts by simultaneously incorporating large myriads of variables driven from surface remodeling.

This study also provides a quantitative normative database for the skull surface morphology in adult population above the age of 10 years. These values can be used as an approximate source of data for more anatomical skull reconstruction in defects with different size, shape and location.

Based on the above factors we suggest the following:

1) The skull profile topographic organization can be viewed as two distinct territories: Frontal and Parieto-occipital zones which are hinging at the coronal suture region
2) There is a large normal variation in the values of different part of the skull based on the three described zones in this study.

3) The coronal suture is the predominant variable in shaping the final configuration of the skull profile.
4) The variation in the timing of suture closure with anterior or posterior skewed skull growth may be more frequent than suspected.

REFERENCES

1. Bruner E. Geometric morphometrics and paleoneurology: brain shape evolution in the genus Homo. *J.Hum.Evol.* 2004;**47**:279-303.

2. Axelsson S, Kjaer I, Bjornland T, Storhaug K. Longitudinal cephalometric standards for the neurocranium in Norwegians from 6 to 21 years of age. *Eur.J.Orthod.* 2003;**25**:185-98.

3. Morriss-Kay GM,.Wilkie AO. Growth of the normal skull vault and its alteration in craniosynostosis: insights from human genetics and experimental studies. *J.Anat.* 2005;**207**:637-53.

4. Bradley JP, Levine JP, Roth DA, McCarthy JG, Longaker MT. Studies in cranial suture biology: IV. Temporal sequence of posterior frontal cranial suture fusion in the mouse. *Plast.Reconstr.Surg.* 1996;**98**:1039-45.

5. Jabs EW, Muller U, Li X, Ma L, Luo W, Haworth IS *et al*. A mutation in the homeodomain of the human MSX2 gene in a family affected with autosomal dominant craniosynostosis. *Cell* 1993;**75**:443-50.

6. Ma L, Golden S, Wu L, Maxson R. The molecular basis of Boston-type craniosynostosis: the Pro148-->His mutation in the N-terminal arm of the MSX2 homeodomain stabilizes DNA binding without altering nucleotide sequence preferences. *Hum.Mol.Genet.* 1996;**5**:1915-20.

7. Wilkie AO. Bad bones, absent smell, selfish testes: the pleiotropic consequences of human FGF receptor mutations. *Cytokine Growth Factor Rev.* 2005;**16**:187-203.

8. Morriss-Kay GM. Derivation of the mammalian skull vault. *J.Anat.* 2001;**199**:143-51.

9. Fong KD, Warren SM, Loboa EG, Henderson JH, Fang TD, Cowan CM *et al*. Mechanical strain affects dura mater biological processes: implications for immature calvarial healing. *Plast.Reconstr.Surg.* 2003;**112**:1312-27.

10. Warren SM, Greenwald JA, Nacamuli RP, Fong KD, Song HJ, Fang TD *et al*. Regional dura mater differentially regulates osteoblast gene expression. *J.Craniofac.Surg.* 2003;**14**:363-70.

11. Greenwald JA, Mehrara BJ, Spector JA, Fagenholz PJ, Saadeh PB, Steinbrech DS *et al*. Immature versus mature dura mater: II. Differential expression of genes important to calvarial reossification. *Plast.Reconstr.Surg.* 2000;**106**:630-8.

12. Rogers TL. Determining the sex of human remains through cranial morphology. *J.Forensic Sci.* 2005;**50**:493-500.

13. Miller JP,.German RZ. Protein malnutrition affects the growth trajectories of the craniofacial skeleton in rats. *J.Nutr.* 1999;**129**:2061-9.

14. Carter DR. Mechanical loading history and skeletal biology. *J.Biomech.* 1987;**20**:1095-109.

15. Yu JC, Lucas JH, Fryberg K, Borke JL. Extrinsic tension results in FGF-2 release, membrane permeability change, and intracellular Ca++ increase in immature cranial sutures. *J.Craniofac.Surg.* 2001;**12**:391-8.

16. Lieberman DE, Pearson OM, Polk JD, Demes B, Crompton AW. Optimization of bone growth and remodeling in response to loading in tapered mammalian limbs. *J.Exp.Biol.* 2003;**206**:3125-38.

17. Frost HM. The Utah paradigm of skeletal physiology: an overview of its insights for bone, cartilage and collagenous tissue organs. *J.Bone Miner.Metab* 2000;**18**:305-16.

18. Enlow DH,.Azuma M. Functional growth boundaries in the human and mammalian face. *Birth Defects Orig.Artic.Ser.* 1975;**11**:217-30.

19. Enlow DH, Kuroda T, Lewis AB. The morphological and morphogenetic basis for craniofacial form and pattern. *Angle Orthod.* 1971;**41**:161-88.

20. Enlow DH,.Moyers RE. Growth and architecture of the face. *J.Am.Dent.Assoc.* 1971;**82**:763-74.

21. Webster. Webster's New Universal U abridged Dictionary. 1983.

22. PENROSE LS. Distance, size and shape. *Ann.Eugen.* 1954;**18**:337-43.

23. Lele S. Some comments on coordinate-free and scale-invariant methods in morphometrics. *Am.J.Phys.Anthropol.* 1991;**85**:407-17.

24. McIntyre GT,.Mossey PA. Size and shape measurement in contemporary cephalometrics. *Eur.J.Orthod.* 2003;**25**:231-42.

25. Chen SY, Lestrel PE, Kerr WJ, McColl JH. Describing shape changes in the human mandible using elliptical Fourier functions. *Eur.J.Orthod.* 2000;**22**:205-16.

26. Hennessy RJ,.Moss JP. Facial growth: separating shape from size. *Eur.J.Orthod.* 2001;**23**:275-85.

27. Moyers RE,.Bookstein FL. The inappropriateness of conventional cephalometrics. *Am.J.Orthod.* 1979;**75**:599-617.

28. Richtsmeier JT,.Cheverud JM. Finite element scaling analysis of human craniofacial growth. *J.Craniofac.Genet.Dev.Biol.* 1986;**6**:289-323.

29. Lestrel PE. Some approaches toward the mathematical modeling of the craniofacial complex. *J.Craniofac.Genet.Dev.Biol.* 1989;**9**:77-91.

30. Lele S,.Richtsmeier JT. Euclidean distance matrix analysis: a coordinate-free approach for comparing biological shapes using landmark data. *Am.J.Phys.Anthropol.* 1991;**86**:415-27.

31. Bookstein FL. On the cephalometrics of skeletal change. *Am.J.Orthod.* 1982;**82**:177-98.

32. Hamdan AM,.Rock WP. Cephalometric norms in an Arabic population. *J.Orthod.* 2001;**28**:297-300.

33. Ranly DM. Craniofacial growth. *Dent.Clin.North Am.* 2000;**44**:457-70.

34. Schillaci MA, Jones-Engel L, Heidrich JE, Miller GP, Froehlich JW. Field methodology for lateral cranial radiography of nonhuman primates. *Am.J.Phys.Anthropol.* 2001;**116**:278-84.

35. Levine RA, Garza JR, Wang PT, Hurst CL, Dev VR. Adult facial growth: applications to aesthetic surgery. *Aesthetic Plast.Surg.* 2003;**27**:265-8.

36. Jeffery N,.Spoor F. Brain size and the human cranial base: a prenatal perspective. *Am.J.Phys.Anthropol.* 2002;**118**:324-40.

37. Bardinet E,.Duhart AM. [Orthopedic approach to asymmetry]. *Orthod.Fr.* 2002;**73**:215-28.

38. Papadopoulos MA, Christou PK, Christou PK, Athanasiou AE, Boettcher P, Zeilhofer HF *et al*. Three-dimensional craniofacial reconstruction imaging. *Oral Surg.Oral Med.Oral Pathol.Oral Radiol.Endod.* 2002;**93**:382-93.

39. Raberin M. [Orthodontic implications in the correction of the transverse dimension in orthognathic surgery]. *Rev.Stomatol.Chir Maxillofac.* 2001;**102**:325-33.

40. Friede H. Abnormal craniofacial growth. *Acta Odontol.Scand.* 1995;**53**:203-9.

41. Enlow DH,.Azuma M. Functional growth boundaries in the human and mammalian face. *Birth Defects Orig.Artic.Ser.* 1975;**11**:217-30.

42. Enlow DH, Kuroda T, Lewis AB. The morphological and morphogenetic basis for craniofacial form and pattern. *Angle Orthod.* 1971;**41**:161-88.

43. Rah DK. Art of replacing craniofacial bone defects. *Yonsei Med.J.* 2000;**41**:756-65.

44. Lee C, Antonyshyn OM, Forrest CR. Cranioplasty: indications, technique, and early results of autogenous split skull cranial vault reconstruction. *J.Craniomaxillofac.Surg.* 1995;**23**:133-42.

45. Eppley BL. Alloplastic implantation. *Plast.Reconstr.Surg.* 1999;**104**:1761-83.

46. Artico M, Ferrante L, Pastore FS, Ramundo EO, Cantarelli D, Scopelliti D *et al*. Bone autografting of the calvaria and craniofacial skeleton: historical background, surgical results in a series of 15 patients, and review of the literature. *Surg.Neurol.* 2003;**60**:71-79.

47. Burstein FD. Bone substitutes. *Cleft Palate Craniofac.J.* 2000;**37**:1-4.

48. Schmitz JP, Hollinger JO, Milam SB. Reconstruction of bone using calcium phosphate bone cements: a critical review. *J.Oral Maxillofac.Surg.* 1999;**57**:1122-6.

49. Fong KD, Nacamuli RP, Song HM, Warren SM, Lorenz HP, Longaker MT. New strategies for craniofacial repair and replacement: a brief review. *J.Craniofac.Surg.* 2003;**14**:333-9.

50. Eppley BL, Kilgo M, Coleman JJ, III. Cranial reconstruction with computer-generated hard-tissue replacement patient-matched implants: indications, surgical technique, and long-term follow-up. *Plast.Reconstr.Surg.* 2002;**109**:864-71.

51. Swennen GR, Schutyser F, Barth EL, De Groeve P, De Mey A. A new method of 3-D cephalometry Part I: the anatomic Cartesian 3-D reference system. *J.Craniofac.Surg.* 2006;**17**:314-25.

52. Chim H,.Schantz JT. New frontiers in calvarial reconstruction: integrating computer-assisted design and tissue engineering in cranioplasty. *Plast.Reconstr.Surg.* 2005;**116**:1726-41.

53. Toth BA, Ellis DS, Stewart WB. Computer-designed prostheses for orbitocranial reconstruction. *Plast.Reconstr.Surg.* 1988;**81**:315-24.

54. Eufinger H,.Wehmoller M. Individual prefabricated titanium implants in reconstructive craniofacial surgery: clinical and technical aspects of the first 22 cases. *Plast.Reconstr.Surg.* 1998;**102**:300-8.

55. Kline p. An Easy Guide to Factor Analysis. Routledge, London, 1994.

56. Multivariate Analysis. In Portney LG WM, ed. *Foundations of Clinical Research*, pp 587-620. Prentice Hall Health, 2000.

57. Pett M. LNSJ. Making Sense of Factor Analysis. SAGE Publications, 2003.

58. Alexander T.Basilevsky. Statistical Factor Analysis and Related Methods: Theory and Applications. John Wiley & Sons, Inc., 1994.

59. Child D. The Essentials of Factor Analysis. Cassel, London, 1990.

60. Allison Paul D. Multiple Regression. Thousand Oaks, CA: Pine Forge Press, 1999.

61. Ogle RC, Tholpady SS, McGlynn KA, Ogle RA. Regulation of cranial suture morphogenesis. *Cells Tissues.Organs* 2004;**176**:54-66.

62. Jiang X, Iseki S, Maxson RE, Sucov HM, Morriss-Kay GM. Tissue origins and interactions in the mammalian skull vault. *Dev.Biol.* 2002;**241**:106-16.

63. Alden TD, Lin KY, Jane JA. Mechanisms of premature closure of cranial sutures. *Childs Nerv.Syst.* 1999;**15**:670-5.

64. Opperman LA, Passarelli RW, Morgan EP, Reintjes M, Ogle RC. Cranial sutures require tissue interactions with dura mater to resist osseous obliteration in vitro. *J.Bone Miner.Res.* 1995;**10**:1978-87.

65. Kabbani H,.Raghuveer TS. Craniosynostosis. *Am.Fam.Physician* 2004;**69**:2863-70.

66. Mao JJ,.Nah HD. Growth and development: hereditary and mechanical modulations. *Am.J.Orthod.Dentofacial Orthop.* 2004;**125**:676-89.

67. Meling TR, Orstavik KH, Heiberg A. [Complex craniofacial synostoses]. *Tidsskr.Nor Laegeforen.* 2004;**124**:1230-4.

68. Ridgway EB,.Weiner HL. Skull deformities. *Pediatr.Clin.North Am.* 2004;**51**:359-87.

69. Mooney MP, Moursi AM, Opperman LA, Siegel MI. Cytokine therapy for craniosynostosis. *Expert.Opin.Biol.Ther.* 2004;**4**:279-99.

70. Matsumoto K, Nakanishi H, Kubo Y, Yokozeki M, Moriyama K. Advances in distraction techniques for craniofacial surgery. *J.Med.Invest* 2003;**50**:117-25.

71. Abuelo D. Genetic evaluation and counseling for craniofacial anomalies. *Med.Health R.I.* 2002;**85**:373-8.

72. Flores-Sarnat L. New insights into craniosynostosis. *Semin.Pediatr.Neurol.* 2002;**9**:274-91.

73. Wilkie AO, Patey SJ, Kan SH, van den Ouweland AM, Hamel BC. FGFs, their receptors, and human limb malformations: clinical and molecular correlations. *Am.J.Med.Genet.* 2002;**112**:266-78.

74. Warren SM, Greenwald JA, Spector JA, Bouletreau P, Mehrara BJ, Longaker MT. New developments in cranial suture research. *Plast.Reconstr.Surg.* 2001;**107**:523-40.

75. Opperman LA. Cranial sutures as intramembranous bone growth sites. *Dev.Dyn.* 2000;**219**:472-85.

76. Singer S, Bower C, Southall P, Goldblatt J. Craniosynostosis in Western Australia, 1980-1994: a population-based study. *Am.J.Med.Genet.* 1999;**83**:382-7.

77. Panchal J,.Uttchin V. Management of craniosynostosis. *Plast.Reconstr.Surg.* 2003;**111**:2032-48.

78. Thilander B. Basic mechanisms in craniofacial growth. *Acta Odontol.Scand.* 1995;**53**:144-51.

79. Persson M. The role of sutures in normal and abnormal craniofacial growth. *Acta Odontol.Scand.* 1995;**53**:152-61.

80. Sparks CS,.Jantz RL. A reassessment of human cranial plasticity: Boas revisited. *Proc.Natl.Acad.Sci.U.S.A* 2002;**99**:14636-9.

81. Song HM, Fong KD, Nacamuli RP, Warren SM, Fang TD, Mathy JA *et al*. Mechanisms of murine cranial suture patency mediated by a dominant negative transforming growth factor-beta receptor adenovirus. *Plast.Reconstr.Surg.* 2004;**113**:1685-97.

82. Warren SM, Greenwald JA, Nacamuli RP, Fong KD, Song HJ, Fang TD *et al*. Regional dura mater differentially regulates osteoblast gene expression. *J.Craniofac.Surg.* 2003;**14**:363-70.

83. Hopper RA, Zhang JR, Fourasier VL, Morova-Protzner I, Protzner KF, Pang CY *et al*. Effect of isolation of periosteum and dura on the healing of rabbit calvarial inlay bone grafts. *Plast.Reconstr.Surg.* 2001;**107**:454-62.

84. Mehrara BJ, Most D, Chang J, Bresnick S, Turk A, Schendel SA *et al*. Basic fibroblast growth factor and transforming growth factor beta-1 expression in the developing dura mater correlates with calvarial bone formation. *Plast.Reconstr.Surg.* 1999;**104**:435-44.

85. Winograd JM, Im MJ, Vander Kolk CA. Osteoblastic and osteoclastic activation in coronal sutures undergoing fusion ex vivo. *Plast.Reconstr.Surg.* 1997;**100**:1103-12.

86. Mathy JA, Lenton K, Nacamuli RP, Fong KD, Song HM, Fang TD *et al*. FGF-2 stimulation affects calvarial osteoblast biology: quantitative analysis of nine genes important for cranial suture biology by real-time reverse transcription polymerase chain reaction. *Plast.Reconstr.Surg.* 2003;**112**:528-39.

87. Moursi AM, Winnard PL, Winnard AV, Rubenstrunk JM, Mooney MP. Fibroblast growth factor 2 induces increased calvarial osteoblast proliferation and cranial suture fusion. *Cleft Palate Craniofac.J.* 2002;**39**:487-96.

88. Opperman LA, Galanis V, Williams AR, Adab K. Transforming growth factor-beta3 (Tgf-beta3) down-regulates Tgf-beta3 receptor type I (Tbetar-I) during rescue of cranial sutures from osseous obliteration. *Orthod.Craniofac.Res.* 2002;**5**:5-16.

89. Greenwald JA, Mehrara BJ, Spector JA, Warren SM, Fagenholz PJ, Smith LE *et al*. In vivo modulation of FGF biological activity alters cranial suture fate. *Am.J.Pathol.* 2001;**158**:441-52.

90. Mehrara BJ, Steinbrech DS, Saadeh PB, Gittes GK, Longaker MT. Expression of high-affinity receptors for TGF-beta during rat cranial suture fusion. *Ann.Plast.Surg.* 1999;**42**:502-8.

91. Warren SM, Brunet LJ, Harland RM, Economides AN, Longaker MT. The BMP antagonist noggin regulates cranial suture fusion. *Nature* 2003;**422**:625-9.

92. Ibrahimi OA, Zhang F, Eliseenkova AV, Itoh N, Linhardt RJ, Mohammadi M. Biochemical analysis of pathogenic ligand-dependent FGFR2 mutations suggests distinct pathophysiological mechanisms for craniofacial and limb abnormalities. *Hum.Mol.Genet.* 2004.

93. Shotelersuk V, Mahatumarat C, Ittiwut C, Rojvachiranonda N, Srivuthana S, Wacharasindhu S *et al*. FGFR2 mutations among Thai children with Crouzon and Apert syndromes. *J.Craniofac.Surg.* 2003;**14**:101-4.

94. Gibson G,.Wagner G. Canalization in evolutionary genetics: a stabilizing theory? *Bioessays* 2000;**22**:372-80.