The Effect of Neurocranial Surgery on Basicranial Morphology in Isolated Sagittal Craniosynostosis

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Objective: **Isolated sagittal craniosynostosis produces a scaphocephalic neurocranium associated with abnormal basicranial morphology, providing additional evidence of the developmental relationship of the neurocranium and basicranium. Corrective surgical procedures vary, but the immediate impact of the surgical procedure is restricted to the neurocranium. This study addresses the secondary effects of neurocranial surgery on the cranial base.**

Design: **Three-dimensional (3-D) computed tomography (CT) scans were obtained for preoperative (n = 25) and postoperative (n = 12) patients with isolated sagittal synostosis. Landmark data from 14 landmarks on and around the cranial base were collected from 3-D CT reconstructions and analyzed using Euclidean distance matrix analysis. Subsamples of age-matched patients were used to identify basicranial differences in pre- and postoperative patients and to compare postoperative growth patterns identified in longitudinal data with preoperative growth patterns characterized in cross-sectional data.**

Results: **Statistically significant differences ($p \leq 0.10$) were found in the morphology of the cranial base in preoperative and postoperative patients. The relative positions of the landmarks nasion, right asterion, and left asterion are similar in preoperative and postoperative patients. However, the position of these landmarks relative to the cranial base is different in the two groups, being positioned relatively more anteriorly in postoperative patients. In addition, we found that the cranial base angle, on average, neither increases nor decreases in the first postoperative year. These morphological differences are associated with divergent growth trajectories in the operated and unoperated cranial base.**

Conclusion: **Regardless of specific procedure, neurocranial surgery in sagittal synostosis patients affects growth patterns of the cranial base. The lack of change in the postoperative cranial base angle suggests that neurocranial surgery alleviates the occipital rotation and decreased cranial base angle described in the sagittal synostosis basicranium.**

KEY WORDS: *cranial base, craniosynostosis, Euclidean distance matrix analysis (EDMA), growth*

Craniosynostosis is generally defined as premature closure of one or more cranial sutures (Cohen, 1986). The natural biological suture system required for normal craniofacial growth and development is altered, and a redirection of craniofacial growth is initiated. The character and degree of the resulting dysmorphology depends on the particular suture or sutures that are synostosed (Virchow, 1851; Delashaw et al., 1991). A variety of surgical procedures may be undertaken to restore the neurocranium to a more ''normal'' morphology by removing, opening, or displacing the synostosed suture or sutures. There is evidence that cranial base morphology is also affected by neurocranial synostosis (Marsh and Vannier, 1986; Richtsmeier et al., 1991; Slomic et al., 1992; Zumpano et al., 1999), but the specific effects of neurocranial surgical intervention on the basicranium have not been well documented in humans.

Isolated sagittal synostosis (ISS) is a relatively common form (1 out of 2,000 live births) of craniosynostosis in which the sagittal suture closes prematurely. Patients with ISS generally possess a larger neurocranium along the anteroposterior axis, relative to normal children of the same age. In addition, patients

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with ISS may display a decreased cephalic index, increased head circumference, a bony ridge overlying the synostosed sagittal suture, biparietal narrowing, bitemporal narrowing, and frontal and occipital prominences (Ebel, 1974; Barritt et al., 1981; Kreiborg, 1986; Richtsmeier et al., 1991; Slomic et al., 1992; Posnick et al., 1993; Richtsmeier et al., 1998). The overall appearance of these dysmorphologies is that of a narrow and elongated skull (dolichocephaly; scaphocephaly).

In an attempt to restore the neurocranium to a normal shape and to alleviate the potential for increased intracranial pressure, the majority of patients with ISS undergo various types of corrective surgeries, including strip craniectomy, parasagittal craniotomies, cranial expansion, pi procedure, and endoscopic interventions (Venes and Sayers, 1976; Barritt et al., 1981; Jane and Persing, 1986; Marsh et al., 1991; Posnick et al., 1993; Posnick, 1995; Jimenez, 1999). The aesthetic results of surgery vary based on the initial severity of dysmorphology, the intervention utilized, and age at surgery. Regardless of the specific operative technique, neurocranial surgery in patients with ISS involves the surgical interruption or removal of the sites of one or more cranial sutures. Although surgical manipulation of the neurocranium may return it to a more ‘‘normal’’ morphology (Kaiser, 1988; Marsh et al., 1991; Posnick et al., 1993), it fails to restore the natural biological suture system because a functional suture is not created or restored. The synostosed sagittal suture is removed, sectioned, or displaced, creating a modified suture system that is neither a ‘‘natural’’ suture system nor a synostosed suture system. Whereas the preoperative suture system places physical constraints on the craniofacial complex, the postoperative system involves the release of these constraints and creates a new environment to which the developing craniofacial complex must adjust.

Studies addressing the dependent nature of the cranial vault and base have been conducted in three contexts: (1) culturally motivated, artificial cranial deformation (e.g., Anton, 1989; Cheverud et al., 1992); (2) congenital cranial malformations in humans and animal models (e.g., Abramson et al., 1996; Smith et al., 1996; Mooney et al., 1998; Burrows et al., 1999); and (3) experimental deformations in animal models (e.g., Moss, 1960; Babler and Persing, 1980). These studies generally demonstrate a relationship between neurocranium and cranial base, but the character of this relationship remains undefined. Based on the results of these studies, we expect the constrained sagittal suture and subsequent neurocranial surgery to alter the mechanical forces of the growing cranium, thereby having an impact on growth of the cranial base.

Several studies have investigated the impact of a fused sagittal suture on the cranial base. Reports vary in terms of samples used, methods employed, and conclusions. Some researchers have focused primarily on cranial base morphology in the presence of isolated sagittal synostosis (Carmel et al., 1981; Slomic et al., 1992; Richtsmeier et al., 1998), while others have examined growth of the cranial base before and after suture release (Marsh and Vannier, 1986; Kaiser, 1988; Richtsmeier et al., 1991). Generally, these studies indicate that suture fusion in ISS results in reduced mediolateral growth of the cranial base and an overrotation of the cranium as a result of the posterior and inferior movement of the synostosed calvaria relative to a point of registration on the cranial base (sella). Both of these dynamics are thought to be caused by the constraint of the fused sagittal suture.

Although surgical release of a fused sagittal suture has been shown to improve neurocranial morphology in most cases of ISS, the specific effects on the cranial base are less clear. The results of studies that have addressed cranial base morphology following neurocranial surgery in patients with ISS are equivocal (Marsh and Vannier, 1986; Richtsmeier et al., 1991). More detailed analyses of the effect of neurocranial surgery on the cranial base in patients with ISS are needed.

This study used Euclidean distance matrix analysis (EDMA) and three-dimensional (3-D) coordinate landmark data collected from computed tomography (CT) scans of patients with ISS in order to test the hypothesis that basicranial morphology in postoperative patients is distinct from that in age-matched preoperative patients with ISS. In addition, longitudinal and cross-sectional data were used to compare basicranial growth in a surgically modified system with that in a synostosed system.

Materials and Methods

Patient Sample and Landmark Data

The mixed, cross-sectional sample consisted of 25 preoperative and 12 postoperative cranial CT scans from children with ISS (including 12 patients with both pre- and postoperative data) who were diagnosed and treated at the Johns Hopkins Medical Institutions, Baltimore, MD. All postoperative patients had undergone craniectomies, cranial expansions, or a combination of both. Although there is controversy about which surgical procedure provides optimal results in terms of neurocranial shape, our purpose was not to differentiate among operative procedures on the basis of outcome but rather to determine the generalized effect of removing the constraint of the fused suture on morphology and growth of the cranial base. All postoperative patients were combined into a single sample in order to assess whether any neurocranial surgical intervention has a notable impact on basicranial morphology. The preoperative CT scans were taken just prior to the initial surgery, and the postoperative CT scans were taken approximately 1 year (43 to 96 weeks) after surgery. The age distribution of the sample is provided in Table 1. All but three patients were males. Three-dimensional coordinates of 14 basicranial landmarks (Fig. 1, Table 2) were collected from CT scans for each patient using Remedi, a rendering and visualization software package developed by the Centre for Information-Enhanced Medicine, National University of Singapore.

Methods of Analysis

EDMA is a coordinate system invariant, landmark-based method that compares forms and/or growth patterns between two samples in two or three dimensions (Lele and Richtsmeier,

TABLE 1 Preoperative and Postoperative Findings of Patients With Isolated Sagittal Synostosis

*Preoperative**			*Postoperative†*			
Patient	*Age at Scan (wk)*	*Sex*	*Patient*	*Age at Scan (wk)*	*Sex*	*Postsurgical Period (wk)*
1	5.1	M	1	95	M	52
2	5.4	M				
3	6.9	M				
4	8	M	4	68	M	58
5	8.7	M	5	94	M	55
6	9	M				
7	10	M	7	75	M	48
8	11.7	M				
9	12	M	9	88	M	52
10	12.7	F				
11	13.6	M				
12	16	M	12	66	M	50
13	17	M				
14	18	M	14	115	M	96
15	18.3	F				
16	23	M	16	72	M	43
17	24	M	17	89	M	49
18	27	F				
19	35	M				
20	36	M	20	96	M	56
21	44	M	21	113	M	65
22	70	M				
23	95	M	23	160	M	52
24	116	M				
25	239	M				

* For preoperative patients, the average age at scan was 35.3 weeks; the number of patients was 25.
† For postoperative patients, the average age at scan was 94.3 weeks; the number of patients was 12.

1991; Richtsmeier and Lele, 1993; Lele and Richtsmeier, 1995; Lele and Cole, 1996; Lele and Richtsmeier, 2000). EDMA compares forms by first calculating a mean form matrix (FM) from landmark coordinate data for each sample. A FM consists of linear distances computed for all possible interlandmark distances within each sample.

The FMs for two samples are compared by computing a form difference matrix (FDM). Simply, the FDM reports a matrix of ratios of like linear distances calculated for each landmark pair within each population (e.g., the ratio of the line sella-basion in population 1 to sella-basion in population 2). If there is no difference between pre- and postoperative groups for a given interlandmark distance, the FDM ratio for that interlandmark distance equals 1. A ratio greater than 1 indicates that the linear distance is larger in the sample used in the numerator, and a ratio less than 1 indicates that the linear distance is smaller in the numerator sample. A bootstrapping algorithm tests for significant differences in the overall shape of the two samples being compared (Lele and Richtsmeier, 1991), and nonparametric confidence intervals ($\alpha = 0.10$) are calculated for each interlandmark distance to determine those linear distances that are significantly different between the two samples (Lele and Richtsmeier, 1995). Differences in growth patterns can also be addressed using a growth difference matrix (GDM), which is the ratio of two FDMs, each representing growth in one of the two groups being compared (Richtsmeier and Lele, 1993). The EDMA computer program was written by Theodore M. Cole III, Ph.D., and is available for downloading from the Richtsmeier Laboratory Website at http://faith.med.jhmi.edu/.

A principal coordinate analysis application of EDMA (PCOORD) is used as an exploratory data analysis procedure that examines the distribution of individuals in a multidimensional morphological space (Richtsmeier et al., 1998). This is simply a clustering procedure that aids in finding clusters of similarly shaped forms and identifying linear distances that are influential in distinguishing clusters. Each unique pair of individuals is compared using EDMA, and the result of each comparison is expressed as a single number indicating the dissimilarity between these two individuals. This dissimilarity index is calculated for all pairs of individuals, and a matrix of these values is constructed. This matrix is subjected to a spectral decomposition that groups patients according to their dissimilarity with respect to the sets of anatomical features measured for analysis. Each individual is represented by a single point that is a function of the original landmark data. Because the spatial relationship of individuals is dependent on the number of individuals and the landmarks used in the analysis, any change in either of these factors will affect results.

Analyses Conducted

PCOORD analysis of all-patient sample (n = 37)

A PCOORD analysis was conducted using the 14 basicranial landmarks collected from 25 preoperative and 12 post-

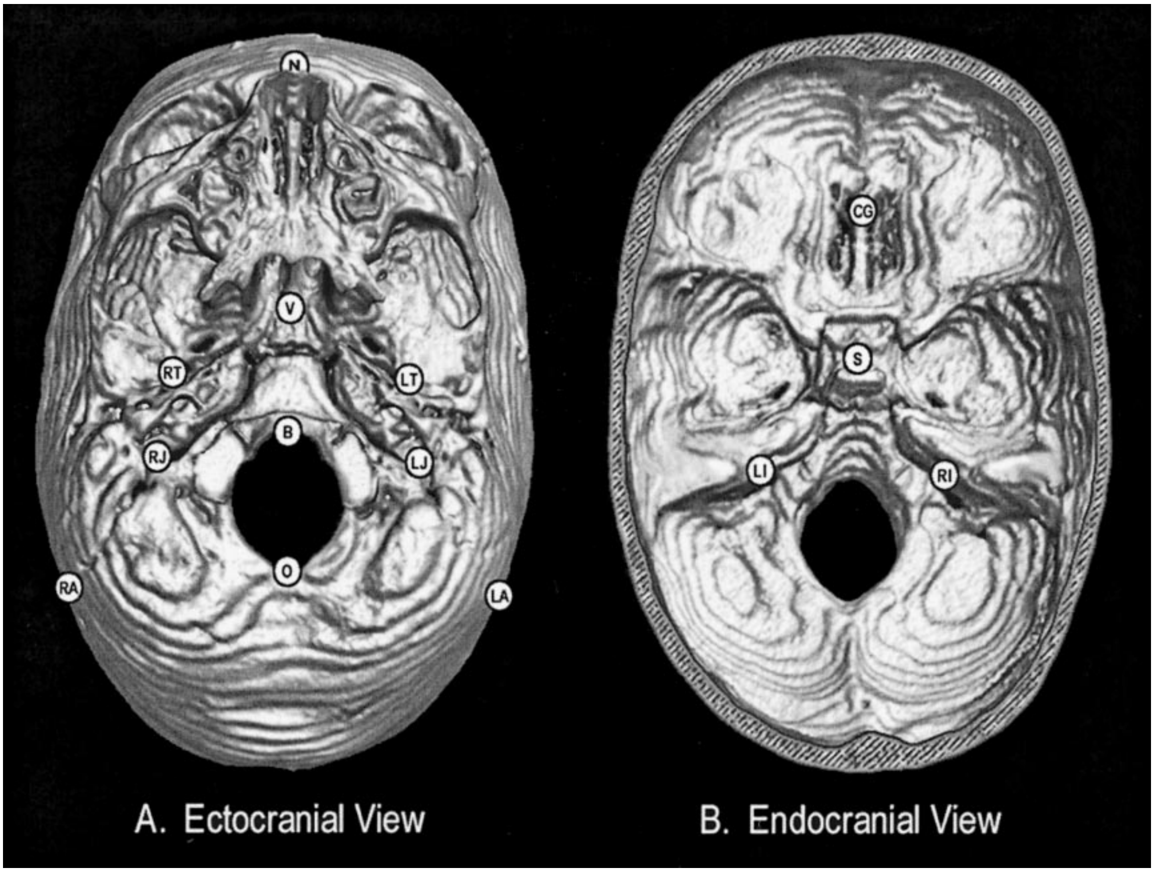

FIGURE 1 These landmarks, described in Table 2, were used for analyses in this study. Nasion (N) is not actually visible in this figure but was collected at the ectocranial junction of the frontonasal and nasal sutures. In postoperative patients subjected to frontal advancement surgery, nasion was collected from the stable bone that was not displaced by surgery.

operative patients to determine whether the patients would cluster into their respective pre- and postoperative groups on the basis of basicranial morphology. To compensate for size differences among individuals, each individual was scaled by dividing each linear distance by the geometric mean of all linear distances in that individual following Lele and Cole (1996).

TABLE 2 Basicranial Landmarks Used in This Study

Landmark	*Landmark Description*
N	Nasion
RA	Right asterion
LA	Left asterion
V	Vomer-sphenoid junction, posterior midline
RJ	Right jugular process, anterior point
LJ	Left jugular process, anterior point
B	Basion (ectocranial surface)
O	Opisthion (ectocranial surface)
RT	Right temporal–sphenoid junction at petrous
LT	Left temporal–sphenoid junction at petrous
CG	Crista galli
RI	Right internal auditory meatus
LI	Left internal auditory meatus
S	Center of sella turcica on the endocranial surface

Test of form difference in all-patient sample (n = 37)

Next, EDMA was used to compare basicranial morphology between preoperative and postoperative patients with ISS. Because we were interested in testing for differences in both shape and size (i.e., form differences), the original landmark data were used, without scaling for size. An initial EDMA form comparison of male and female preoperative morphology indicated that there was no significant difference ($p \leq 0.10$) between male and female shape in any region of the cranial base, so males and females were considered in a combined patient sample. To test for statistically significant differences between pre- and postoperative shape, EDMA analyses were performed on subsets of landmarks such that the sample size of the larger sample was greater than the number of landmarks in the subset. These landmark subsets are given in Table 3 and represent specific regions of the cranial base. The null hypothesis was that the shape of the preoperative ISS cranial base is the same as that of the basicranium in children who had undergone corrective neurocranial surgery one year previously.

Confidence intervals were then calculated for each linear distance in order to isolate any localized, significant differences or similarities between the preoperative and postoperative

TABLE 3 Landmark Subsets Analyzed to Permit Statistical Testing of Form Differences

Subset	*Landmarks Included**
Anterior base	N, RT, LT, RI, LI, S
Posterior base	RA, LA, RJ, LJ, B, O
Sphenoid	V, RT, LT, S
Midline	N, V, B, O
Marginal neurocranium	N, RA, LA
Right base	N, RA, RJ, B, RT, RI, S
Left base	N, LA, LJ, B, LT, LI, S

* Landmarks are summarized in Table 2.

TABLE 4 Age-Matched Subsample of 1- to 3-Year-Old Preoperative and Postoperative Individuals

*Preoperative**			*Postoperative†*		
Patient	*Age at Scan (wk)*	*Sex*	*Patient*	*Age at Scan (wk)*	*Sex*
22	70	M	12	66	M
23	95	M	4	68	M
24	116	M	16	72	M
			7	75	M
			9	88	M
			17	89	M
			5	94	M
			1	95	M
			20	96	M
			21	113	M
			14	115	M

* For preoperative patients, the average age at scan was 93.7 weeks; the number of patients was 3.

† For postoperative patients, the average age at scan was 88.3 weeks; the number of patients was 11.

basicrania. This calculation considers each linear distance individually, and each test determines whether a particular linear distance is equivalent in the preoperative and postoperative patients with ISS.

Test of form difference in age-matched patient sample (n = 14)

Because basicranial form changes with age, age-matched subsamples were created consisting of 3 preoperative and 11 postoperative patients (Table 4) to address the difference between pre- and postoperative cranial base morphology. The two groups each included patients whose ages spanned the range from 66 to 116 weeks and whose mean ages (preoperative: 93.7 weeks; postoperative: 88.3 weeks) were similar. This age-matched subsample was subjected to the same EDMA analyses discussed above, including tests of similarity of overall shape and of regional shape using landmark subsets and calculation of confidence intervals for each linear distance. The sample size of age-matched preoperative CT scans is small (n = 3), because surgery is usually performed during the first year after birth. There are several reasons that a patient with ISS would not have undergone surgery within the first year of life, including ascertainment bias. Patients with ISS that are not referred to a surgeon until later in infancy may be less dysmorphic. However, it is equally possible that the referring physician delayed the referral, that the parents delayed seeing the surgeon, or that the parents originally opted to forgo surgery. The cranial morphology of the three unoperated, older individuals with ISS was found to be characteristically scaphocephalic and were considered representative of the sagittal synostosis morphology for this age range. Therefore, although small sample size limits the ability to address statistical significance in this age-matched sample, results of the analyses provide descriptive evidence of morphologic differences between preoperative and postoperative ISS basicrania.

Comparison of growth patterns

If differences were found between age-matched preoperative and postoperative cranial base morphologies, the age-matched pre- and postoperative mean forms would be considered to represent alternative ''destinies'' for a younger individual with a fused suture. Without surgery, one cranial base morphology is the outcome, and if surgery is performed, another morphology results (Fig. 2). Given that the cranial base is not directly manipulated during surgery, these differences were interpreted to be the result of differing basicranial growth patterns in the surgically modified system (''surgically modified growth'') and the unoperated, synostosed system (''synostosed growth''). Based on the results of the age-matched pre- and postoperative form comparison, inferences were made about differential growth patterns with and without surgery. To test these inferences, additional EDMA analyses addressing growth were conducted.

Surgically modified growth was assessed using longitudinal data for 11 children taken from the patient sample discussed above (Table 5). Preoperative scans were acquired just prior to surgery (mean age 18.6 weeks, ranging from 5 to 44 weeks), and the postoperative scans were obtained approximately 1 year after surgery (mean age 88.3 weeks, ranging from 66 to 115 weeks). EDMA analysis of these longitudinal cases provided information on mean, surgically modified growth patterns in these 11 operated children.

Cross-sectional data from preoperative scans were used to make inferences about synostosed growth in which no surgery has yet taken place (Table 6). Preoperative scans that were not included in the longitudinal analysis were divided into a young group (mean age 15.7 weeks, ranging from 5 to 35 weeks, n = 10) and an old group (mean age 93.7 weeks, ranging from 70 to 116 weeks, n = 3). These groups are similar in age to those used in the longitudinal analysis of surgically modified growth. Cross-sectional data are routinely used in studies to make inferences about growth (Healy, 1986; Farkas, 1994; Ishii et al., 1998; Ferrario et al., 1999). In this study, longitudinal data for unoperated patients with ISS were unavailable, and the use of cross-sectional data allowed us to make inferences about synostosed growth in patients with ISS who have not had surgery.

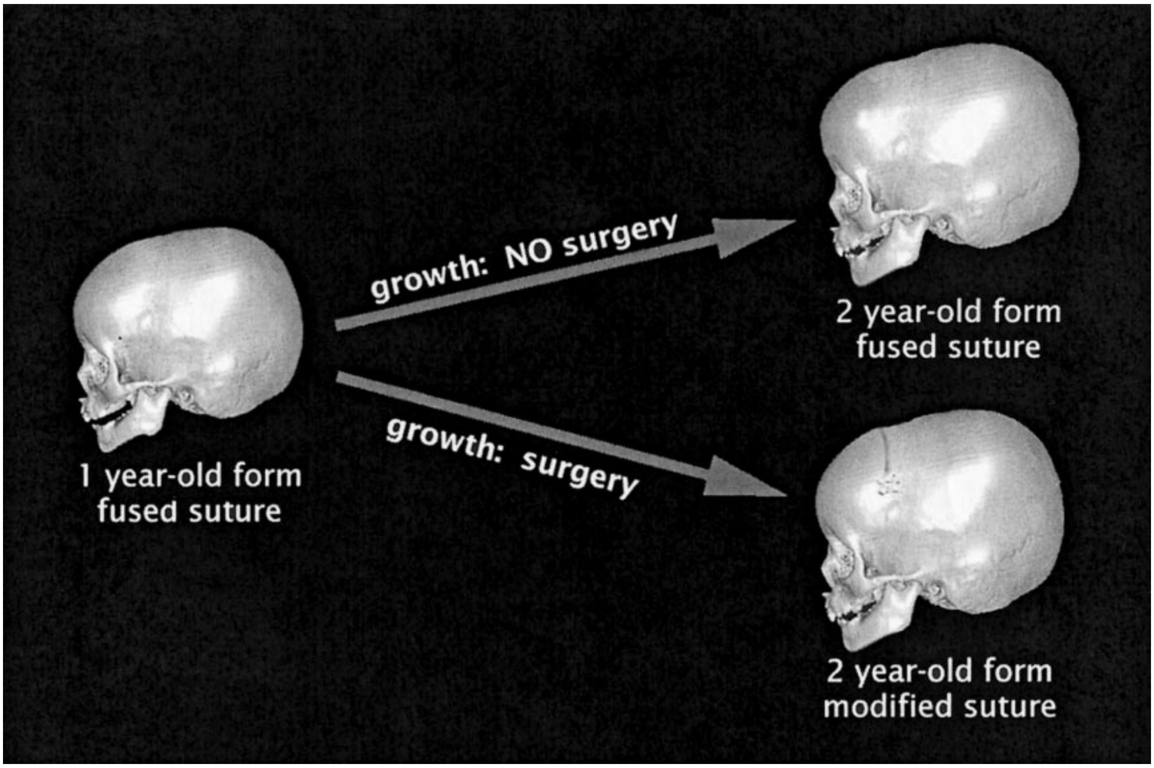

FIGURE 2 In comparing growth patterns, surgically modified growth was measured as the morphological change displayed in longitudinal data. Synostosed growth was measured as the morphological differences between cross-sectional data.

Results

PCOORD analysis of all-patient sample (n = 37)

Figure 3 summarizes the results of PCOORD analysis using all 37 scans and all cranial base landmarks, scaling the data for size. Preoperative and postoperative patients with ISS cluster differentially, with some overlap. The scaling factor was moderately correlated with position along the first principal axis ($r = 0.59$) but less so along the second principal axis ($r = 0.41$). A Pearson correlation of age and position along the principal axes showed that age is not significantly associated with position along the first ($r = 0.51$) or second ($r = 0.45$) principal axis. It was concluded that morphology associated with preoperative or postoperative status explains the separation of the two groups.

The following linear distances were moderately to strongly correlated with the position of individuals on the first principal axis: nasion to crista galli ($r = 0.91$), right jugular process to left internal auditory meatus ($r = 0.72$), and left internal auditory meatus to right internal auditory meatus ($r = 0.65$). These linear distances in particular tended to be larger in in-

TABLE 5 Patients Included in Longitudinal Analysis of Surgically Modified Growth*

Preoperative†			*Postoperative‡*		
Patient	*Age at Scan (wk)*	*Sex*	*Patient*	*Age at Scan (wk)*	*Sex*
1	5.1	M	1	95	M
4	8	M	4	68	M
5	8.7	M	5	94	M
7	10	M	7	75	M
9	12	M	9	88	M
12	16	M	12	66	M
14	18	M	14	115	M
16	23	M	16	72	M
17	24	M	17	89	M
20	36	M	20	96	M
21	44	M	21	113	M

* Longitudinal data for a 12th patient (patient 23) was not included because this patient was significantly older than the rest of the sample.
† For preoperative patients, the average age at scan was 18.6 months.
‡ For postoperative patients, the average age at scan was 88.3 months.

TABLE 6 Patients Included In Cross-Sectional Analysis of Unoperated, Synostosed Growth

*Young Preoperative**			*Old Preoperative†*		
Patient	*Age at Scan (wk)*	*Sex*	*Patient*	*Age at Scan (wk)*	*Sex*
2	5.4	M	22	70	M
3	6.9	M	23	95	M
6	9	M	24	116	M
8	11.7	M			
10	12.7	F			
11	13.6	M			
13	17	M			
15	18.3	F			
18	27	F			
19	35	M			

* For young preoperative patients, the average age at scan was 15.7 months.
† For old preoperative patients, the average age at scan was 93.7 months.

dividuals falling at the positive end of the first principal axis, including all postoperative patients and about half of the preoperative patients. In addition, the broad distribution of preoperative patients along this axis, compared with the clustering of the postoperative patients, suggested that the linear distance crista galli to nasion is highly variable among preoperative patients with ISS and less variable postoperatively. No linear distances were strongly, negatively correlated with the first principal axis.

Several linear distances contributed to the separation of pre- and postoperative patients along the second principal axis (Table 7). Distances that displayed highly positive correlations with the second principal axis included six linear distances connecting crista galli and nasion with other landmarks on the cranial base. All other linear distances from crista galli or nasion to other points on the cranial base were also positively correlated with the second principal axis. As a group, these distances tended to be longer in the postoperative patients and shorter in the preoperative patients. Those linear distances that were negatively correlated with the second principal axis included three linear distances involving right or left asterion. These distances were smaller in the postoperative patients, relative to the preoperative patients and suggest that the location of asterion relative to other cranial base landmarks may be important in distinguishing the morphology of these two groups.

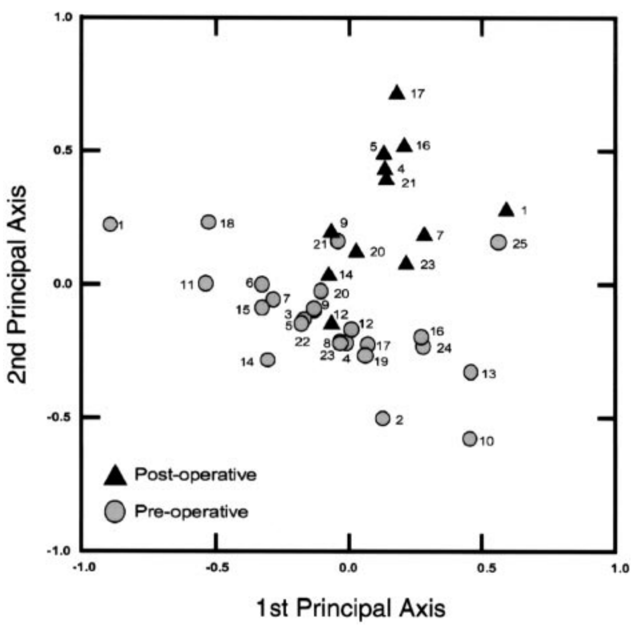

FIGURE 3 Using the principal coordinate analysis application of EDMA (PCOORD) in the all-patient sample, preoperative and postoperative patients with isolated sagittal synostosis (ISS) were found to cluster differentially with minor overlap. Linear distances that were highly correlated with position along the second principal axis are listed in Table 7. Nasion, crista galli, and asterion were important in distinguishing the two groups.

Test of form difference in all-patient sample (n = 37)

The results of the EDMA bootstrap test of form difference between all preoperative (n = 25) and postoperative (n = 12) patients with ISS for each of the landmark subsets are provided in Table 8. Six of the seven landmark subsets showed significant differences in form ($p = .10$) for the all-patient sample, but the subset of landmarks at the marginal neurocranium was not significantly different between these two groups ($p = .33$). Crista galli was highly variable in our dataset and was removed from statistical analyses of form, because extreme variability makes bootstrap testing unreliable and can obscure significant results.

TABLE 7 Principal Coordinate Analysis (PCOORD)*

Positive Correlations		*Negative Correlations*	
Distance	*r*	*Distance*	*r*
CG, V	.78	RA, RJ	−.76
CG, RI	.77	LA, V	−.74
CG, LI	.76	RA, V	−.70
CG, RJ	.72		
CG, RT	.71		
N, V	.70		

* These linear distances were highly correlated ($r \geq 0.70$) with the second principal axis in the PCOORD analysis of all preoperative and postoperative patients (N = 37) shown in Figure 3. Nasion, crista galli, vomer-sphenoid junction, and right and left asterion are primarily involved in the linear distances that distinguish these two groups. Descriptions of landmarks are summarized in Table 2.

TABLE 8 p Values for Form Differences Between Pre- and Postoperative Patients*

Subset	*p Values for Test of Significant Difference in Form*	
	All-Patient Sample	*Age-Matched Sample*
Anterior base	.02	.38
Posterior base	.01	.04
Sphenoid	.07	.01
Midline	.01	.01
Marginal neurocranium	.33	.66
Right base	.01	.01
Left base	.01	.21

* These *p* values were obtained for form differences between preoperative and postoperative isolated sagittal synostosis patients in EDMA analyses of the indicated landmark subsets.

The results of these analyses indicate that the morphology of the cranial base (as represented by the landmarks utilized in this study) is significantly different in preoperative and postoperative patients with ISS. Confidence intervals showed 68 of the 78 linear distances (87%) to be significantly greater in the postoperative patients ($\alpha = 0.10$). These results may be related to the age distribution of preoperative patients in the total patient sample, which was significantly younger than that of the postoperative age distribution.

Test of form difference in age-matched patient sample ($n = 14$)

To control for the effect of age-associated differences in form, the same analyses were conducted on the age-matched sample of pre- and postoperative patients (see Table 4). Results of the bootstrap test of form difference for the seven landmark subsets are provided in Table 8. Four of the seven landmark subsets showed statistically significant differences in morphology between age-matched pre- and postoperative patients with ISS ($p \leq .10$). Confidence intervals showed 8 of 13 linear distances involving nasion to be significantly greater in the postoperative mean form ($\alpha = 0.10$; Fig. 4). In addition, a number of mediolateral distances on and in close proximity to the petrous temporal bone were significantly greater in the postoperative group, indicating that the width of the middle cranial fossa, between right and left petrous temporal regions, was relatively greater in postoperative patients than in age-matched preoperative patients.

In contrast, the length and width of the posterior basicranium was significantly reduced in the postoperative group, as was the height of the sphenoid body between sella and vomer-sphenoid junction (Fig. 4). In addition, distances from right and left asterion to other ipsilateral and midline landmarks of the cranial base were significantly shorter in the postoperative patients. However, the distance from right to left asterion was similar in the two groups. Therefore, width of the posterior neurocranium measured from right to left asterion showed no difference whether or not a child has had surgery, but the relationship of asterion to points on the cranial base proper was different between the two groups.

Nasion and asterion played a significant role in distinguishing the preoperative and postoperative forms, but there was no significant difference in the linear distances joining nasion to right and left asterion or that joining right and left asterion as mentioned above. In other words, the triangle joining these three landmarks on the marginal neurocranium (nasion-right asterion-left asterion) appeared to be unaffected by surgery, but its relationship to the cranial base was impacted significantly.

A marked difference in the cranial base angle (nasion-sella-basion) in age-matched preoperative and postoperative patients with ISS was also observed. The cranial base angle in the mean postoperative form was 18% greater than that in the mean preoperative form. The distance between nasion and basion was significantly greater in postoperative patients, and the distance between nasion and sella was slightly larger on average in the postoperative sample but not statistically significant. However, the linear distance between sella and basion was significantly smaller in postoperative patients relative to the preoperative patients.

Comparison of growth patterns

Based on observations of form differences using age-matched pre- and postoperative individuals (above), it was hypothesized that growth of the cranial base is affected by neurocranial surgery. Operated patients (surgically modified growth) were expected to show a greater magnitude of growth in the mediolateral linear distances in and around the middle cranial fossa and in the linear distances that stretch from nasion to other landmarks on the cranial base. But it was anticipated that these operated patients, relative to unoperated patients (synostosed growth), would show less growth along the posterior basicranium from sella to basion, in the height of the sphenoid body from sella to the vomer-sphenoid junction, and in linear distances between right or left asterion and other basicranial landmarks. It was also predicted that growth in linear distances on the marginal neurocranium (the triangle nasion-right asterion-left asterion) would be similar in operated and unoperated patients. Finally, operated patients were not expected to have as great a decrease in the cranial base angle as that seen in unoperated patients.

These hypotheses were tested by comparing surgically modified growth from just prior to surgery to 1 year postoperatively using our longitudinal dataset (see Table 5) with an inferred pattern of synostosed growth from a cross-sectional subsample of preoperative patients grouped into two age classes (see Table 6). This comparison of surgically modified growth patterns using longitudinal data and synostosed growth patterns from cross-sectional data produced results that were consistent with our expectations. Figure 5 shows linear distances in which magnitude of growth differed by more than 5% between surgically modified and synostosed growth patterns. These represent the extremes of differences in magnitudes of growth between the two groups. As expected, a number of mediolateral distances in the posterior region of the middle cranial fossa showed greater magnitudes of growth in the sur-

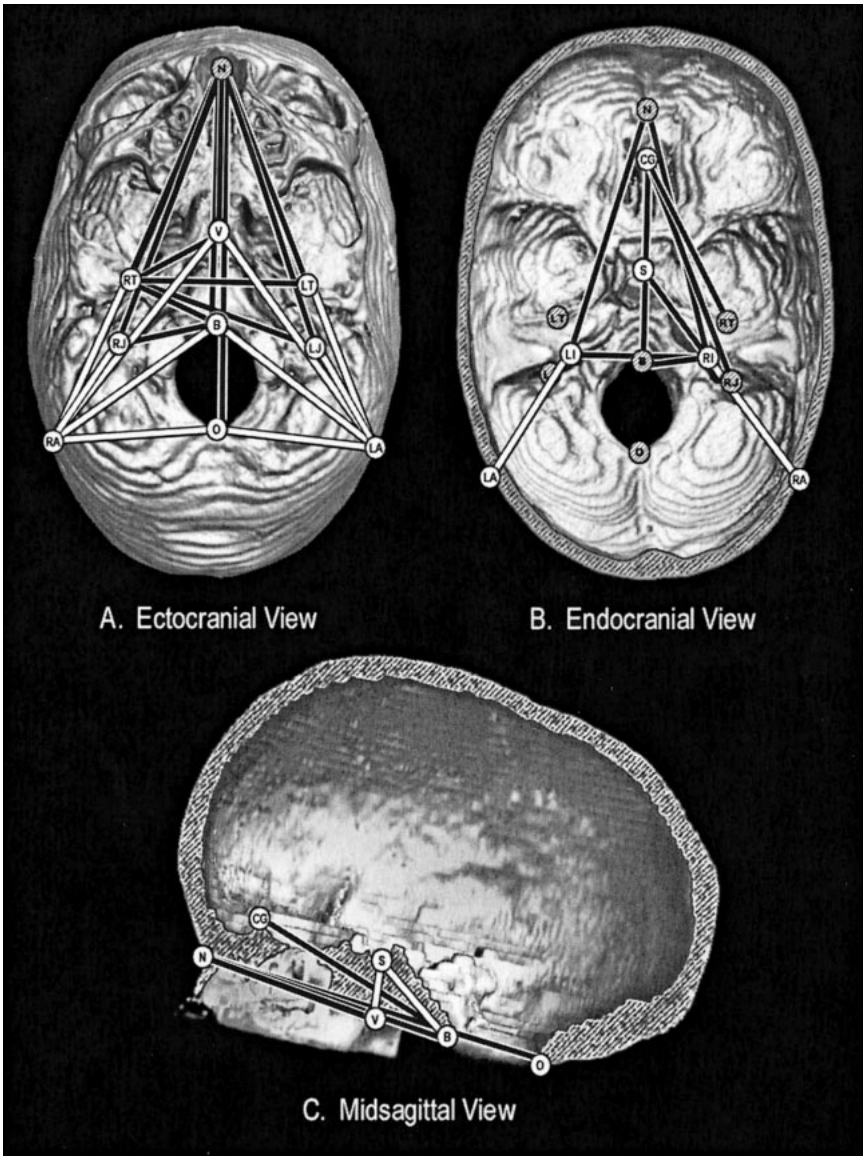

FIGURE 4 The EDMA analysis of the age-matched patient sample showed that certain linear distances were significantly different ($\alpha = 0.10$) between preoperative and postoperative 1- to 3-year-old mean forms (black lines were greater in the postoperative mean form, and white lines were greater in the preoperative form). Landmarks are listed in Table 2. Note that mediolateral distances and distances involving nasion were greater in the postoperative form, and that distances involving asterion were greater in the preoperative form.

gically modified sample relative to the unoperated sample, including that between right and left temporal-sphenoid junctions. This suggested that the right and left temporal-sphenoid sutures are displaced laterally to a greater degree in the surgically modified system, relative to the rest of the cranial base. A number of linear distances from nasion to other landmarks on the middle and posterior cranial base also displayed a higher magnitude of growth postoperatively.

Operated patients displayed lesser magnitudes of growth, relative to the unoperated sample, in the linear distances from right or left asterion to points on the cranial base. There was also substantially less growth in the height of the sphenoid. However, although it was anticipated that growth along the posterior basicranium (sella to basion) would be significantly less in the surgically modified system, the observed magnitude of growth differed by only 1% between operated and unoperated patients. Also, growth in linear distances on the marginal neurocranium (the triangle nasion, right asterion, left asterion) was very similar (within 2%) in operated and unoperated patients. Ipsilateral distances from internal auditory meatus to jugular process displayed greater growth in operated patients on the left side but a lesser magnitude of growth on the right side, relative to the unoperated sample. The short distance between these two landmarks may explain this result, because small differences in length represent relatively large proportions of the total length. Therefore, it is likely that growth of the linear distance internal auditory meatus to ipsilateral jugular process is comparable in operated and unoperated patients.

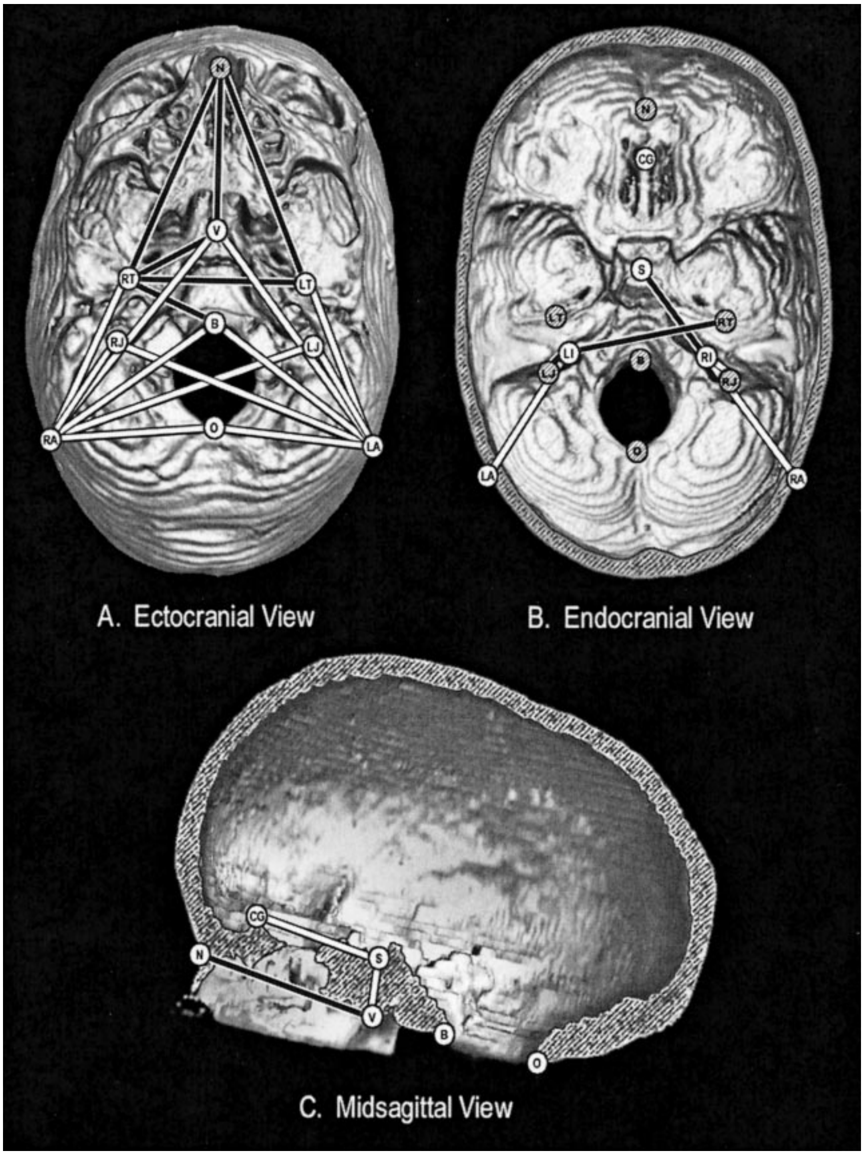

FIGURE 5 Results of EDMA analysis represent the greatest differences in magnitudes of growth between cross-sectional, synostosed and longitudinal, surgically modified growth patterns. Black lines show distances in which the magnitude of growth was at least 5% greater in the operated patients, and white lines show distances in which growth was at least 5% greater in the unoperated patients.

Finally, the cranial base angle, on average, remained constant in patients who had corrective surgery. The magnitude of change in the cranial base angle had only a moderate correlation with age at time of surgery ($r = 0.55$). In contrast, cross-sectional evidence of synostosed growth in unoperated patients indicated a 10% average decrease in cranial base angle.

Discussion

Previous studies have demonstrated that surgical release of the fused sagittal suture produces improvement in neurocranial morphology for patients with ISS (Kaiser, 1988; Marsh et al., 1991; Posnick et al., 1993). However, the effect of these surgical procedures on the cranial base has not been well understood. We have demonstrated that basicranial morphology is significantly different in preoperative and postoperative children with ISS and provided additional information about specific growth patterns of the cranial base in synostosed and surgically modified systems.

The data indicate that a number of mediolateral distances across the cranial base are, on average, larger in the postoperative sample. Significantly greater distances between the right and left temporal-sphenoid junctions, and from the right temporal-sphenoid junction to basion, sella, and vomer-sphenoid junction, indicate that the temporal-sphenoid sutures are positioned more laterally in postoperative patients. We were able to confirm that mediolateral growth in this area was greater in the surgically modified system than in the synostosed system. The significantly greater linear distance between right

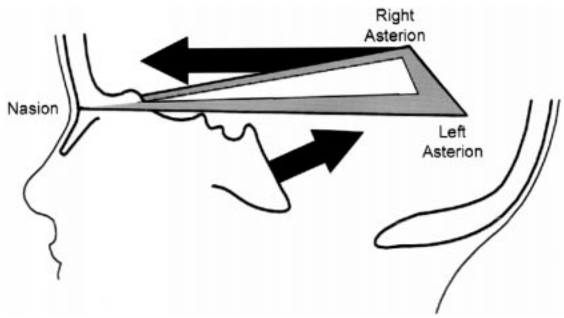

FIGURE 6 **The marginal neurocranium (nasion, right asterion, left asterion) was similar in both preoperative and postoperative patients with isolated sagittal synostosis but positioned differently relative to the cranial base. Either the marginal neurocranium was anteriorly translated or the cranial base was posteriorly translated, or a combination of both of these processes occurred in postoperative patients. There was no evidence to indicate that any portion of the cranium remained stable.**

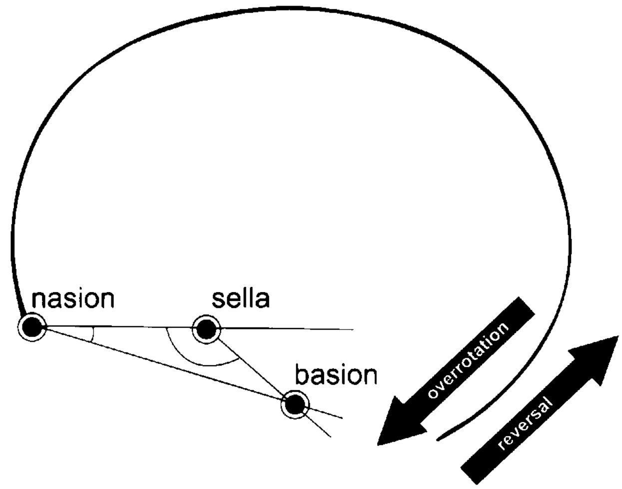

FIGURE 7 **Regarding the concept of "occipital overrotation," Slomic and colleagues (1992) found that the cranial base angle (nasion-sella-basion) was more acute in patients with isolated sagittal synostosis (ISS) than normal controls and that the angle sella-nasion-basion was more obtuse. From this, they inferred an overrotation of the occipital region in patients with ISS. The results of the present analysis demonstrate that, on average, the cranial base angle remains constant following neurocranial surgery.**

and left internal auditory meati in age-matched, postoperative patients supports an interpretation of lateral displacement of the temporal bones following surgery. Further, linear distances from nasion to points in the petrous temporal region were significantly longer in the postoperative form. This suggests a more pronounced anteroposterior expansion of the anterior cranial fossa following neurocranial surgery, discussed in more detail below. In contrast, linear distances between the asterions and the same group of landmarks around the petrous temporal region are significantly shorter in the postoperative form, suggesting that unoperated patients are experiencing more pronounced growth in the posterior cranial fossa. Interestingly, the triangle formed by the landmarks nasion, right asterion, and left asterion (the marginal neurocranium) is nearly equivalent in the preoperative and postoperative forms. These results indicate that, although the relative position of these three landmarks on the marginal neurocranium is not affected by surgery, neurocranial manipulation does impact the position of the marginal neurocranium relative to the cranial base. Because we cannot assume the stability of any part of the skull during growth, the marginal neurocranium may be moving anteriorly relative to the cranial base, or the cranial base may move posteriorly relative to the neurocranium (Fig. 6).

In addition, the cranial base angle, which became more acute over time in unoperated patients, remained constant on average following surgery in the operated patients. This finding was related to an alleviation of the cranial overrotation in patients with ISS reported by Slomic and colleagues (1992). They compared cephalometric data from a group of 13 preoperative patients with ISS to an age-matched normal group (n = 492). Occipital overrotation was inferred from a number of linear and angular measurements, including a significant decrease in the cranial base angle and a significant increase in the angle sella-nasion-basion (Fig. 7). Excessive posterior and inferior movement of the calvaria in relation to a fixed cranial base was proposed as the mechanism for the observed overrotation (Slomic et al., 1992). This proposed mechanism may be an artifact of the method of superimposition, with registration on sella and orientation along the sella-nasion line. Superimposition minimizes variation along the line of orientation, increasing the apparent variation in more distantly located landmarks (Moyers and Bookstein, 1979; Richtsmeier and Cheverud, 1986; Cole, 1996). Therefore, one may not determine from these results whether the mechanism was posterior and inferior movement of the calvaria, anterior and superior movement of the cranial base, or a combination of both. Nevertheless, calculation of the cranial base angle is independent of any particular registration or orientation, and the finding of a reduced cranial base angle in patients with ISS by Slomic and colleagues (1992) is supported by our results.

A decrease in or reversal of this pattern of overrotation was observed in our longitudinal, surgically modified sample of patients with ISS. The results suggest that surgical release of a fused sagittal suture, on average, results in the cranial base angle remaining constant in the first postoperative year, rather than becoming more acute as in unoperated patients with ISS. The combination of larger cranial base angle relative to preoperative patients, and anterior displacement of the neurocranium relative to the cranial base, leads to the conclusion that any occipital overrotation in young, preoperative patients with ISS is mitigated, or even reversed, by surgical intervention. Moreover, this finding may be correlated with the apparent lengthening of the anterior cranial base following surgery. Although typical ISS morphology includes anteroposterior lengthening of the neurocranium, only the posterior cranial base clearly undergoes above-normal anteroposterior lengthening, while the anterior cranial base grows at a lesser rate (Richtsmeier et al., 1991). The occipital overrotation in ISS, described above, may actually create a constraint on the anteroposterior growth of the anterior cranial base, for example, by abnormal tensional forces in dural tracts (Moss, 1960). On the release of the fused suture and alleviation of the occipital overrotation growth trajectory, the anterior cranial base may experience increased anteroposterior growth, and the posterior cranial base may show reduced anteroposterior growth. This pattern is consistent with the results of this study.

In conclusion, this study has shown that cranial base morphology in pre- and postoperative patients with ISS is significantly different. Comparison of surgically modified growth in a longitudinal sample with synostosed growth in an unoperated, cross-sectional sample supports the conclusion that these differences are the product of different growth trajectories in the presence of a fused suture and in the presence of a surgically modified suture system. Specifically, following surgery the cranial base displays increased growth along a mediolateral axis through the petrous temporal region and in linear distances between nasion and landmarks in the petrous temporal region. In contrast, the posterior cranial fossa shows a smaller magnitude of growth following surgery in linear distances involving right and left asterion, relative to that seen in unoperated patients. Despite these differences, the triangle formed by the landmarks nasion, right asterion, and left asterion is nearly equivalent in the preoperative and postoperative forms and appears to have comparable magnitudes of growth in the surgically modified and synostosed systems. This triangle, which is representative of the inferior margin of the neurocranium, is anteriorly translated relative to the cranial base in operated patients, raising the possibility that the entire neurocranium is anteriorly translated following neurocranial surgery. Alternatively, these findings may be explained by the maintenance of a constant cranial base angle postoperatively and an associated posterior translation of the cranial base relative to the neurocranium. Further study is required to address the differential impact of various surgical interventions on growth of the cranial base.

This study provides additional support for the proposition that the neurocranium and the basicranium are developmentally interrelated and that manipulations (surgical or otherwise) restricted to the neurocranium do impact morphology and growth of the cranial base. Increasing our knowledge of the interrelated nature of the cranial components will aid us in understanding growth of the skull under normal and pathologic conditions and help in developing predictive algorithms for surgical planning.

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References

Abramson DL, Janecka IP, Mulliken JB. Abnormalities of the cranial base in synostotic frontal plagiocephaly. *J Craniofac Surg.* 1996;7:426–428.

Anton S. Intentional cranial vault deformation and induced changes of the cranial base and face. *Am J Phys Anthropol.* 1989;79:253–267.

Babler W, Persing J. Changes in facial and basicranial dimensions related to premature closure of the coronal suture in rabbits. *Anat Rec.* 1980;196:11A–12A.

Barritt J, Brooksbank J, Simpson D. Scaphocephaly: aesthetic and psychosocial consideration. *Dev Med Child Neurol.* 1981;23:183–191.

Burrows A, Richtsmeier J, Mooney M, Smith T, Losken H, Siegel M. Three-dimensional analysis of craniofacial form in a familial rabbit model of nonsyndromic coronal suture synostosis using Euclidean distance matrix analysis. *Cleft Palate Craniofac J.* 1999;36:196–206.

Carmel PW, Luken MG, Ashcerl GF. Craniosynostosis: computed tomographic evaluation of skull base and calvaria deformities and associated intracranial changes. *Neurosurgery.* 1981;9:366–372.

Cheverud JM, Kohn LA, Konigsberg LW, Leigh SR. Effects of fronto-occipital artificial cranial vault modification on the cranial base and face. *Am J Phys Anthropol.* 1992;88:323–345.

Cohen MM Jr. *Craniosynostosis: Diagnosis, Evaluation, and Management.* New York: Raven Press; 1986.

Cole TM III. Historical note: early anthropological contributions to ''geometric morphometrics.'' *Am J Phys Anthropol.* 1996;101:291–296.

Delashaw JB, Persing JA, Jane JA. Cranial deformation in craniosynostosis. *Neurosurg Clin N Am.* 1991;2:611–620.

Ebel K. Craniostenosis. Roentgenological and craniometric features. *Pediatr Radiol.* 1974;2:1–13.

Farkas LG. *Anthropometry of the Head and Face.* 2nd ed. New York: Raven Press; 1994.

Ferrario V, Sforza C, Poggio C, Schmitz J. Soft-tissue facial morphometry from 6 years to adulthood: a three-dimensional growth study using a new modeling. *Plast Reconstr Surg.* 1999;103:768–778.

Healy MJR. Statistics of growth standards. In: Falkner F, Tanner JM, eds. *Human Growth.* Vol. 3, 2nd ed. New York: Plenum Press; 1986.

Ishii K, Nielsen I, Vargervik K. Characteristics of jaw growth in cleidocranial dysplasias. *Cleft Palate Craniofac J.* 1989;35:161–166.

Jane J, Persing J. Neurosurgical treatment of craniosynostosis. In: Cohen M Jr, ed. *Craniosynostosis: Diagnosis, Evaluation, and Management.* New York: Raven Press; 1986:249–320.

Jimenez D. Endoscopic release of craniosynostosis. Presented at 56th Annual Meeting and Postconference Symposium of American Cleft Palate–Craniofacial Association; 1999; Scottsdale, Arizona.

Kaiser G. Sagittal synostosis—its clinical significance and the results of three different methods of craniectomy. *Childs Nerv Syst.* 1988;4:223–230.

Kreiborg S. Postnatal growth and development of the craniofacial complex in premature craniosynostosis. In: Cohen MM Jr, ed. *Craniosynostosis: Diagnosis, Evaluation, and Management.* New York: Raven Press; 1986.

Lele S, Cole TM III. A new test for shape differences when variance-covariance matrices are unequal. *J Hum Evol.* 1996;31:193–212.

Lele S, Richtsmeier JT. *An Invariant Approach to the Statistical Analysis of Shapes. Interdisciplinary Studies in Statistics Series.* London: Chapman and Hall-CRC Press; 2000. In press.

Lele S, Richtsmeier JT. Estimating confidence intervals for the comparison of forms. *J Hum Evol.* 1995;98:73–86.

Lele S, Richtsmeier JT. Euclidean distance matrix analysis: a coordinate free approach to comparing biological shapes using landmark data. *Am J Phys Anthropol.* 1991;98:73–86.

Marsh J, Jenny A, Galic M, Picker S, Vannier M. Surgical management of sagittal synostosis. A quantitative evaluation of two techniques. *Neurosurg Clin N Am.* 1991;2:629–640.

Marsh J, Vannier M. Cranial base changes following surgical treatment of craniosynostosis. *Cleft Palate J.* 1986;23:9–18.

Mooney MP, Siegel MI, Burrows AM, Smith TD, Losken HW, Dechant J, Cooper G, Kapucu MR. A rabbit model of human familial, nonsyndromicunicoronal suture synostosis. I. Synostotic onset, pathology, and sutural growth patterns. *Childs Nerv Syst.* 1998;14:236–246.

Moss ML. Inhibition and stimulation of sutural fusion in the rat calvaria. *Anat Rec.* 1960;136:457–468.

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

Posnick J. Commentary on correction of sagittal craniosynostosis. *J Craniofac Surg.* 1995;6:224–226.

Posnick J, Lin K, Chen P, Armstrong D. Sagittal synostosis: quantitative assessment of presenting deformity and surgical results based on CT scans. *Plast Reconstr Surg.* 1993;92:1015–1024.

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

Richtsmeier J, Grausz H, Morris G, Marsh J, Vannier M. Growth of the cranial base in craniosynostosis. *Cleft Palate Craniofac J.* 1991;28:55–67.

Richtsmeier JT, Lele S. Quantitative analysis growth: models and theoretical considerations. *Biol Rev.* 1993;68:381–411.

Richtsmeier J, Valeri C, Krovitz G, Cole T, Lele S. Pre-operative morphology and development in sagittal synostosis. *J Craniofac Genet Dev Biol.* 1998; 18:64–78.

Slomic AM, Bernier JP, Morissette J, Renier D. A craniometric study of sagittal craniosynostosis (SC). *J Craniofac Genet Dev Biol.* 1992;12:49–54.

Smith TD, Mooney MP, Burrows AM, Losken HW, Siegel MI. Postnatal changes in the cranial base in rabbits with congenital coronal suture synostosis. *J Craniofac Genet Dev Biol.* 1996;16:107–117.

Venes J, Sayers M. Sagittal synostectomy. Technical note. *J Neurosurgery.* 1976;44:390–392.

Virchow R. Uber dem Cretinismus, namentlich in Franken, und uber pathologische Schadelformen. *Verh Physikalische-Medizinische Gesellschaft in Wurzburg.* 1851;2:230–271.

Zumpano MP, Carson BS, Marsh JL, Vander Kolk CA, Richtsmeier JT. A three-dimensional morphological analysis of isolated metopic synostosis. *Anat Rec.* 1999;256:1–12.