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# Dysmorphology And Dysfunction In The Brain And Calvarial Vault Of Nonsyndromic Craniosynostosis

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**Dysmorphology and Dysfunction in the Brain and Calvarial Vault of Nonsyndromic  
Craniosynostosis**

Yale University School of Medicine  
in Partial Fulfillment of the Requirements for the  
Degree of Doctor of Medicine

by  
Joel Stanley Beckett  
2013

## **Abstract**

Craniosynostosis is a premature pathologic fusion of one or more sutures in the calvarial vault. The six calvarial sutures are growth sites between adjacent intramembranous bones, which allow for flexibility during passage through the birth canal and accommodation for the growing brain. (1) Premature fusion results in obvious cranial morphologic abnormality and can be associated with elevated intracranial pressure, visual dysfunction, mental retardation and various forms of subtler learning disability. (2)

A category of disease called isolated nonsyndromic craniosynostosis (NSC) represents nearly 85% of cases. It results in prototypical skull deformities and has newly-discovered correlations with poor neuropsychologic and visual functioning. Herein we utilize new techniques in magnetic resonance and three-dimensional computed tomographic analysis to explore neural and bony structural foundations to functional deficit. To our knowledge, this is the first report of evidence of microstructural and functional brain abnormalities in sagittal synostosis, and the first characterization of orbital abnormalities from coronal craniosynostosis that may underlie visual abnormalities.

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## Chapter 1: Background

### *History of Craniosynostosis*

The great anatomist Adolph Otto was first to coin the term “craniosynostosis” in 1830 and Virchow the first to describe the correlation between abnormal head shape and craniosynostosis in 1851 as “cessation of growth across a prematurely fused suture [in the calvarial vault]...with compensatory growth along nonfused sutures in a direction parallel to the affected suture.” (3-5)

Despite entering western medical vernacular in the 1800s, craniosynostosis is an ancient pathology. Kutterer and Alt studied 76 skulls from a prehistoric population in Switzerland that included three cases of craniosynostosis. (6) Pospíšilová and Procházková studied 745 dry skulls dated between the 13<sup>th</sup> and 18<sup>th</sup> centuries and found an incidence of lambdoid synostosis that matches today’s incidence. (7, 8) Most recently, Gracia et al. reported on a skull that is at least 530,000 years old with lambdoid synostosis. (9)

Perhaps the most famous and descriptive examples of disease come out of Ancient Greece. Pericles was a popular and successful fifth-century B.C. Athenian military general and statesman who saw the Athenian democracy and economic state flourish. (10) Greek historian Plutarch describes Pericles in his writings, *Lives*, as “overall handsome but with the head enormously long”. All known statues (Figure 1) and drawings of Pericles have a helmet placed over the occiput. It is thought that the artists of the time did not want to put into evidence such a defect. (11) It is from such

artwork and descriptions like those from Plutarch that modern medical scholars hypothesize that Pericles had scaphocephaly from sagittal craniosynostosis. At the other end of the spectrum was Thersites, a Greek warrior in the Trojan War, who was described by Homer (*Iliad, II, CCXV*) as “bow legged, lame... with a head shaped like a sugar loaf, coming to a point and full of obscenities, teeming with rant." As it is likely that both Pericles and Thersites had craniosynostosis (11), these two cases demonstrate the spectrum of impact on mental function.

Medical historians and anthropologists of today continue to find evidence that other famous historical figures, such as Abraham Lincoln and King Tutankhamen, may have had craniosynostosis. (12, 13) However, more than identifying simple deformity, the research focus of today is on the functional impact of craniosynostosis. To uncover the causes of functional deficit, we must first review some of the biology behind the morphological development of the bony calvarial vault.

### *Foundations of Cranial Vault Development*

The intermembranous bones-- paired frontal, parietal, squamosal bones, and part of the occipital bone-- and cranial sutures-- including the metopic, sagittal, coronal suture and lambdoid suture-- make up the calvarial vault. The precursor tissues to the frontal bones, metopic and sagittal suture are of neural crest origin, while the parietal bones and coronal sutures are derived from paraxial mesoderm. (14) The neural crest also contributes significantly to the dura mater, leptomeninges of forebrain and midbrain (15), and paryenchmal forebrain and midbrain (16).

The skull develops through migration of neural crest and mesenchymal cells to between the brain and ectoderm at the skull base, where they form mesenchymal blastemas. The blastemas differentiate along the osteogenic path through intramembranous ossification from the skull base toward the apex. (17) Cranial sutures develop between growing bones, which also happens to be at neural crest-mesoderm interfaces (aside from the metopic-frontal bone interface which is purely neural crest).(14) The sutures also tend to overlie areas in which brain tissue is not intimately associated with the bone (e.g., interhemispheric fissure and sagittal suture). Growth at the sutures is via mesenchymal cell differentiation into osteoblasts that express collagen 1, bone sialoprotein, and osteocalcin, and synthesize bone matrix at the osteogenic fronts. (18, 19)

There is significant interaction between bone, meninges and brain in the production of skull shape. The evidence is rooted in observations of close phenotypic integration of brain and calvarium across all walks of animal life. (20, 21) More direct evidence is found in certain craniofacial pathologies that demonstrate interactions of skull, meninges, and brain in development of the head including anencephaly, in which the calvarial bones do not form, and microcephaly, which produces prematurely fused sutures. (22, 23) It is thought that the dura may be the intermediary that allows for coordination of bone and brain growth. Moss and colleagues developed a hypothesis centered on biomechanical forces as the stimulus for osteogenic growth. His functional matrix theory states that tensile forces placed on the dura by brain growth drive osteogenic cells at the patent sutures to promote bone growth. (24) More recent



experimental work also suggests that dural tissue is responsible for preservation of suture patency and maintenance of skull shape. (25)

The calvarial sutures provide several important functions. First, they are the major sites of cranial vault growth that allows the vault to reach 90% of adult size by 3 years of age. (26) Additionally, the sutures are flexible joints that permit passage through the birth canal and are thought to act as shock absorbers during trauma. (14)

### *Craniosynostosis: Pathologic Suture Fusion*

Normally, the sagittal, coronal and lambdoid sutures remain patent well into adulthood while the metopic suture undergoes fusion during the first year of life; however, in an estimated 1 in 1,800 to 1 in 2,500 live births, one or more of the cranial sutures fuse prematurely resulting in the disease process called craniosynostosis.(27, 28) The traditional definition of craniosynostosis is a premature fusion of cranial vault sutures that results in an abnormal head shape as growth is accelerated at the remaining open sutures to accommodate for brain growth. (3) It is obvious, however, that craniosynostosis is a pathologically and etiologically heterogeneous process and as such needs to be described a number of ways.

The pathology can be described as syndromic (accompanied by other dysmorphic features in the face and extremities) or isolated/nonsyndromic (occurring without other skeletal anomalies beyond the region affected). Additionally, both syndromic and isolated can be either simple (involving a single suture) or complex (involving two or more sutures). Finally, the root cause can be defined as primary (caused by an intrinsic

defect in the suture) or secondary (premature closure of normal sutures secondary to another developmental or metabolic abnormality). (29)

This body of work is focused on the isolated/nonsyndromic population with simple primary synostosis, but a brief discussion of syndromic craniosynostosis is included below.

### *Lessons from Syndromic Craniosynostosis*

Syndromic cases make up a minority of the total craniosynostosis population, 15% in total (30, 31). However, while the cause of craniosynostosis remains mostly unclear, the pathoetiology of syndromic craniosynostosis is the most clear, with the greatest correlation to autosomal dominant genetic insults. There are nearly 180 identified syndromes and, to date, over 60 single gene mutations are identified as causal. (32, 33) The most frequently mutated genes include FGFR1, FGFR2, FGFR3, TWIST1, and MSX2.(29) Below, we touch on a few of the most common syndromes.

The first identified syndrome, Apert Syndrome, was described in 1906, by one of France's most eminent pediatricians. The characteristic features are craniosynostosis of bilateral coronal sutures, midface hypoplasia and variable symmetric syndactyly of hands and feet. It occurs in 15–16 of every 1,000,000 births.(34) Apert syndrome is associated with two mutations in FGFR2. Two-thirds of cases are associated with p.S252W, while one third are attributable to p.P253R mutation.(32) The cranial abnormality is termed acrocephaly (“peaked head”) – one could postulate that Thersities suffered from Apert Syndrome. (33)

Shortly thereafter, Louis Crouzon described a number of patients with craniosynostosis, shallow orbits, ocular proptosis, strabismus and maxillary hypoplasia in 1912. The frequency is approximately 40 in 1,000,000 births (35) and several different mutations in the FGFR2 gene cause the clinical sequelae.

Saethre-Chotzen syndrome, described in 1931, is characterized by coronal craniosynostosis, low set frontal hairline, broad great toes, ptosis, facial asymmetry, and cutaneous syndactyly. It is attributable to autosomal dominant mutations in the TWIST gene with high penetrance and variable expressivity. (36)

Pfeiffer Syndrome was described in 1964 and is associated with mutations in FGFR1 or FGFR2. (32, 37) Clinically, they have craniosynostosis of the coronal suture, midface hypoplasia, broad, medially deviated halluces; and variable cutaneous syndactyly. (3) The FGFR2 mutations are associated with more severe forms of Pfeiffer and can be correlated with cloverleaf skull (complete synostosis of all sutures) and additional extracranial anomalies like elbow ankylosis/synostosis. (38)

It is well known that syndromic craniosynostosis can affect mental development. This is classically thought to be secondary to growth conflict between the brain and cranial vault and resulting intracranial hypertension. In a classic study, Renier and coworkers documented increased intracranial pressure in 47% of patients with syndromic diagnoses including Apert's and Crouzon's and furthermore found a significantly decreased IQ in the Apert population. All-in-all, elevated intracranial pressure was associated with adverse effects on cognitive development as measured by linear regression analysis of intracranial pressure and IQ (as measured by Brunet–Levine and Binet–Simon tests). (39, 40)

In addition to elevated ICP, a recent study investigated white matter microstructure with diffusion-tensor imaging in 45 infants with Apert syndrome and 14 with Crouzon syndrome, among others, and found significant white matter integrity differences between children with craniosynostosis and healthy control subjects, which they conclude “could imply that the developmental delays seen in these patients could be caused by the presence of a primary disorder of the white matter microarchitecture.” (41)

Children with syndromic craniosynostosis have a number of other functional issues. These include obstructive sleep apnea from abnormal upper airway anatomy, central sleep apnea from compression on the medullary respiratory centers from a small posterior fossa (42), malocclusion, strabismus, extropia, divergent gaze, and optic atrophy among others. (43)

#### *Nonsyndromic craniosynostosis*

Eighty-five percent of individuals with craniosynostosis or 1 in 2100-3000 live births are affected by nonsyndromic/isolated craniosynostosis (NSC).(28, 44-46) NSC comes in several varieties with corresponding craniofacial dysmorphology: metopic craniosynostosis results in trigonocephaly, unicoronal craniosynostosis results in anterior plagiocephaly, bicoronal craniosynostosis results in turribrachycephaly, sagittal craniosynostosis results in dolichocephaly or scaphocephaly, and lambdoid synostosis causes posterior plagiocephaly. Additionally, there are thought to be a number of other nonsyndromic multiple suture craniosynostoses; however, an increasing number of these are shown to be mild presentations of known syndromic craniosynostoses. (27)

### *Pathoetiology of Nonsyndromic Craniosynostosis*

Unlike syndromic craniosynostosis, NSC most frequently occurs in a sporadic fashion. The cause appears to stem from a variety of yet unknown gene-gene and gene-environment interactions. (47) Thus far, Ephrin-A4 (EFNA4) is the only clearly identified gene proposed to play a role in nonsyndromic craniosynostosis. (48) There is also evidence that FGFR3 mutations may be implicated in up to 50% of children with unicoronal NSC, but these results have been challenged by some evidence that these children may actually be afflicted with Muenke Syndrome. (49, 50) Autosomal dominant familial inheritance, in the absence of a known identifiable gene, is reported to account for approximately 8–14% of NSC cases. (51)

There is much unknown about the etiology and causal factors of the remaining or sporadic NSC. Environmental factors are posited to play a role. Studies demonstrating higher rates of NSC in twins support the theory that antenatal cranial vault compression can cause synostosis. (51) Furthermore, Higginbottom *et al.* reported three cases of craniosynostosis purported to be from external force to the head-- breech position, amniotic band, and a morphologic abnormality of the uterus, respectively. (52) However, there are a number of other studies that fail to show correlation between compression and synostosis. (53)

Laboratory explorations of a compression theory have also yielded mixed results. Mouse studies demonstrate that intrauterine constraint results in 88% suture fusion, with increased FGFR2 and TGF- $\beta$  expression in the fused sutures. Furthermore, head constraint induces BMP-4, Noggin and Indian Hedgehog expression in the sutures. (54-

56) However, restriction of sutural expansion in lambs by rigid plating across the coronal sutures 8 weeks antepartum failed to cause any suture fusion. (57)

In addition to fetal constraint, a number of other environmental risk factors are reported in association with NSC. They include, but are not limited to: maternal smoking, white race, advanced maternal age, use of nitrosatable drugs<sup>1</sup>, fertility treatments, hyperthyroidism, and warfarin ingestion during gestation. (58, 59)

Regardless of genetic and environmental cause, there exist two different fundamental theories of pathological origin. The first is the classic “primary bone hypothesis” as suggested by Virchow, which others have since supported. (3, 5) This concept intimates that any change in cranial base length, brain volume, cerebrospinal fluid (CSF) volume, and intracranial pressure are secondary to primary suture fusion. There are several clinical signs that suggest cortical brain tissue is compressed in the process of growing within a limited skull. As many as 70% of children with craniosynostosis have the X-Ray finding of a “copper beaten skull”, which is indicative of gyral compression on the membranous bone and related to growth restriction. (60) Additionally, it is not uncommon to find compression of the neighboring ventricular system and papilledema (61, 62), some studies have shown elevated intracranial pressure (2, 63), while others have been mostly equivocal. (64-66) This discrepancy in ICP monitoring is likely directly related to the variability of pediatric ICP. (63)

Several recent investigations provide evidence for this “primary bone hypothesis”. Aldridge and colleagues examined preoperative infants with isolated sagittal, metopic, unilateral coronal or lambdoid synostosis and compared them with unaffected infants.

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<sup>1</sup> Drugs containing secondary or tertiary amines or amides, form *N*-nitroso compounds. Examples include chlordiazepoxide, nitrofurantoin, and chlorpheniramine

Significant differences in morphology were found that seemed to correspond to regions of bony compression. (67) For example, sagittal patients displayed anteriorly displaced ventricles and genu of the corpus callosum relative to the unaffected group.

Furthermore, recent studies demonstrate decreases in brain parenchymal volume when surgical decompression is delayed, indicating that NSC may cause tissue injury as the brain grows and can result in reduction of brain mass in patients without prompt corrective surgery. (63, 68, 69)

The second theory relates the concept that suture fusion is secondary to another process. It is proposed that NSC cases are due to underlying pathology, perhaps originating early in the course of embryonic development. (70) Obvious examples of this exist in the presence of overt disease states such as rickets (71) and microcephaly (23). More interestingly, a number of studies propose that even in those cases of sporadic NSC the suture fusion may be a secondary finding to an intrinsic problem within the dura or CNS.

The evidence for this theory is rooted in the known genetic risk factors for craniosynostosis that include FGFR and TWIST, albeit mostly in syndromic craniosynostosis, and their important role in neurodevelopment. (72-75) Furthermore, there is a growing body of literature which describes “prototypical” NSC head shapes in the absence of synostosis- for example scaphocephaly without sagittal craniosynostosis, perhaps indicating that the head shape is not driven by suture fusion alone. (76-80) Several imaging studies also seem to corroborate a more diffuse developmental problem. Two studies examined brain morphology in children with sagittal and unicoronal NSC, respectively, each comparing the preoperative brain to the postoperative brain as well as

to normal controls. Aldridge et al. (2005) concluded that the NSC brain is fundamentally different in gross subcortical morphology unrelated to skull compression and that it has a growth pattern that is independent of skull constriction. (81, 82) Richtsmeier et al. (2006) conducted a morphologic analysis of infants with either sagittal or right coronal synostosis and found significant differences in skull-brain integration throughout the calvarial vault. They suggest from these findings “the current focus on the suture as the basis for this condition may identify a proximate, but not the ultimate cause for these conditions”. (47)

#### *Functional Disability in Nonsyndromic Craniosynostosis*

In addition to overt skeletal dysmorphology, children with NSC frequently suffer from functional disabilities. One of the most extensively studied in recent decades is cognitive development. (83) A myriad of studies have used developmental quotients (DQ) and IQ testing to reveal that children with NSC have neuropsychological problems, but the cause of such disabilities remain mysterious. (84)

The second disability of interest is visual and ocular malfunction in unicoronal craniosynostosis. Strabismus, refractory problems and visual field cuts have been identified in a number of NSC subtypes, but seem to be most prevalent in unicoronal craniosynostosis. (85)

#### *Neuropsychological deficit*

While up to 50% of children with *syndromic* craniosynostosis develop elevated intracranial pressure, which may lead to mental impairment and blindness (86), the same



is not true in NSC- the highest estimates of elevated ICP range around 15% and are generally more mild than syndromic cases. (39) Others have found no correlation between NSC and elevated ICP (66, 87), which lead early investigators to proclaim that NSC leads to no cognitive disability. (88, 89) In the past decade, however, there is growing evidence that NSC is associated with neuropsychological problems, including learning disabilities and behavior problems. (83, 84, 90, 91)

Recent studies demonstrate that an estimated 30-50% of children with NSC have subtle, but persistent behavioral problems and/or learning disabilities. (83, 90, 91) A large case-control study examining neurodevelopment in NSC recently corroborated this theory. (92) The authors enrolled and followed 209 cases of NSC and 222 matched controls during a 3-year period. Utilizing the Bayley Scales of Infant Development (Second Edition) and Preschool Language Scale, the authors found that the NSC children had a 1.5-2.0 increased odds ratio for being developmentally delayed in Mental Development Index, Psychomotor Development Index, receptive communication, and expressive communication. Many of the findings coincide with smaller studies, which demonstrate that children with NSC have decreased processing speed and difficulty performing tasks, which assess learning or memory, visual-spatial planning ability, and planning/problem-solving ability. (90, 93, 94)

Two main hypotheses for the etiology of learning disability exist. The first, is that the fused suture constricts skull growth during the most concentrated period of brain volume growth during human life and thus may lead to altered brain morphology, localized areas of increased parenchymal pressure and hypoperfusion, or overt elevated intracranial pressure. (3, 67) Alternatively, in line with the theories of an intrinsic CNS

(or modular) developmental problem (see pp 13-14), the learning disability may be due to primary brain malformations.

### *Visual Function in Unicoronal Craniosynostosis*

Unicoronal synostosis (UCS) results in a complex, asymmetric craniofacial dysmorphology. The ipsilateral side has characteristic frontal flattening, retrusion of the supraorbit and a vertically ovoid orbital aperture. (95) The contralateral side typically has marked frontal bossing and lateral fullness. (96)

Morax et al. (1984) found that 89% of unicoronal synostosis (UCS) patients had extropia or vertical deviation of the ipsilateral globe (the orbit on the same side as the fused coronal suture). (97) His thorough morphologic analysis concluded that abnormalities of the ipsilateral orbit resulted in an abnormal pulley system of the extraocular muscles and may be at the root of a structure-function relationship for strabismus in UCS. A number of recent studies have shown a high incidence of ocular abnormalities including strabismus, atypical eye movements, astigmatism and visual field defects, on both the ipsilateral and *contralateral* side. (98-100) To date, studies have focused on characterizing dysmorphology for causes of eye dysfunction in the ipsilateral orbit.(101-103) The possibility for contralateral globe dysfunction provides impetus for contralateral morphologic characterization.

### *Surgical Correction*

The primary goal in surgical management of NSC is to allow normal cranial vault development to occur by removing the growth restriction caused by the particular fused

suture. Without correction of the fusion the skull will continue to develop abnormally and will impact craniofacial structure.

In general, the surgical outcome from a morphologic perspective is good in NSC. The surgical techniques evolved from a limited strip craniectomy in use as early as 100 years ago to increasingly more extensive cranioplasty and orbital surgery tailored for each form of NSC to improve morphologic outcome. (104) Recently, there is a reemergence of endoscopic minimally invasive techniques for the treatment of isolated NSC- particularly sagittal craniosynostosis. (105-108) Versus the traditional approach, endoscopic strip craniectomy may result in less blood loss, shorter hospital stay and can be performed at an earlier age. (107) Depending on the severity of dysmorphology, the endoscopic procedure relies on helmet therapy for up to one year postoperatively to assist the correction of skull shape. The decision between traditional and endoscopic repair to this point is typically surgeon dependent, although the age of presentation may play a role.

Although the benefit from surgical intervention for morphologic reasons alone is clear, surgical intervention for minimization of functional deficits is not. A number of studies have failed to show a beneficial impact of surgical correction on neurodevelopment. (65, 109-112) and current treatments of UCS seem to have no impact on strabismus. (101)

### *Void in Understanding*

There is a deficiency in our understanding of and therefore treatment approach to NSC. In neuropsychiatric disability, the recent findings of IQ and DQ testing demonstrate significant evidence that learning deficits exist, but pathogenesis of such disability is not understood. This void in understanding is at a time of significant flux in the approach to the surgical correction of NSC. The important item to understand is the mechanism of neuro-deficit (whether be intrinsic to the brain or secondary to bony compression). In visual disability, recent research has brought significant attention to strabismus and ocular dysfunction in the contralateral orbit in UCS. As current operative techniques employ ipsilateral but not contralateral orbital reconstruction, it is important to identify if contralateral dysmorphology exists.

### *Hypothesis*

The first step in understanding if the developmental and visual disabilities are surgically correctable is to understand their structural basis. Herein, we examine the structural foundations for learning disability in sagittal craniosynostosis by using magnetic resonance imaging to investigate microstructural and functional connectivity in the brain of adolescents with previously corrected sagittal craniosynostosis. We hypothesize that similarly to what was found in children with syndromic craniosynostosis (see pp. 11-12), the white matter architecture and functional connectivity is significantly different in those children with sagittal NSC versus control children.

Secondly, we examine orbital morphology of infants with UCS utilizing 3D reconstructions of computed tomographic scans to investigate the morphology of the

contralateral orbit, we hypothesize that similarly to the previously described structural foundations of strabismus in the ipsilateral eye- the contralateral eye is also dysmorphic which may underlie the recently discovered contralateral ocular dysfunction.

## Chapter 2:

### Structural and Functional Connectivity in Sagittal Craniosynostosis

#### *Sagittal Craniosynostosis*

Sagittal craniosynostosis is the most prevalent form of nonsyndromic craniosynostosis (NSC) at about 50% of all cases and has a 3:1 male: female predominance. (113) It results a skull deformity called dolichocephaly, which is defined as a Cranial Index<sup>2</sup> less than 70%. (45) In addition, the cranial vault may be widest temporally and narrow toward the vertex with ridging over the fused sagittal suture resulting in a shape resembling an inverted boat with keel, which is sometime called scaphocephaly. (114)

The incidence of learning disability in sagittal NSC is estimated to be as high as 50%. (84) The children tend to have executive functioning disability, such as ADHD, verbal learning disability and visuospatial problems. (90) No studies have utilized imaging techniques to investigate differences in brain architecture or functional connectivity. Magnetic resonance imaging may grant insight into the structural foundations and pathoetiology of learning disability.

#### *Magnetic Resonance Imaging*

The basis of Magnetic Resonance Imaging (MRI) is rooted in the Nobel Prize winning work on Nuclear Magnetic Resonance by Bloch and Purcell in 1946. (115, 116)

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<sup>2</sup> Width from euryon to euryon divided by the distance from glabella to the opisthocranium.

Each investigator demonstrated methods of how to measure and manipulate the quantum mechanical property of atomic nuclei called spin angular momentum utilizing magnetic fields. Since then, this atomic property has been utilized extensively for laboratory and industrial analysis of small molecule and protein structure and composition and in medical imaging. In medical imaging, magnetic resonance technology is primarily used to measure the specific changes in magnetic dipole (macroscopic manifestation of pooled changes in atomic angular momentum) of hydrogen nuclei of a water molecule.

When a subject enters the MRI scanner, the hydrogen atoms in water ( $^1\text{H}$ ) experience a static ( $B_0$ ) magnetic field (orientated in the z-plane) of the MR scanner. Once in that field, the vast majority of  $^1\text{H}$  adopt a low energy state in which the dipole moments are inline with the field. As the MR procedure commences, the subject is pulsed with a radio frequency (rf) equal to the Larmor frequency<sup>3</sup>, which excites the  $^1\text{H}$  into a higher energy dipole state. In addition to control of the, or multiple, rf pulses, additional magnetic field gradients can be superimposed on  $B_0$  to permit investigation of different properties of neural tissue including structure and function.

The information about the local environment of the tissue is encoded in the rate at which the dipole relaxes back down to its low-energy state following the rf pulse. The dipole relaxes by processing down to its lower energy state (envision the opposite motion of gyroscope falling as it loses energy after balancing on end). The procession is measured in two planes by time constants  $T_1$  and  $T_2$ .  $T_1$ , measures the relaxation time in the direction of the  $B_0$  field (z-plane)- that is how long until the dipole vector in the  $B_0$  plane is equal to its original state.  $T_2$  measures relaxation in the x-z plane. The  $T_2$  or

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<sup>3</sup> The Larmor Frequency is proportional to the external magnetic field strength and the gyromagnetic constant. For a more detailed description of MR physics see (117)

transverse relaxation is a measure of spin-spin interactions- that is the impact of local magnetic fields and shielding from nearby proteins and other compounds on the relaxation of the excited  $^1\text{H}$ .

### *Diffusion Imaging*

Diffusion weighted MR imaging relies on the Brownian movement of water molecules in tissue. In a uniform solution, diffusion is a probabilistic sphere, however, tissue contains a number of membranes, proteins and barriers that restrict diffusion. In regards to the nervous system, the most exploitable barrier for diffusion tensor imaging is the axonal tract in the CNS. The axons are myelinated, anisotropic<sup>4</sup> structures that make up the white-matter tracts of the brain and are essentially highways of water diffusion.

Diffusion weighted magnetic resonance tags the anatomic location of  $^1\text{H}$  by utilizing a field gradient. After excitement with rf, a spatially-dependent field gradient is applied to the “in-phase”-relaxing  $^1\text{H}$  which causes them to “de-phase”. After a set amount of time a “re-phasing” gradient (inverse of the dephaser) is applied to reverse dephasing and sync all  $^1\text{H}$  back into the same phase. However, since the  $^1\text{H}$  have diffused from their original location by Brownian motion, the re-phaser does not cause  $^1\text{H}$  to regain original phasing. This results in loss of signal intensity and therefore measurable diffusion. (118)

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<sup>4</sup> Diffusion is greater in one axis than others.



There are four main measures of diffusion that are used in neuroimaging: axial diffusion (AD), radial diffusion (RD), mean diffusivity (MD), and fractional anisotropy (FA). Diffusion is characterized by six parameters that quantify the direction (eigenvector) and size (eigenvalue) along three axes. The direction of maximal diffusion  $\lambda_1$  is also the AD, diffusion in the other axes ( $\lambda_2$  and  $\lambda_3$ ) are averaged together to provide RD. Mean diffusivity is an unweighted average of diffusion in all directions that is  $(\lambda_1 + \lambda_2 + \lambda_3)/3$ . Fractional anisotropy is a square root sum of squares calculation

$$FA = \frac{\sqrt{(\lambda_1 - \lambda_2)^2 + (\lambda_2 - \lambda_3)^2 + (\lambda_1 - \lambda_3)^2}}{\sqrt{2} \sqrt{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}}$$

### *BOLD MR Imaging*

Blood oxygen level dependent (BOLD) MR imaging is a modality that relies on magnetic properties of hemoglobin and physiologic properties of oxygen usage in the brain. Deoxyhemoglobin is paramagnetic which introduces local field inhomogeneity whereas oxyhemoglobin is diamagnetic and does not. Greater inhomogeneity results in spin-spin interaction, increased relaxation time ( $T_2^*$ ) and decreased image intensity.

The brain increases the local blood flow in reaction to the demand for glucose and oxygen. The details of this process are not fully understood but one theory posits that blood flow follows directly from increased, or even the prediction of increased, synaptic activity and not necessarily from increased neural activity. (119) Whatever the cause, blood flow and oxygen delivery surpass the brain requirement for oxygen and areas of activity have an excess of oxygenated hemoglobin. Taken together, areas with increased neural activity have a greater percentage of oxygenated hemoglobin and results in increased image intensity measured using MR BOLD imaging.

Resting state functional connectivity MRI or rs-fcMRI is a new technique, first described by Biswal in 1995, which uses an extended sequence to investigate low frequency ( $>0.1$  Hz) BOLD fluctuations at rest. (120) The technique is powerful in revealing “temporal correlations between spatially remote neurophysiological events”. (121, 122) Spatially distant brain regions characterized by synchronized fluctuations in BOLD signal are mapped to visualize functionally connected neural networks.

To date, rs-fcMRI has been used to examine the “functional connectomes” of visual (123), motor (120), memory (124), language (125), attention (126), and task control systems (127). And is used extensively in the study of autism and ADHD (126, 128-131).

### *Study Design and Methods*

This study was conducted in accordance with Yale IRB #1004006656. Eight adolescents with sagittal craniosynostosis previously corrected by Drs. John Persing and Charles Duncan via total vault cranioplasty at Yale-New Haven Hospital at eight control children without craniosynostosis were enrolled. The subject children were without signs of syndromic craniosynostosis (specifically extracranial skeletal manifestations), and both subject and control groups were without cardiac pacemaker, defibrillator, artificial heart valve, aneurysm clip, cochlear implant, neurostimulators, history of metal fragments in eyes or skin, braces, mental retardation, known neurological disorder or history of traumatic head injury or hemorrhage. The groups were matched by age, gender, race, handedness, and performance intelligence quotient (PIQ) and verbal intelligence quotient (VIQ) as measured by the Wechsler Intelligence Scale of Children

3<sup>rd</sup> edition (WISC-III). (Table 1)

### *Scan Protocol*

Using a single 3 T Siemens (Erlangen, Germany) Trio MR system with a 32 coil polarized head coil, a localizing scan, an anatomic scan (160 slices, 1.00 mm thickness, FoV= 256 mm, TR 1900 ms, TE 2.96 ms) and three runs of diffusion weighted imaging (TR= 6.4 s, TE = 86 ms, slice thickness = 2.5 mm, FoV = 240 mm, matrix 96 x 96, 30 directions, voxel size 2.5 x 2.5 x 2.5, b = 1000 s/mm<sup>2</sup>) were obtained.

For functional scanning, 34 axial slices (slice thickness 4.0 mm, no gap, FoV= 220 mm, matrix size 64 x 64) were acquired using a T1-weighted sequence (TR = 270 ms, TE = 2.46 ms, FoV = 220 mm, matrix size 256 x 256, flip angle 60°). Functional imaging volumes were collected in the same slice position as the preceding T1-weighted data. Two functional runs were acquired using a T2-sensitive gradient (TR = 2 s, TE = 25 ms, FoV = 220 mm, flip angle 60°, matrix size 64 x 64). Each volume consisted of 34 slices and each functional run was comprised of 160 volumes. The subjects and controls were instructed to visually fixate on a black computer screen displaying a 1-inch white plus sign during the functional scanning, to avoid movement and to “think of nothing or zone out”.

### *Analysis*

The three diffusion runs were manually inspected for movement artifact, and those with artifact discarded. The remaining runs were averaged and then processed

utilizing FSL (Oxford, UK. <http://fsl.fmrib.ox.ac.uk/>). Eddy current correction was utilized to correct for gradient-coil distortions and small head motions. Voxel-wise statistical analysis of the FA data was carried out using TBSS (Tract-Based Spatial Statistics, (132) part of FSL (133). First, FA images were created by fitting a tensor model to the raw diffusion data using FDT, and then brain-extracted using BET (134) All subjects' FA data were then aligned into a common space using the nonlinear registration tool FNIRT, which uses a b-spline representation of the registration warp field. Next, the mean FA image was created and thinned to create a mean FA skeleton, which represents the centers of all tracts common to the group. Each subject's aligned FA data was then projected onto this skeleton and the resulting data fed into voxel-wise cross-subject statistics.

The functional data was corrected for movement and slice time utilizing Matlab (Natick, Massachusetts). The brain tissue was extracted and transferred into Montreal Neurologic Institute (MNI) space. Independent component analysis was conducted with BioImageSuite with a cluster threshold of 50 and  $p < 0.1$  ([www.bioimagesuite.org](http://www.bioimagesuite.org), Yale University). After initial independent component analysis, a follow-up seed based analysis utilizing ROI identified from the independent component analysis (BA 8, 39 and 40) was performed where cluster threshold of 200 and  $p < 0.05$  was accepted.

### *Results*

Diffusion weighted imaging revealed trends toward extensive white matter alterations in all supratentorial lobes, and some areas of statistically significant changes in MD. There were no differences in axial diffusivity between control and subject

group. The strongest statistical relationship was located in the right superior longitudinal fasciculus (SLF) ( $p = 0.3$ ). Radial diffusivity differences did not reach statistical significance; however there is diffuse trend toward a control RD > subject RD ( $0.2 > p > 0.08$ ). This includes frontal, parietal, occipital and temporal white matter as well as major tracts such as the corpus callosum, inferior longitudinal fasciculus, SLF and corona radiata. (Figure 2a) Mean diffusivity statistical analysis also demonstrated trends toward widespread differences such that control MD > subject MD ( $0.2 > p > 0.04$ ), which anatomically mirrored those shown by RD analysis. (Figure 2b) There was a region of white matter under the right supramarginal gyrus (MNI 46, -48, 36), which demonstrated statically significant ( $p < 0.05$ ) MD changes. (Figure 2b2) Fractional anisotropy differences again mirrored the anatomic regions of RD and MD, but a trend toward control FA < subject FA ( $0.2 > p > 0.08$ ) was found. (Figure 2c)

Independent component analysis of the resting state functional scans revealed the sagittal NSC adolescents had trends toward decreased activation in the right angular gyrus, right superior parietal lobule, and precentral gyrus and increased activation in in the vermis of the cerebellum, right thalamus, right supramarginal gyrus and left paracingulate gyrus when a cluster size of 50 and  $p < 0.1$  was accepted. (Table 2, Figure 3) Seed to whole brain based analysis demonstrated statistically significant negative connectivity (anticorrelations) of BA 8 to precuneous cortex (MNI 0, -71, 29) and operculum (MNI 43, -33, 20). (Figure 4a) BA 39 had stronger anticorrelations to right angular gyrus (49, -49, 21), but stronger positive connectivity is to the cingulate gyrus, and left BA 39. (Figure 4b) Finally BA 40 had stronger anticorrelations to contralateral

angular gyrus and nearby occipital cortex (MNI -33, -70, 32). (sagittal - controls,  $p < 0.05$ ) (Figure 4c)

### *Discussion*

Recent studies on neurobehavioral outcomes in NSC indicate that while IQ and development scores fall within the normal range, nearly 50% of subjects demonstrate deficiency in visual-spatial planning ability, language impairment, or “cognitive abnormality”. (90, 91)

These findings come at a time of overall flux in the approach to surgical correction of NSC. Traditionally, an extensive open-procedure was favored; however, recently, there is an emergence of minimally invasive techniques for the treatment of isolated craniosynostosis. (108) Versus the traditional approach, minimally invasive endoscopic strip craniectomy is reported to result in less blood loss, shorter hospital stay and can be performed at an earlier age. The technique, however, requires helmet therapy for up to 1-year post operatively to complete morphological correction of the calvarial vault. What remains unknown is if there is a role for surgical correction in the abatement or prevention of neurocognitive deficit.

As this is, to our knowledge, the first application of MRI techniques to analysis of NSC brain microstructure and function. We demonstrate that adolescents with sagittal synostosis previously corrected via the total vault cranioplasty have trends towards extensive diffusional differences in white matter tracts throughout the neocortex.

It should be noted that few of our values reached  $p < 0.05$  statistical significance (MD values of  $p < 0.05$  were found at 40, -41, 36- in the white matter under the right

supramarginal gyrus and angular gyrus), but this data shows significant trends towards statistical differences and provides strong impetus for future studies.

In general, we found that AD was equivalent between controls and subjects, but in nearly all white matter structures that RD and MD values trended toward greater in controls, while FA values trended toward greater in subjects. The trend toward lower RD and MD values with a higher FA value in our patient group may provide some interesting information about the microarchitecture of the white matter. Lower MD and RD diffusion parameters may be indicative of diffusion changes radial (perpendicular) to white matter tracts- that is, there is less radial diffusion and overall diffusion in the sagittal craniosynostosis brain. While increased FA may indicate increased directionality of diffusion in line with the white matter tracts. Thus, the finding of increased FA in the NSC group seems to be due to a decrease in diffusion along secondary and tertiary directions (decreased RD), as opposed to an increased axial diffusion (unchanged AD).

These findings may indicate a higher degree of myelination of the tracts or a lower degree of neural branching. In respect to the former hypothesis it is possible that hypermyelination can exist as a compensatory effort to once damaged to nerve sheaths.(135) This could happen if the NSC brain is damaged early in life secondary to compression by the fused skull (see primary bone hypothesis). The latter hypothesis, networks with less branching, could indicate an intrinsic white-matter malformation (136, 137) and may lend evidence to a more diffuse modular development problem underlying craniosynostosis.

Other studies of neurodevelopmental disorders have also reported increase in FA

in ADHD (138) and Williams Syndrome (139). Similarly to our study, both studies found high FA values in the superior longitudinal fasciculus and correlated them with visuospatial learning disability (visuospatial learning disability is also reported in children with sagittal NSC (90)).

Resting state functional connectivity data failed to reach statistical significance in independent component analysis. Regions loosely identified (cluster 50,  $p < 0.1$ ) include decreased activation in the right angular gyrus, superior parietal lobule, and precentral gyrus and increased activation in in the cerebellum, occipital cortex, thalamus, supramarginal gyrus and paracingulate gyrus. Follow-up seed to whole brain ROI analysis of BA 8, the angular and supramarginal gyrus demonstrated statistically significant altered connectivity to the cingulate gyrus, a region thought to be a major node within the “default mode network”, a network of the brain that is thought to play roles in conscious introspection and planning as well as the unconscious consolidation of experiences (126) (140) The altered activation and connectivity of the angular gyrus is particularly interesting in this patient population as it is well known to be altered in children with abnormal reading and dyslexia. (141) Furthermore, it has recently been shown to play a major role in semantic processing, word reading and comprehension, number processing, the default mode network, memory retrieval, attention and spatial cognition- disabilities shared by many children with NSC. (90, 142)

It seems that the functional differences found in this study may be rooted in anatomic microstructural disparities. In DTI, the single area of statistically significant difference was is the white matter under the right angular gyrus. This correlated with altered functional connectivity in independent component analysis and in seed networks



that utilize the right supramarginal gyrus. This relationship between DTI and functional connectivity has been demonstrated in a number of other studies. (143, 144)

The evidence in this study demonstrates that indeed DTI and fcMRI can be used to tease apart network differences in NSC and our preliminary evidence indicates that altered connectivity at the angular gyrus may underlie some of the learning disability in sagittal NSC. Of note, we also demonstrate trends toward diffuse architectural and connectivity differences, which may lend evidence to a diffuse developmental alteration in the white-matter of children with NSC.

Ultimately, a prospective infant study needs to be conducted to determine the impact of surgical correction on brain structure and function. In addition to the techniques in this study, arterial spin labeling (ASL) should be used to determine if there are changes in blood flow to the brain parenchyma associated with release of bony constriction. The great purpose is to determine if the neuropsychological outcomes can be altered via surgical correction. We are capable of correcting superficial morphological deformity utilizing a number of techniques, but is there a best, if any, corrective technique for correction of brain abnormality?

### *Conclusion*

Sagittal craniosynostosis is associated with an increased rate of learning disability. This study lends evidence to the fact that this learning disability is rooted in a diffuse microstructural difference with control children. Unsurprisingly, these changes correlate with a number of functional network differences particularly with connectivity

to the angular gyrus. This study provides foundational basis of an altered neocortical structure-function relationship in NSC. Future studies are needed to completely tease apart this relationship.

## Chapter 3:

### Orbital Morphology in Unicoronal Craniosynostosis<sup>5</sup>

In addition to aesthetic implications, unicoronal craniosynostosis adversely impacts visual functioning. A number of studies show a high incidence of ocular abnormalities including strabismus and atypical eye movements, on both the ipsilateral and *contralateral* side. (100, 103, 145) Thus far, studies have focused on describing dysmorphology and anatomic foundations of eye dysfunction of the ipsilateral orbit. Evidence of contralateral globe dysfunction provides impetus for further morphologic characterization.

The purpose of this study is to characterize orbital morphology and relationships in UCS patients compared to unaffected controls. We intend to document the dysmorphology and asymmetry of the UCS orbits. We hypothesize that volumetric and topographical differences underpin the functional orbital changes in UCS.

#### *Study Design and Methods*

This is a retrospective analysis performed in concordance with the Yale University Institutional Review Board (IRB# 1101007932). Demographic data and computed tomographic (CT) scan information were obtained for unicoronal synostosis and control subjects. Exclusion criteria included any additional synostosis or other

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<sup>5</sup> Chapter contains excerpts from: Beckett JS, Persing JA, Steinbacher DM. Bilateral orbital dysmorphology in unicoronal synostosis. *Plast Reconstr Surg.* 2013;131(1):125–130.

craniofacial pathology. Controls were included from infants who received head CT scans for evaluation minor pathology without orbital or intracranial implication. The three-dimensional CT scans were analyzed using a surgical planning program (*Surgicase*; Materialise, Leuven Belgium). A mask was created of the intraorbital soft tissue using a previously described method. (146) The surface osteotomy tool was used to isolate the intraorbital contents at the anterior orbital aperture (Figure 5). Volumetric data were obtained for each ipsilateral (right in controls) and contralateral (left in controls) orbit in cubic millimeters. Horizontal and vertical orbital cone angles, orbital depth and corneal projection were calculated as described in Table 3 and shown in Figure 6. The null hypothesis was used and statistical analysis involved Student's *t* test and ANOVA with *post hoc* Tukey HSD; a value of  $p < 0.05$  was considered significant. {Beckett:2013fd}

### *Results*

31 subjects and a total of 62 orbits were analyzed from three-dimensional computed tomographic scans of 21 unicoronal synostosis patients and 10 control subjects. The sample included 12 male and 9 female UCS patients, with a mean age of 5 months, 52% had right-sided disease. The control group contained 6 males and 4 females with a mean age of 6 months (Table 4).

Volumetric analysis of the UCS group revealed that the bony volume of the ipsilateral orbital cone was significantly smaller than the contralateral orbit. The orbital cone volume ratio for the UCS group was  $93.8 (sd \pm 5.3)$  (ipsi/contralateral) while the volume ratio of the control group was  $99.3 \pm 2.1$  ( $p = 0.001$ ).

Craniometric analysis of the bony orbits revealed significant dysmorphology of

both the ipsilateral and contralateral sides compared to controls. The contralateral horizontal orbital cone was significantly larger than both the ipsilateral ( $p < 0.0001$ ) and the control orbits ( $p = 0.0011, 0.0004$ ). The ipsilateral vertical orbital cone was also greater than both the contralateral side ( $p < 0.0001$ ) and the control orbits ( $p = 0.0326, 0.003$ ). Analysis of the horizontal cone on the ipsilateral side and the vertical cone on the contralateral side revealed a not significantly smaller angle in each case when compared to controls (Figure 7 and 8, Table 5). The ipsilateral globe projected 27% further than the contralateral side ( $p < 0.0001$ ). There was no difference in orbital depth or globe projection between sides in the control group. {Beckett:2013fd}

### *Discussion*

The high incidences of vertical strabismus, asymmetrical visual fields and abnormal eye movements in UCS are thought to be secondary to anatomic abnormalities characterized in the ipsilateral orbit. (101, 102) It is postulated that the dysmorphic orbit results in an abnormal pulley location of the superior oblique and shortening of the paramedian segment are fundamental to the pathoetiology. (97, 98, 101) Increasing attention is being paid to the laterality of visual problems in UCS. MacIntosh et al. 2007 found that in roughly half of UCS patients with strabismus the abnormality was in the contralateral eye and Levy et al. 2007 found a predominance of astigmatism in the contralateral eye. (102, 103) Corresponding concepts of anatomical dysmorphology may be underpinning these recent findings.(145)

Recently, modern techniques in three-dimensional CT reconstruction have been demonstrated to be a powerful technique in defining bony and soft-tissue morphology in

a number of craniofacial pathologies, and soft tissue masks can be used to calculate the volume and morphology of bony cavities. (147-149)

A previous study used 3D CT analysis to calculate ratios of orbital volume, globe volume, globe position and shape of orbital aperture between sides in UCS patients pre- and post-operatively. (95) Fronto-orbital bar advancement on the ipsilateral side will address elements of the ipsilateral aesthetic deformity, but our study suggests that both orbits are dysmorphic. Volume differences may not be adequately corrected if in part the asymmetry is due to the contralateral orbit being larger than normal. Our findings indicate a more horizontally ovoid contralateral orbit. This morphology is likely mediated through compensatory growth of the sphenoid in a vector transmitted through the skull to the contralateral side as evidenced by previously described changes in angulation of the bones of the facial structures. (96) Forward shift of the contralateral lateral orbital rim from this growth could increase orbital volume.

While physiologic foundations of astigmatism and strabismus are not fully understood there is evidence that ocular asymmetry may contribute to their formation. The “oculomotor plant” represents the network of the visual organ, extraocular muscles, neural input and coordination which functions to control functions like visual alignment, gaze and tracking. (150, 151) Strabismus may occur when the two extraocular motor systems exist in asymmetric compartments. The asymmetry may cause errors as the oculomotor plant attempts to coordinate the motion of two unique orbital pulley systems. (145) Additionally, astigmatism may arise from increased extraocular muscle tone from less efficient orbital movements or increased passive tone from stretching of muscle fibers. (152)

Variation of volume between individuals and age dependent changes make control-matched absolute measurements difficult. Kamer et al. 2010 found distinct symmetry between orbits of one individual, but significant variation in orbital and globe volumes between individuals. (153) Coupled with age dependent changes, direct comparison of volume between UCS children and controls is problematic.

In addition to the dysmorphic ipsilateral orbit in UCS, given the relatively enlarged contralateral orbit, it may be prudent to surgically address both orbits in when correcting anterior synostotic plagiocephaly. The most comprehensive current techniques typically involve only ipsilateral unilateral fronto-orbital advancement with uni- or bilateral forehead reshaping. (154, 155) Existing methods of fronto-orbital reconstruction have not been found to correct underlying strabismus. (101) Recognizing that orbital asymmetry may underlie strabismus (156), we propose that correction of the contralateral orbital deformity should be considered in an effort to achieve side-to-side orbital symmetry similar to that observed in unaffected individuals.

### *Conclusion*

This study provides evidence that both orbits in patients with UCS are dysmorphic. The volume of the contralateral orbit is significantly larger than the ipsilateral side. The ipsilateral orbit is tall and narrow, while the contralateral side is vertically short and wide. Meanwhile, unaffected individuals have a great deal of orbital symmetry in both volume and morphology. Orbital asymmetry may underlie many of the ocular abnormalities associated with UCS, thus, we propose that additional consideration be given to bilateral reconstructive efforts.

## Chapter 4: Closing

The first reports of surgical intervention for craniosynostosis came from Lannelongue in Paris in 1890 and from Lane in San Francisco in 1892. (157) In his 1892 report, Lane describes being approached by the mother of a child with sagittal craniosynostosis who pleaded to him: “Can you not unlock my poor child’s brain and let it grow?” (158) While this mother’s plead is emotionally provoking, over 100 years later researchers and physicians are not certain of the relationship between structural abnormality and functional disability in nonsyndromic craniosynostosis (NSC). This is fundamentally secondary to the fact that children in countries with access to medical care are universally corrected early in life for aesthetic normalization. Thus, studies seeking to tease apart the structure-function relationship are limited to populations of children with surgically corrected NSC. Despite this, a number of functional disabilities have been identified in children with surgically corrected NSC.

The goal of this work was to investigate the structural foundations of disability in NSC. We approached this from two angles, with each study utilizing new techniques in imaging science. On one hand, we use diffusional and blood oxygen level dependent resting state MRI imaging to explore connectivity networks in the sagittal NSC brain. Neuropsychological studies indicate that adolescents with previously corrected sagittal NSC have a high incidence of wide ranging disabilities- including ADHD, verbal IQ disability, and spatial reasoning. (83) Evidence provided in this study indicates that these disabilities may be rooted in widespread microstructural and functional network differences; however, the causation of such structural differences remains opaque.



Additionally, we utilized three-dimensional reconstruction software to perform craniometric analysis of skeletal anatomy that may underlie ocular dysfunction in unicoronal craniosynostosis. Advancements in computing power and visualization software have opened a new area of accessibility in the analysis of skeletal anatomy. In our study, we are able to demonstrate that, in addition to the known orbital dysmorphology of the ipsilateral side, the contralateral orbit is also dysmorphic. Taken in the context of emerging evidence of contralateral ocular dysfunction and the hypothesis that orbital asymmetry may underlie such dysfunction, it may be prudent to explore corrective techniques, which create symmetry of the orbits in children with UCS. (150, 156) One must also consider, however, that ocular dysfunction may be rooted in intrinsic brain abnormalities- perhaps altered microstructural connectivity disrupts the visual plant.

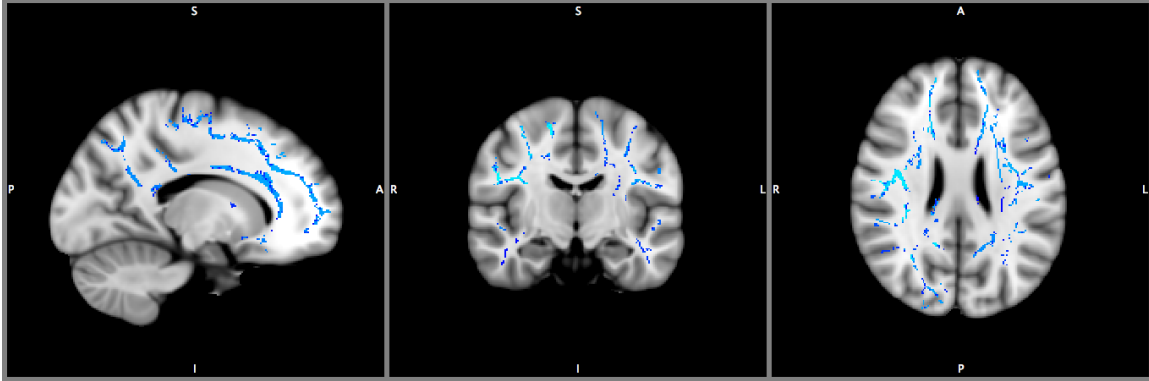
In Lane's case from 1892, he performed a strip craniectomy of the sagittal suture, but the child died 14 hours postoperatively, reportedly from complications of anesthesia. Thankfully, through advances in surgical technique and anesthesia, teams of today comprised of craniofacial surgeons and neurosurgeons are capable of achieving safe, reproducible and aesthetically good results in the surgical correction of NSC. Our next objective is to determine what role the surgical correction plays in correction of disability. This fundamentally complex question is only made more difficult recently as we begin to appreciate the detrimental impact of general anesthesia on young children. (159) As we move forward-- are more comprehensive procedures warranted to correct skeletal anatomy that is deforming brain and orbital anatomy, or are functional disabilities intrinsic to a disease process that causes cranial suture synostosis and

architectural dysmorphology in the brain. Future imaging studies should start with the infant population to determine the impact of timing and type of surgical correction on brain architecture and should continue into adolescence and include long-term neuropsychological follow-up.

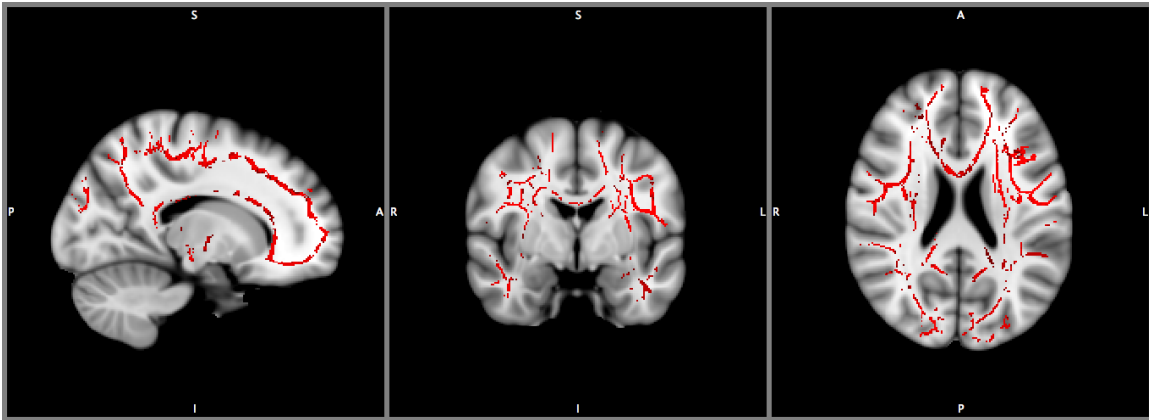
## Figures



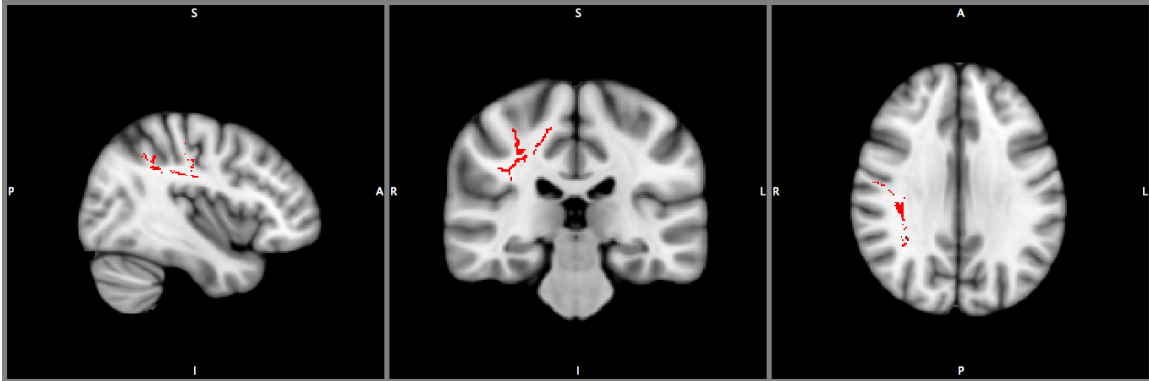
**Figure 1:** Bust of Pericles bearing the inscription “Pericles, son of Xanthippus, Athenian”. Marble, Greek from ca. 430 BC



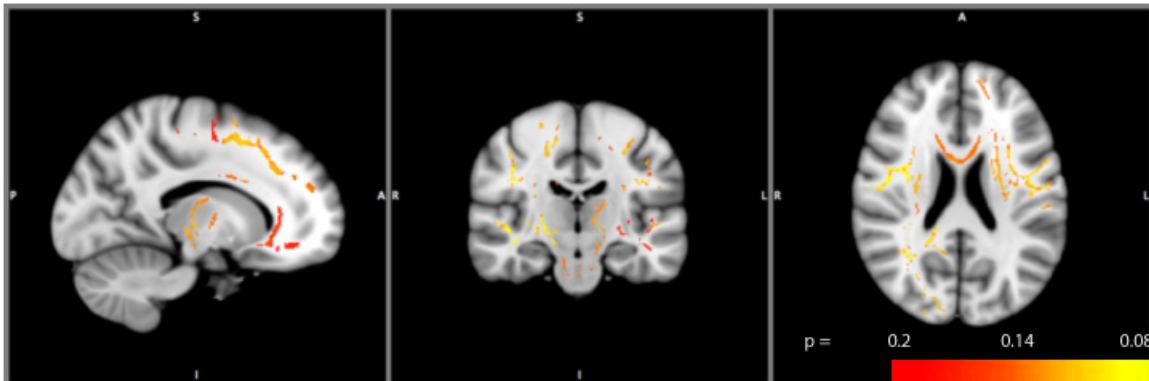
**Figure 2a:** Statistical map of radial diffusion (RD) differences in adolescents with previously corrected sagittal craniosynostosis versus controls such that subject RD < control RD ( $0.2 < p < 0.08$ ). Areas of stronger correlation are lighter blue.



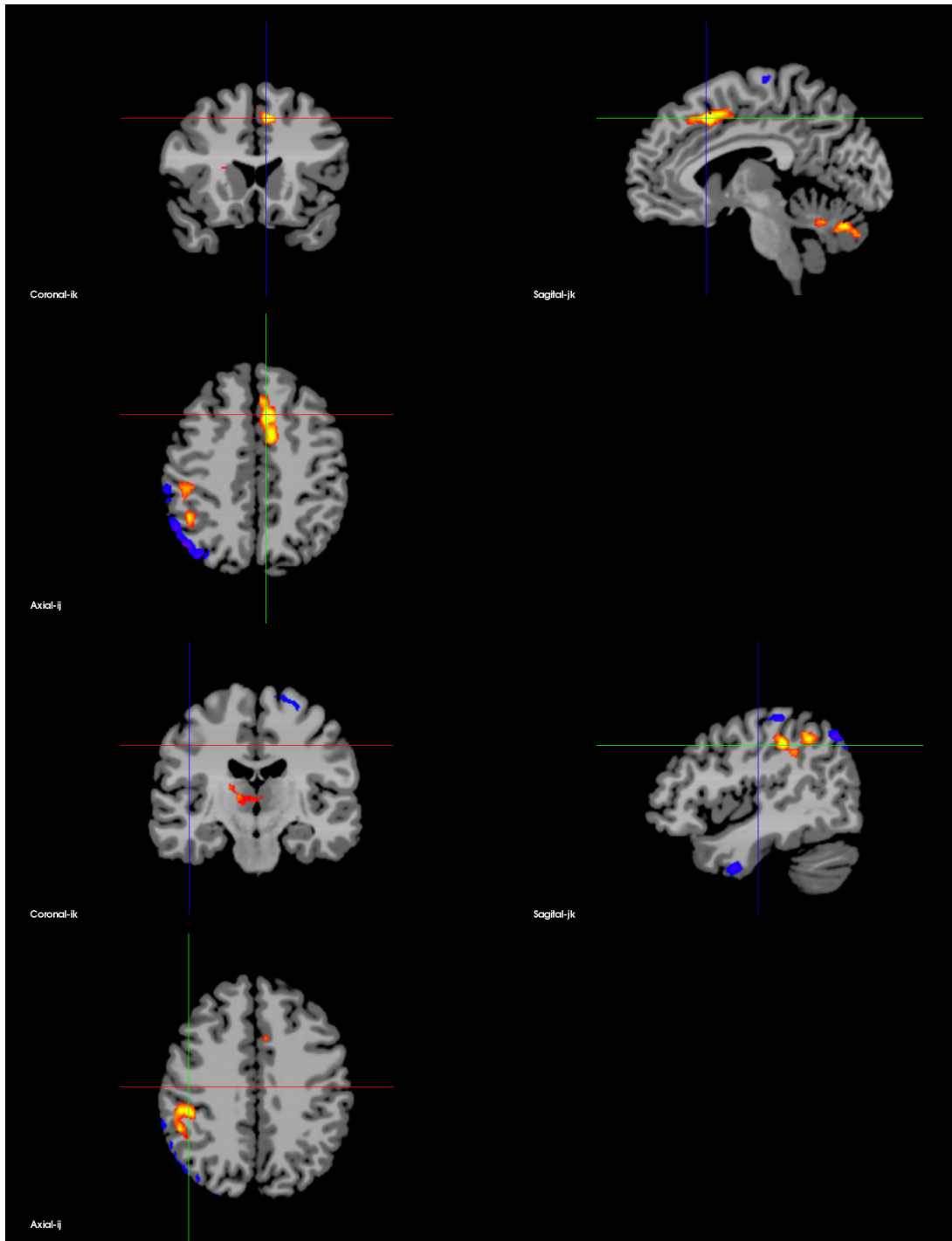
**Figure 2b:** Statistical map of medial diffusion (MD) differences in adolescents with previously corrected sagittal craniosynostosis versus controls such that subject MD < control MD ( $0.2 < p < 0.04$ ).



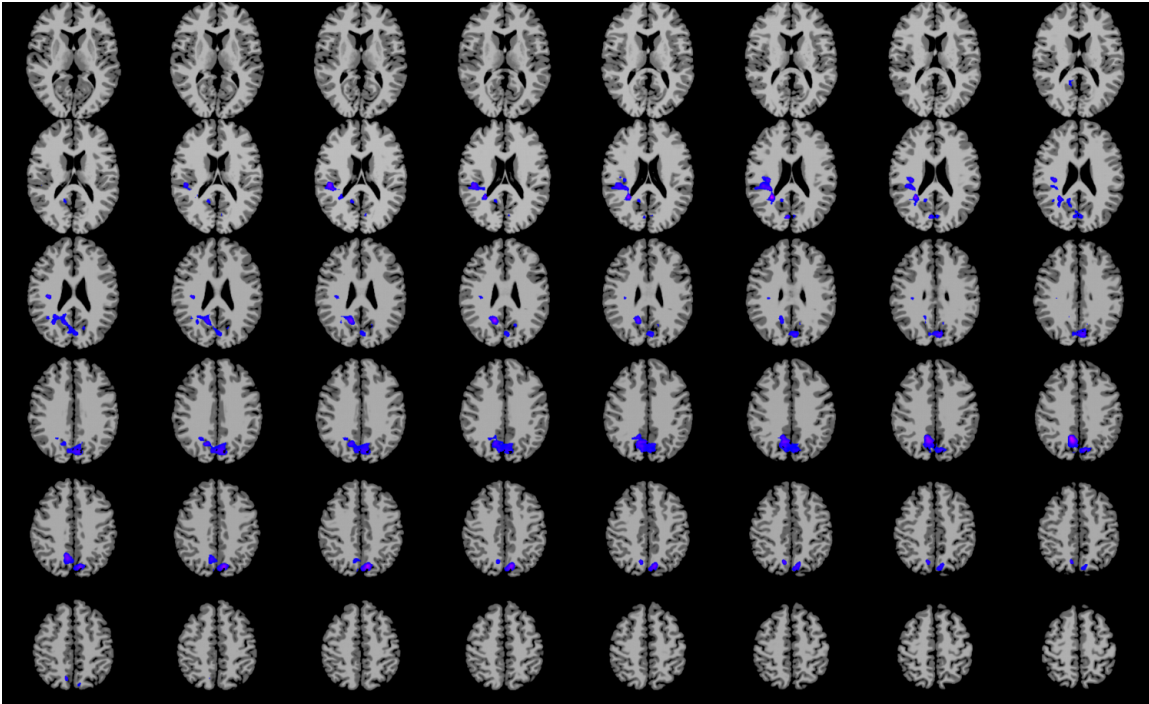
**Figure 2b2:** Statistical map of medial diffusion (MD) differences in adolescents with previously corrected sagittal craniosynostosis versus controls such that subject MD < control MD ( $p < 0.05$ ).



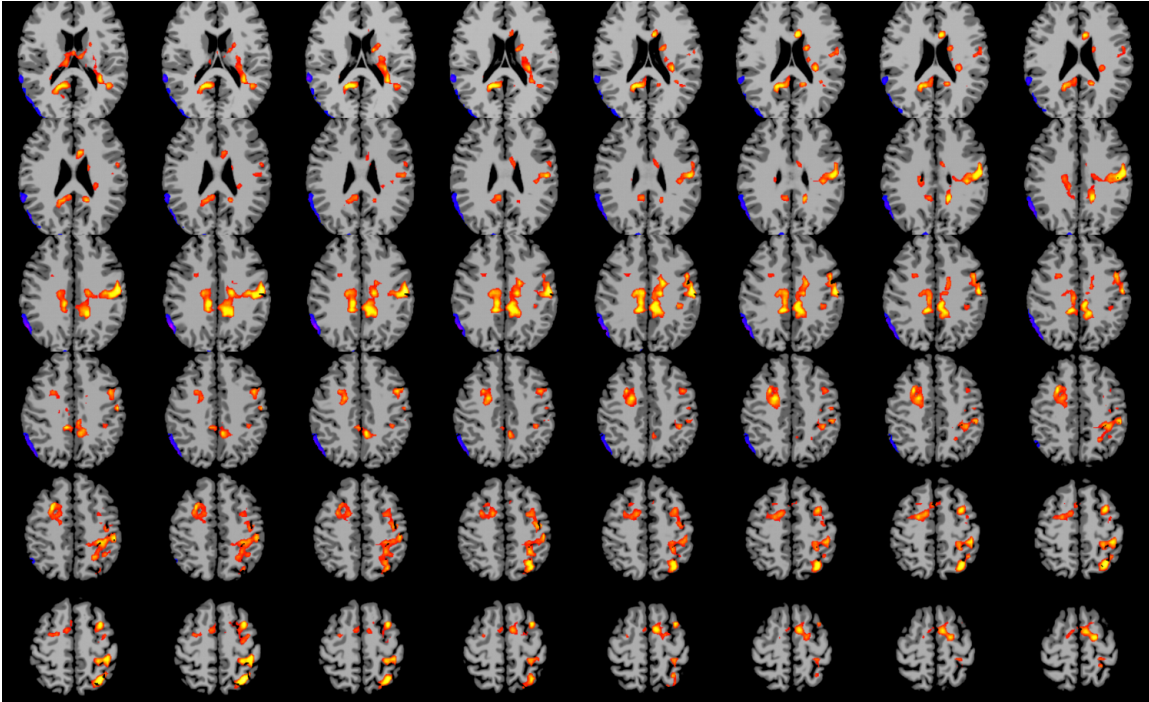
**Figure 2c:** Statistical map of fractional anisotropy (FA) differences in adolescents with previously corrected sagittal craniosynostosis versus controls such that subject FA > control FA ( $0.2 < p < 0.08$ ).



**Figure 3:** Map showing group differences (subject-control,  $p < 0.1$ ) in ipsilateral independent component analysis of intrinsic connectivity. Warm colors represent greater activation in subject group, blue colors represent greater activation in control group.

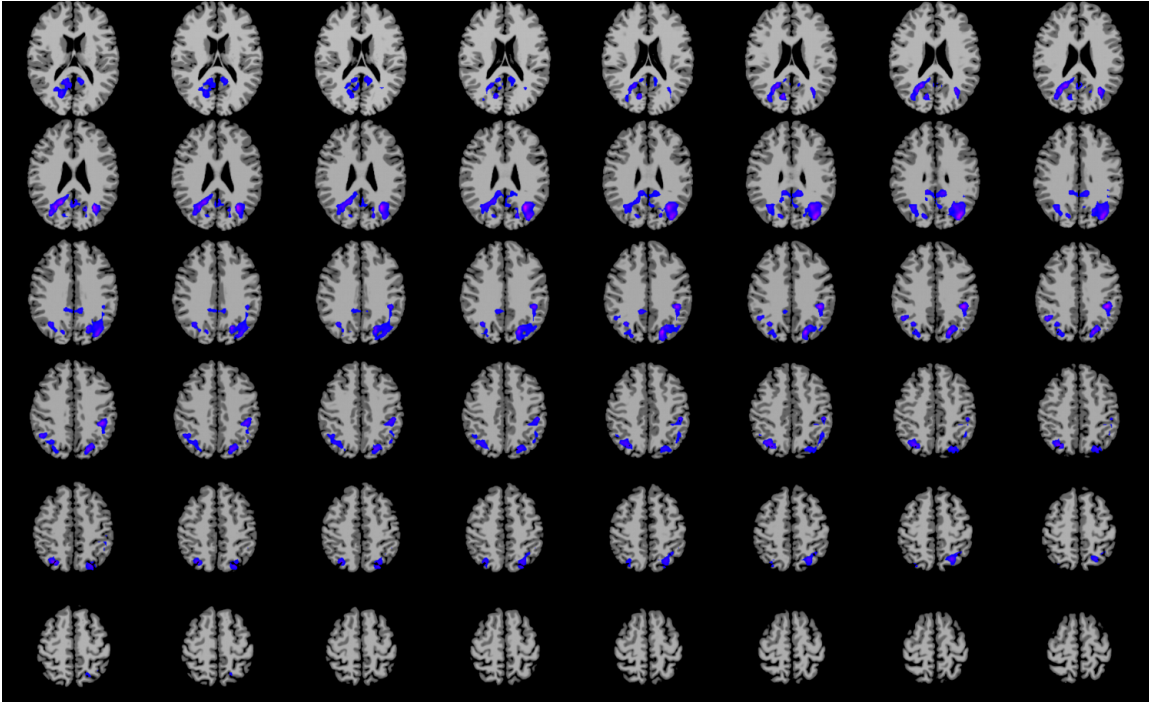


**Figure 4a:** Map showing group differences (subject–control,  $p < 0.05$ ) in connectivity from right BA 8 seed-to-whole-brain analysis. Stronger negative connectivity (anticorrelations) to precuneus cortex and operculum are observed for the sagittal craniosynostosis group compared to the controls.

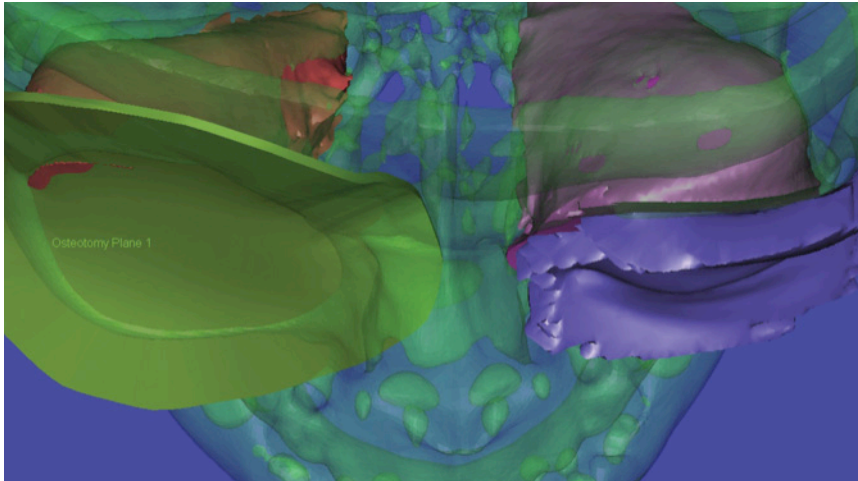


**Figure 4b:** Map showing group differences (subject–control,  $p < 0.05$ ) in connectivity from right BA 39 seed-to-whole-brain analysis. Stronger negative connectivity (anticorrelations) to R angular gyrus, while stronger positive connectivity is seen to the cingulate gyrus, and left BA 39 for the sagittal craniosynostosis group compared to the controls.



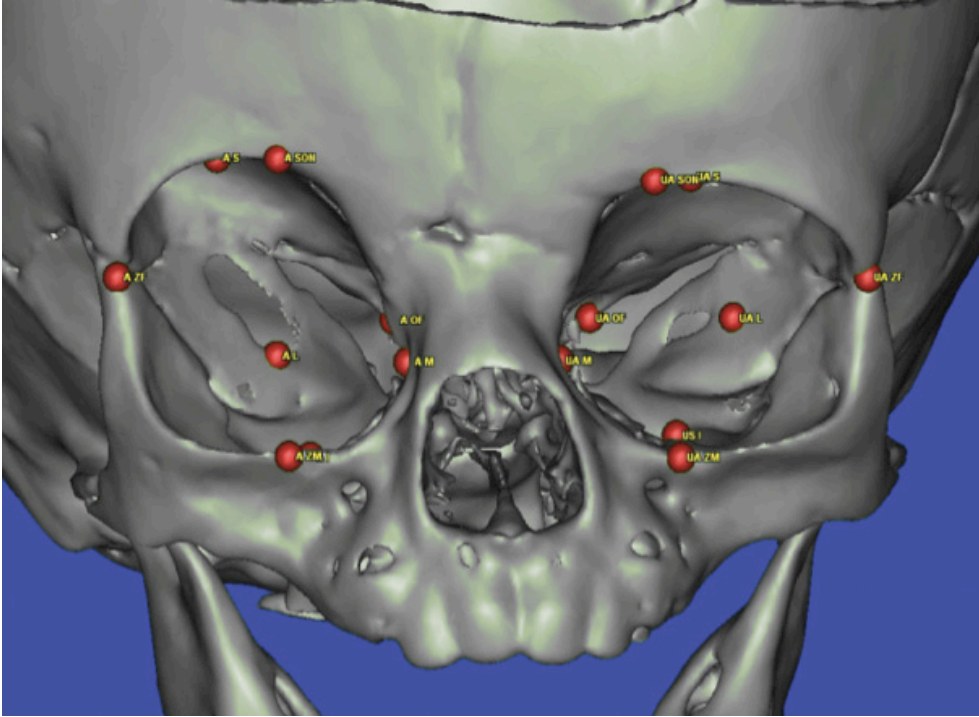


**Figure 4c:** Map showing group differences (subject–control,  $p < 0.05$ ) in connectivity from right BA 40 seed-to-whole-brain analysis. Stronger negative connectivity (anticorrelations) to posterior paracingulate gyrus and left supramarginal gyrus are observed for the sagittal craniosynostosis group compared to the controls.



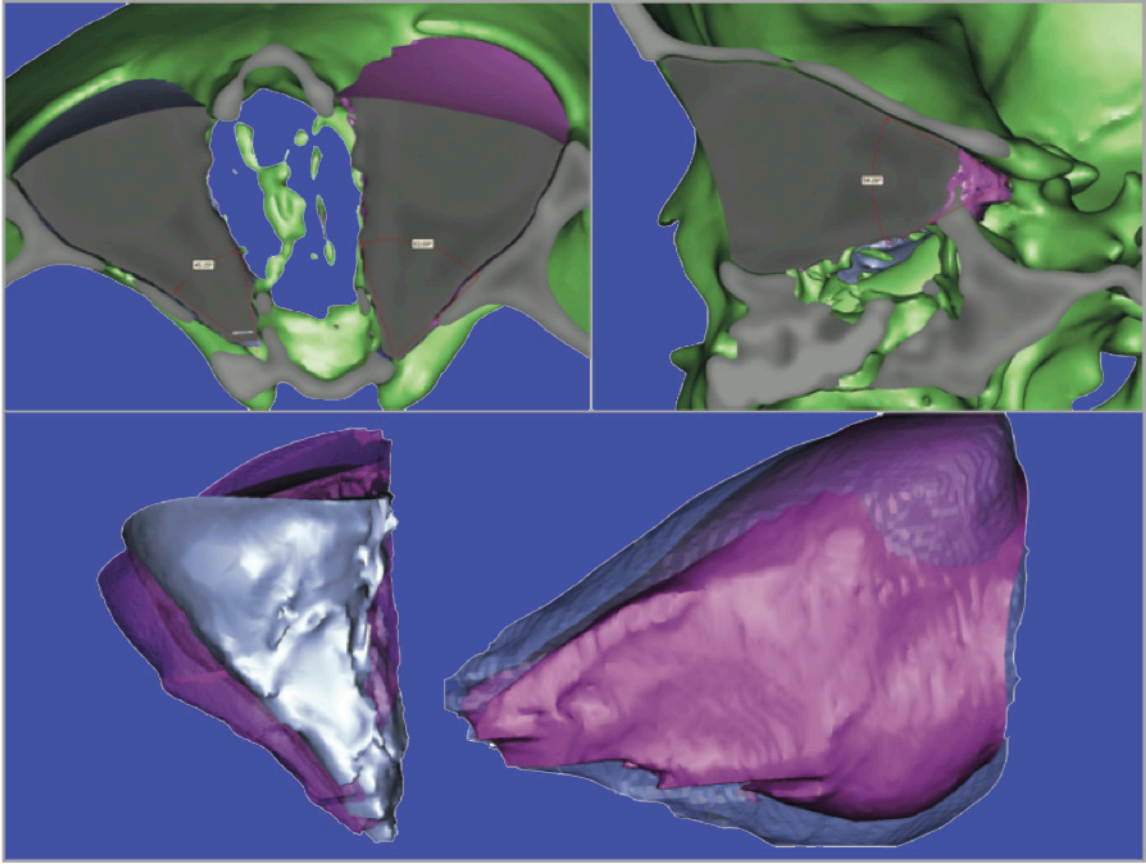
**Figure 5:**

Right orbit shows demarcation of orbital aperture (shown in green) used to divide intraorbital (red) tissue from extraorbital tissue. Left orbit shows result of division: purple is left intraorbital soft tissue, blue is extra orbital soft tissue.



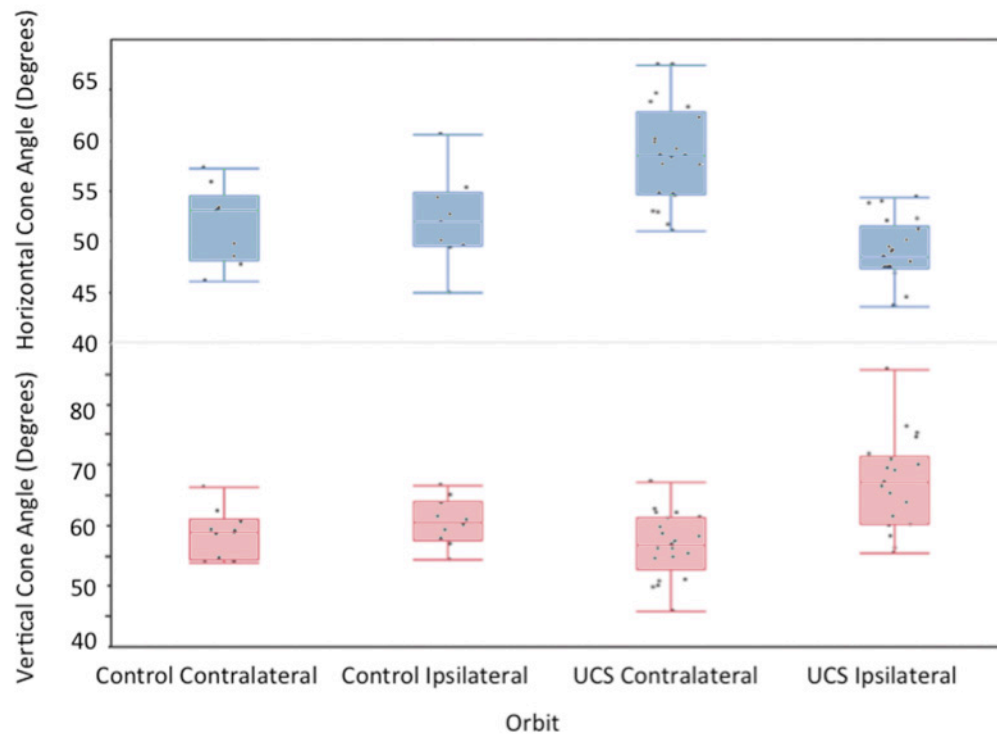
**Figure 6:**

Skull of six-month old infant with UCS. Points used in craniometric analysis indicated.



**Figure 7:**

Orbital cone analysis of ipsilateral and contralateral orbits of UCS infant. *Top left:* axial section demonstrating horizontal cone angle (blue ipsilateral). *Top right:* sagittal section through contralateral orbit demonstrating vertical cone angle. *Bottom left:* inferior view of orbital overlay. *Bottom right:* lateral view of orbital cone overlay.



**Figure 8:**

Box and whisker plot with data points for horizontal cone angle (top, blue) and vertical cone angle (bottom, red).

## Tables

**Table: 1.** Demographics of subjects and controls in MRI study of sagittal craniosynostosis.

	Corrected Sagittal Synostosis Children	Control Children	<i>p</i>
<b>N</b>	8	8	
<b>Age, years (<i>s.d.</i>)</b>	12.3 (1.8)	12.3 (1.6)	<i>ns</i>
<b>Gender</b>	6 M 2 F	7 M 1 F	<i>ns</i>
<b>Race</b>	7 W, 1 AA	7 W, 1 AA	
<b>Handedness</b>	8 Right	8 Right	
<b>Age of Operation, months (<i>s.d.</i>)</b>	7 (2)		
<b>WISC-III Testing</b>			
<b>Performance IQ (<i>s.d.</i>)</b>	111 (15)	115 (10)	0.7
<b>Verbal IQ (<i>s.d.</i>)</b>	100 (16)	120 (16)	0.05

**Table 2.** MNI coordinates of independent component analysis regions of interest. C:

controls, S: sagittal synostosis

Location	BA	x	y	z	Voxels	Finding
Cerebellar Vermis		-2	-66	-27	2301	C < S
L Lateral Occipital Cortex	19	-40	-72	-4	2988	C < S
R Thalamus		14	-4	9	2315	C < S
R Angular Gyrus	39	49	-64	43	4715	C > S
R Supramarginal Gyrus	40	48	-39	40	2071	C < S
L Paracingulate Gyrus	6, 8	-6	13	47	1909	C < S
L Superior Parietal Lobule	7	-30	-63	59	2953	C > S
L Precentral Gyrus	4	-11	-30	68	2644	C > S

**Table 3.** Craniometric Parameters used to morphologically characterize unicoronal craniosynostosis.

Parameter	Description
Orbital Volume	Volume of soft tissue contents of the orbit as bounded by orbital aperture, bones of orbit and posterior openings (e.g. optic foramen, inferior and superior orbital fissure)
Horizontal Vertical Cone Angle	Angulation of lateral walls of posterior orbit as defined by 3 points in one axial slice containing the optic nerve: laterally the midpoint of the greater wing of the sphenoid between the sphenofrontal fissure and optic foramen, vertex at the optic foramen and medial point located on the ethmoid bone in the same coronal slice as the lateral point.
Vertical Horizontal Cone Angle	Angulation of the vertical walls of the posterior orbit as defined by 3 points: the most superior point of the orbital roof, vertex at optic foramen, and inferior point on orbital floor in same sagittal slice as superior point.
Orbital Depth	Distance from zygomaticomaxillary suture on orbital rim to optic foramen.
Corneal Projection	Distance from most anterior point of cornea to the orbital rim (defined by plane containing the supraorbital notch, zygomaticofrontal suture, and zygomaticomaxillary suture).



**Table 4.** Demographic Information of subjects and children in unicoronal synostosis study.

	<b>UCS</b>	<b>Control</b>
<b>Number of Subjects</b>	21	10
<b>Sex</b>		
<b>Male</b>	8 (38%)	4 (40%)
<b>Female</b>	13	6
<b>Age (Mean months)</b>	5.5	6.2
<b>Age (Median, 1<sup>st</sup>-3<sup>rd</sup> quartile)</b>	6, 4-8	7, 4-9
<b>Side, %</b>		
<b>Right</b>	52	
<b>Left</b>	48	

**Table 5.** Horizontal and Vertical Cone Angle Analysis

	Control		UCS	
	Left	Right	Contralateral	Ipsilateral
Horizontal	51.6	52.1	58.6	48.9
Vertical	58.7	60.6	56.7	66.9

	Horizontal Orbital Cone		Vertical Orbital Cone	
	UCS		UCS	
<i>P</i> Value Analysis	Contralateral	Ipsilateral	Contralateral	Ipsilateral
UCS Ipsilateral	<b>&lt; 0.0001</b>	-	<b>&lt; 0.0001</b>	-
Control Left	<b>0.0011</b>	0.23211	0.3181	<b>0.0326</b>
Control Right	<b>0.0004</b>	0.367	0.8106	<b>0.0030</b>

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