The Neurological Development Of Sagittal Craniosynostosis
Patients Treated With Whole Vault Cranioplasty

Raysa Cabrejo

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The Neurological Development of Sagittal Craniosynostosis Patients Treated with Whole Vault Cranioplasty

A Thesis Submitted to the Yale University School of Medicine
in Partial Fulfillment of the Requirements for the Degree of Doctor of Medicine

By

Raysa Gabriela Cabrejo

2019
ABSTRACT

Objective: In this study we seek to clarify the neurological changes before and after whole vault cranioplasty (WVC) in patients born with sagittal craniosynostosis.

Methods: A case control study design was performed that included forty fMRI scans, from thirty-five individual patients. Functional MRI (fMRI) and diffusion tension imaging (DTI) data were analyzed with BioImageSuite (Yale University, USA). All nine functional brain networks were analyzed with appropriate regions of interest.

Results: Comparing functional MRI the infants after WVC vs. infants before WVC group, the after WVC group demonstrated an increased connectivity in the left frontoparietal (LFPN), secondary (V2) and third (V3) visual network (p<0.001). The right frontoparietal (RFPN) had decreased connectivity (p<0.001). There is also a decrease and increase in anisotropy in the cingulum and precuneus despite surgery, respectively (p<0.05). Adolescents treated with WVC compared to controls, demonstrated an increased connectivity in the SA and decreased connectivity in the RFPN relative to adolescent controls. ADHD has lower connectivity to BA11 (MNI: -12,26,-21), BA20 (MNI: 62,-24,-25), and BA21 (MNI: 62,-32,-23) compared to sNSC and controls (p<0.001). sNSC has a unique visuospatial defect, compared to ADHD, created by decreased connectivity to BA31 (MNI: -3,-68,37), BA7 (MNI: -4,-68,41), BA19 (MNI: 0,-83,31), visual association cortex (MNI: -4,-78,22), and primary visual cortex (MNI: 7,-74,21) (p<0.001).

Conclusions: Patients born with sagittal craniosynostosis have different connections in infancy in most of the cerebral networks compared to controls. There are specific connectivity changes that occur in the RFPN, LFPN, V2, and V3 networks, which are areas ultimately associated with executive function and emotional control, after surgery. Changes in white matter tract microstructure connections could be influential in changes in functional connectivity. As the child develops, much of the abnormal network connections, seen in infancy pre-operatively, correct after surgery (compared to age-matched controls). Some aberrancies, however in the SA and RFPN networks remain. Adolescent patients with sagittal nonsyndromic craniosynostosis have decreased connections in areas of visual processing and increased connections in areas of attention and auditory processing than patients with ADHD.
ACKNOWLEDGEMENTS

Thank you to my family for their never ending encouragement. Thank you to Dr. Persing for the opportunity and support. Thank you to all research fellows, past and present for making this possible. Thank you to all the collaborators that provided key advice in putting all this together. Ultimately, thank you to all the families that decided to participate so that their family’s experience could be turned into information for future families.
TABLE OF CONTENTS

ABSTRACT ........................................................................................................... 2
ACKNOWLEDGEMENTS ....................................................................................... 3
INTRODUCTION ...................................................................................................... 5
STATEMENT OF PURPOSE .................................................................................... 8
SPECIFIC AIMS ...................................................................................................... 8
METHODS .............................................................................................................. 9
  SUBJECTS ........................................................................................................... 9
  SCAN PROTOCOL ............................................................................................. 13
  ANALYSIS ........................................................................................................... 13
  PERSONAL CONTRIBUTION ........................................................................... 15
RESULTS .............................................................................................................. 16
  FUNCTIONAL MRI ANALYSIS ......................................................................... 16
    Infants Before and After Surgery ................................................................. 16
    Sagittal Craniosynostosis Adolescents Compared to Controls ............... 19
    Sagittal Craniosynostosis Compared to ADHD ........................................ 21
  DIFFUSION TENSOR IMAGING ....................................................................... 32
DISCUSSION ......................................................................................................... 33
  LONGITUDINAL ANALYSIS OF CRANIOSYNOSTOSIS .................................. 33
    Somatosensory (SM) and Primary Visual (V1) Networks ....................... 33
    Auditory Network (AN) ............................................................................... 33
    Secondary Visual Cortex (V2) and Third Visual (V3) networks ............ 34
    Default Mode Network (DMN) ................................................................. 35
    Salience Network (SA) .............................................................................. 35
    Left Frontoparietal and Right Frontoparietal Networks (FPNs) ............ 36
COMPARISON OF CRANIOSYNOSTOSIS AND ADHD ....................................... 38
  DTI ANALYSIS ............................................................................................... 39
CONCLUSION ....................................................................................................... 42
REFERENCES ...................................................................................................... 44
INTRODUCTION

Craniosynostosis is the premature fusion of skull sutures that leads to abnormal shape and affects brain development. The skull sutures affected are sagittal, metopic, coronal and lamboid; the most common prematurely fused skull suture is the sagittal suture. For the midline craniosynostosis, including the metopic and sagittal craniosynostosis, a genetic etiology has been determined in the genes BMP2 and SMAD6. Nonsyndromic craniosynostosis is being recognized as having, in some, a genetic etiology accompanied by subtle neurocognitive delays, associated with change in functionality and connectivity of the brain.\(^1\)–\(^3\)

Nonsyndromic sagittal craniosynostosis (sNSC), the most common isolated craniosynostosis, occurs in 45-58% of all craniosynostosis.\(^4\) It is hypothesized that the fusion of the sagittal suture leads to greater restriction on the developing brain.\(^5\) To date, no studies have explored the anatomical or functional differences in the brains of infant children with nonsyndromic sagittal craniosynostosis and the changes that occur after surgery.

In various neurocognitive testing studies of sagittal craniosynostosis patients after surgical surgeries, it has been demonstrated that 50% of had reading and/or spelling disability with normal intelligence.\(^3\) Previous chart reviews, have demonstrated an increased diagnosis of speech, cognitive and behavioral abnormalities. About 35% of percent of patient had elevations on the Child Behavior Check List.\(^6\) The Child Behavior Check List has been shown to be a very good screening test for Attention-Deficit/Hyperactivity Disorder (ADHD).\(^7\) Previous functional MRI (fMRI) studies demonstrated that adolescents treated for sagittal craniosynostosis had decreased
connectivity in the RFPN network and no differences in the DMN.\textsuperscript{8} Similarly, ADHD patients had decreased connectivity to the fronto-parietal networks compared to controls.\textsuperscript{9}

In the literature and in clinical experience, children with corrected sagittal craniosynsotosis are most often compared to ADHD. ADHD is the most common neurobehavioral disorder of childhood.\textsuperscript{10} The diagnosis of ADHD is made based on the DSM-IV: six or more symptoms of inattention and/or six or more symptoms of hyperactivity-impulsivity for at least 6 months. Impairments must be present in two or more settings. The impairments must be clinically significant and there should be no other reason for the impairments. ADHD has been studied previously using fMRI and it has demonstrated lower connectivity in adolescents with ADHD compared to controls in the fronto-parietal networks. The DMN network is associated with irrelevant mental processes and mind wandering. ADHD patients have difficulty effectively suppressing DMN during task processes in functional MRI studies.\textsuperscript{9}

Resting state functional connectivity MRI measures blood oxygenation level dependent (BOLD) contrast signals throughout the brain to determine likely, functionally interconnected brain regions. Based on coincident region activation, in infants, it has been used to determine associated networks within the brain, and their change over time.\textsuperscript{11} The nine primary basic neural networks were determined to be: medial occipital network (V1), occipital pole network (V2), lateral visual/parietal network (V3), default-mode network (DMN), sensorimotor (SM), the auditory/language network (AN), the salience network (SA), and the two lateralized frontoparietal networks (FPNs). The primary basic neural networks, SM and AN, develop the earliest, and are followed by the V1 and V2 networks, which develop the fastest during 0-3 months of age. These are the
basic functional networks that are related directly to basic survival of the infant (i.e. malformation would have direct impact on survival). However, the higher order networks, corresponding to executive function and emotional processing, are V3 and DMN and relate to more intricate intellectual processing need longer term development. Their growth pattern occurs over a more prolonged range of 0-12 months of age (in contrast to the first or second month of life for basic survival functions like movements of arms and legs). The longer time period developing networks are more likely to be more at risk, due to influences during the highly sensitive extended developmental time frames. This may affect function, but not necessarily early survival. The SA and bilateral FPNs therefore grow fast during 0-3 months of age, but only to a premature state, then complete most of their development toward adult-like connections later at approximately 1 year of age.11,12

Diffusion tensor imaging (DTI), a complementary assessment tool, to fMRI, studies water diffusion throughout the brain to determine white matter tract microstructure, via the degree of myelination, or “anisotropy”. Increased anisotropy correlates with the normal maturation of white matter tracks. Increased of myelination, yields compactness of fiber tracts and reduced extra axonal space over time: all considered good patterns of maturation in development.13

The surgery, in this report was a whole vault cranioplasty and entails the revision of frontal, parietal and occipital segments of the skull. Parietal segments are elevated and remodeled by osteotomies to also enhance lateral expansion and reshaping.14
STATEMENT OF PURPOSE

The purpose of this study was to investigate the effect of craniosynostosis in the long-term development of the functional networks and microstructure of the brain by comparing the same networks development treated patients, versus normal, over time. Then to investigate further findings that corroborate similarities between corrected sagittal craniosynostosis and ADHD previously published. We hypothesized that craniosynostosis can affect the functional networks during brain development, and surgery may influence development of the brain; wholly or in part. We also hypothesized that adolescents with corrected craniosynostosis and ADHD adolescents would have similar functional connectivity, but there would be minor differences.

SPECIFIC AIMS

The specific study aims include the following:

AIM #1: Characterize the functional differences of infants born with nonsyndromic sagittal craniosynostosis and normal children through the use of fMRI and DTI in infancy.

AIM #2: Characterize the differences seen after surgery through the use of fMRI and DTI in infancy and adolescence.

AIM #3: Further characterize the neurocognitive deficits seen in adolescents with corrected craniosynostosis by comparing it to established learning deficits such as attention deficit hyperactivity disorder (ADHD).
METHODS

SUBJECTS

This was a case control study performed in accordance with Yale Institutional Review Board (HIC#: 1004006656). We studied five infants with nonsyndromic sagittal craniosynostosis, which were treated by J.P. with C.D. or M.D. by whole vault cranioplasty at Yale-New Haven Hospital (Table 1). The infants were diagnosed with nonsyndromic sagittal craniosynostosis by headshape evaluation, confirmed by CT and operative findings of a fused sagittal suture. Patients did not have any other known neurological disorder, history of traumatic head injury or any other known medical condition. The participants had the metopic suture fused to some degree during the surgery, but none to a severe degree, defined as a fronto-orbital angle $<124^\circ$. This degree of angulation is correlated with event-related potentials (ERP) abnormalities characteristics of dysfunction in craniosynostosis. All participants were scanned for MRI/DTI before surgery and scanned once again after surgery, and significantly, using no sedation.
<table>
<thead>
<tr>
<th></th>
<th>Infants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mos.)</td>
<td></td>
</tr>
<tr>
<td>Before Scan</td>
<td>5.0 ± 1.9</td>
</tr>
<tr>
<td>Operation</td>
<td>5.7 ± 1.4</td>
</tr>
<tr>
<td>After Scan</td>
<td>8.7 ± 2.1</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>3</td>
</tr>
<tr>
<td>Female</td>
<td>2</td>
</tr>
<tr>
<td>Race</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>5</td>
</tr>
</tbody>
</table>

Table 1: Demographics of infants with craniosynostosis

Another set of 10 adolescents (mean age of 12.1 years) with nonsyndromic sagittal craniosynostosis, previously treated by J.P with C. D. by whole vault cranioplasty at Yale-New Haven Hospital (Table 2) and 10 control children (mean age of 11.9 years) without craniosynostosis. The adolescents with nonsyndromic sagittal craniosynostosis during the surgery based on visible fusion of the sutures at age of surgery and did not have any other known neurological disorder, history of traumatic head injury or any other known medical condition. The adolescents were also tested for the verbal and performance intelligence quotient utilizing Wechsler Intelligence Scale for Children, Third edition (WISC-III).16

The ADHD patients were acquired by New York University as part of the ADHD-200 Sample. The ADHD-Combined diagnosis was based on evaluations with the Schedule of Affective Disorders and Schizophrenia for Children—Present and Lifetime
Version (KSADS-PL) administered to parents and children and the Conners’ Parent Rating Scale-Revised, Long version (CPRS-LV). The children’s performance IQ (PIQ) and verbal IQ (VIQ) measured by the Wechsler Abbreviated Scale of Intelligence (WASI). Inclusion in the ADHD group required a diagnosis of ADHD based on parent and child responses to the KSADS-PL as well as on a ADHD Index (T-score) greater than or equal to 65 on at least one ADHD related index of the CPRS-R: LV. Inclusion criteria required absence of any Axis-I psychiatric diagnoses per parent and child KSADS-PL interview, as well as T-scores below 60 for all the CPRS-R: LV ADHD summary scales.
<table>
<thead>
<tr>
<th>Comparison Group</th>
<th>Corrected sNSC</th>
<th>ADHD</th>
<th>Controls</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>NS</td>
</tr>
<tr>
<td>Mean age ± SD (yrs)</td>
<td>12.1 ± 2.0</td>
<td>11.9 ± 2.1</td>
<td>11.9 ± 2.3</td>
<td>NS</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Male</td>
<td>8</td>
<td>9</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>2</td>
<td>1</td>
<td>3</td>
<td></td>
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<td>Right handedness</td>
<td>10</td>
<td>10</td>
<td>10</td>
<td>NS</td>
</tr>
<tr>
<td>Mean at operation ± SD (mos)</td>
<td>8 ± 4</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Mean Cognitive score ± SD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Performance IQ</td>
<td>111 ± 15</td>
<td>106 ± 18</td>
<td>116 ± 15</td>
<td>NS</td>
</tr>
<tr>
<td>Verbal IQ</td>
<td>100 ± 16</td>
<td>108 ± 21</td>
<td>120 ± 16</td>
<td>NS</td>
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<tr>
<td>ADHD measure</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>ADHD Index</td>
<td>NA</td>
<td>68 ± 5</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Inattentive</td>
<td>NA</td>
<td>66 ± 8</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Hyper/Impulsive</td>
<td>NA</td>
<td>71 ± 10</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

Table 2: Demographics of adolescents with corrected sagittal nonsyndromic craniosynostosis (sNSC), Attention Deficit Hyperactivity Disorder (ADHD), and their respective controls.
SCAN PROTOCOL

All MRI scans were obtained using a single 3-T Siemens (Erlangen, Germany) Tim Trio MR system with a 32-coil polarized head coil. The fMRI scans consist of 165 contiguous whole-brain functional volumes. The functional scan were acquired using a T2-sensitive gradient (TR 2 sec, TE 25msec, FOV 220mm, flip angle 60°, 34 slices, matrix size 64 X 64). Adolescent participants were verbally instructed to relax and remain still with eyes open while the symbol “+” was centrally displayed. Infant scans were attempted during natural asleep; importantly no sedation was used as it could cause brain function alterations. The DTI protocol consist of a localizer scan, MPRAGE anatomical scan and 3 runs of diffusion-weighted imaging.

The ADHD MRI scans consist of 197 contiguous whole-brain functional volumes using echo planar imaging on a Siemens 3.0-Tesla Allegra in New York University. The functional scans were acquired using a T2-sensitive gradient (TR 2 sec, TE 25 msec, FOV 256 mm, flip angle 90°, 39 slices, matrix size 64 X 64). Participants were verbally instructed to relax and remain still with eyes open while the word “Relax” was centrally displayed.

ANALYSIS

The three diffusion runs were manually inspected for movement artifact and those with artifact were excluded from the analysis. The remaining runs were averaged and then processed utilizing FMRIB Software Library (FSL; http://fsl.fmrib.ox.ac.uk). Eddy current correction was used to correct for gradient-coil distortions and small head motions. All subject’s fractional anisotropy data were then aligned into a common space.
using the nonlinear registration tool in BioImage Suite. Then it was analyzed p<0.05 for voxel-wise cross-subject statistics.

The functional data were correct for movement and slice time utilizing Statistical Parametric Mapping (SPM) 8. Warping of the data were accomplished using three nonlinear registrations into a infant brain standard of 6 months or normal brain reference, then registered into Montreal Neurological Institution (MNI) center of mass coordinates.

The seed-based functional connectivity analysis was conducted based on the defined 9 functional networks. The nine networks are: sensorimotor network (SM), auditory/language network (AN), medial occipital network (V1), occipital pole network (V2), lateral visual/parietal network (V3), default mode network (DMN), salience network (SA), and two lateralized frontoparietal networks (FPNs). The following seeds defined the networks: right precentral gyrus, left superior temporal gyrus, calcarine cortex, occipital pole, right lateral occipital lobe, posterior cingulate cortex, anterior cingulate cortex and bilateral inferior parietal lobules, respectively. The infant brain parcellations were calculated previously in the literature. Two-tailed tests were performed to detect significant connections (p<0.05), compared to the rest of the brain, for each network and each group, infants before surgery, infants after surgery, adolescents treated for craniosynostosis, and untreated controls adolescents (Figure 2). The results of these analyses are being compared to previously published controls, doing a similar analysis, techniques and parameters utilizing the same regions of interest and the same threshold of p<0.05. Group differences (infants after surgery vs. infants before surgery)
surgery, treated adolescents with sagittal craniosynostosis vs. controls) are analyzed in network seed-to-whole brain analysis (p<0.001).

Whole brain ipsilateral intrinsic connectivity analysis of the functional data was conducted using BioImage Suite with a cluster threshold of 25 and p<0.001. After initial whole ipsilateral intrinsic connectivity contrast analysis, a follow-up seed-based analysis utilizing a neocortical region of interest (ROI) identified from the intrinsic connectivity contrast analysis was performed where a cluster threshold of 20 and p<0.001.

**Personal Contribution**

Personally, I collected two pairs of the infant fMRI craniofacial scans. Previous students performed all adolescent craniosynostosis fMRI scans. The control infant fMRI data is provided by the published results by Gao et al. The ADHD fMRI scans were obtained from NYU thru a public collaboration called ADHD-200. I performed the analysis under the guidance of Ms. Cheryl Lacadie. I performed the interpretation of the analysis results under the guidance of Dr. John Persing.
RESULTS

FUNCTIONAL MRI ANALYSIS

INFANTS BEFORE AND AFTER SURGERY

Overall network connections in the “before” and “after” surgery are demonstrated clearly in Figure 1 and are used to compared age matched published controls as the scans and analysis are comparable. The “before” surgery scans are aged 5 months and “after” surgery scans are aged 9 months. Previous comparisons demonstrate there is no statistically significant difference as documented by fMR, between the degree of development of the networks that occur between 6 and 9 months in normal controls. However, in this study there are statistically significant differences between before and after surgery (Figure 3). Comparing after to before surgery, the RFPN has decreased connectivity in the left dorsal (MNI: -6,-53,39) and ventral posterior cingulate (MNI: -2,-53,26) (p<0.001). The posterior cingulate is an area associated with attention and cognition. Within the context of the LFPN network, the insula is involved with emotional, behavioral and empathy responses. After surgery, the LFPN has increased connectivity in the right insula (MNI: 37,6,2), right putamen (MNI: 32,3,2), inferior frontal gyrus (MNI: -39,5,8), and left insula (emotional) (MNI: -35,9,3) (p<0.001). Within the context of the visual networks, the insula is involved in visual attention tasks. The V2 networks demonstrate increased connectivity in the right insula (MNI: 37,-2,10), inferior frontal gyrus (MNI: -42,9,7), and the left insula (MNI: -36,10,5) (p<0.001). The V3 network demonstrate increased connectivity in the right putamen (motor skills) (MNI: 30,-6,8) and right (MNI: 39,1,11) and left (MNI: -35,12,3) insula (p<0.001).
Figure 1: The nine networks shown here are: sensorimotor network (SM), auditory/language network (AN), medial occipital network (V1), occipital pole network (V2), lateral visual/parietal network (V3), default mode network (DMN), salience network (SA), and two lateralized frontoparietal networks (FPNs). The Before (6 months) network images are infants diagnosed with craniosynostosis before surgery, average age is 5 months. The After (9 months) network images are infants diagnosed with craniosynostosis about 3 months after whole cranial vault cranioplasty surgery, average age is 9 months. The figures showing controls at 6 months and 9 months are from previously published results. The After (adolescence) network images are adolescents treated with whole vault cranioplasty, average is 11.9 years old. The controls (adolescence) network images are healthy age-matched controls. Warmer colors (orange to yellow) represent greater connectivity to the seed in comparison to the rest of the brain (p<0.05). Blue colors represent decreased connectivity to the seed in comparison to the rest of the brain (p<0.05).
## Network Area of Altered Connectivity* MNI (x,y,z) Connectivity Findings‡

<table>
<thead>
<tr>
<th>Network</th>
<th>Area of Altered Connectivity</th>
<th>MNI (x,y,z)</th>
<th>Connectivity Findings‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>R FPN</td>
<td>Left Dorsal Posterior Cingulate</td>
<td>(-6,-53,39)</td>
<td>decreased</td>
</tr>
<tr>
<td></td>
<td>Left Ventral Posterior Cingulate</td>
<td>(-2,-53,26)</td>
<td>decreased</td>
</tr>
<tr>
<td>L FPN</td>
<td>Right Insula</td>
<td>(37,6,2)</td>
<td>increased</td>
</tr>
<tr>
<td></td>
<td>Right Putamen</td>
<td>(32,3,2)</td>
<td>increased</td>
</tr>
<tr>
<td></td>
<td>Inferior Frontal Gyrus</td>
<td>(-39,5,8)</td>
<td>increased</td>
</tr>
<tr>
<td></td>
<td>Left Insula</td>
<td>(-35,9,3)</td>
<td>increased</td>
</tr>
<tr>
<td>V2</td>
<td>Right Insula</td>
<td>(37,-2,10)</td>
<td>increased</td>
</tr>
<tr>
<td></td>
<td>Inferior Frontal Gyrus</td>
<td>(-42,9,7)</td>
<td>increased</td>
</tr>
<tr>
<td></td>
<td>Left Insula</td>
<td>(-36,10,5)</td>
<td>increased</td>
</tr>
<tr>
<td>V3</td>
<td>Right Putamen</td>
<td>(30,-6,8)</td>
<td>increased</td>
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<tr>
<td></td>
<td>Right Insula</td>
<td>(39,1,11)</td>
<td>increased</td>
</tr>
<tr>
<td></td>
<td>Left Insula</td>
<td>(-35,12,3)</td>
<td>increased</td>
</tr>
</tbody>
</table>

*Found to be significant at p<0.001

‡Infants after surgery relative to infants before surgery

**Table 3: Results of the network ROI seed to whole-brain connectivity analysis between infants after and before surgery**
Figure 3: The nine networks shown here are: sensorimotor network (SM), auditory/language network (AN), medial occipital network (V1), occipital pole network (V2), lateral visual/parietal network (V3), default mode network (DMN), salience network (SA), and two lateralized frontoparietal networks (FPNs). The network images show group differences (infants after surgery vs. infants before surgery, p<0.001) in the network seed-to-whole brain analysis. Warmer colors (orange to yellow) represent greater activation in the after surgery group. Blue colors represent decreased activation in the after surgery group.

SAGITTAL CRANIOSYNOSTOSIS ADOLESCENTS COMPARED TO CONTROLS

Overall network connections sagittal craniosynostosis patients and controls (Figure 4). The BA7 region is specific for spatial forms of attention processing.\textsuperscript{27,28} The RFPN network has decreased connectivity in the right BA7 (MNI: 32,-44,55), right sensory association (MNI: 24,-44,51) and right primary sensory cortex (MNI: 24,-41,44) compared to same age controls (p<0.001). The right sensory association and right primary sensory cortex are areas involved in interpretations of outside stimulation such as physical sensations, proprioception, and nociception.\textsuperscript{29} The SA network has increased
connectivity in the left insula (emotional behavior) (MNI: -37,6,-6) compared to same age control (p<0.001) (Table 3).

<table>
<thead>
<tr>
<th>Network</th>
<th>Area of Altered Connectivity*</th>
<th>MNI (x,y,z)</th>
<th>Connectivity Findings‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>RFPN</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Right BA7</td>
<td>(32,-44,55)</td>
<td>decreased</td>
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<tr>
<td></td>
<td>Right Sensory Association Cortex</td>
<td>(24,-44,51)</td>
<td>decreased</td>
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<tr>
<td></td>
<td>Right Primary Sensory Cortex</td>
<td>(24,-41,44)</td>
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<tr>
<td>SA</td>
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<tr>
<td></td>
<td>Left Insula</td>
<td>(-37,6,-6)</td>
<td>increased</td>
</tr>
</tbody>
</table>

*Found to be significant at p<0.001

‡Adolescents after surgery relative to age matched controls

Table 4: Results of the network ROI seed to whole-brain connectivity analysis between adolescents after surgery and controls
Figure 4: The nine networks shown here are: sensorimotor network (SM), auditory/language network (AN), medial occipital network (V1), occipital pole network (V2), lateral visual/parietal network (V3), default mode network (DMN), salience network (SA), and two lateralized frontoparietal networks (FPNs). The network images show group differences (adolescents after surgery vs. controls, p<0.001) in the network seed-to-whole brain analysis. Warmer colors (orange to yellow) represent greater activation in the adolescents after surgery group. Blue colors represent decreased activation in the adolescents after surgery group.

**Sagittal Craniosynostosis Compared to ADHD**

*Whole-Brain Ipsilateral Intrinsic Connectivity*

Comparing the ADHD versus surgically corrected sagittal nonsyndromic craniosynostosis (sNSC) groups, ADHD demonstrated there was an increased connectivity to the left Brodmann area (BA) 31 (attention and focus) (MNI: -3,-68,37) and BA7 (visuospatial processing) (MNI: -4,-68,41) (p<0.001). Corrected sagittal craniosynostosis demonstrated there was increased connectivity to the orbitofrontal cortex (BA11) (decision making, rewards, planning, reasoning) (MNI: -12,26,-21), right
BA20 (high level visual processing, recognition memory) (MNI: 62,-24,-25) and BA21 (MNI: 62,-32,-23), and left BA21 (auditory processing, language) (MNI: -68,-24,-19) (p<0.001) (Figure 5).
Figure 5: Map showing group differences (ADHD vs. sNSC, p<0.001) in whole-brain ipsilateral intrinsic connectivity contrast analysis. Warm (orange to yellow) colors represent greater activation in the ADHD group. Blue colors represent greater activation in the sNSC group.
Whole brain-based functional connectivity analyses were done to compare the connectivity of region of interest seeds, generated from the intrinsic analysis, in ADHD compared to sNSC patients (Table 5). Whole brain-based functional connectivity analyses demonstrated increased negative connectivity (anticorrelations) of BA11 to different part of BA11 (emotional regulation) in ADHD relative to sNSC (p<0.001) (Figure 6). The right BA20 (complex processing) and BA21 (auditory processing) seed had decreased connectivity to BA19 (MNI: -2,-84,29), BA20 (MNI: -61,-25,-26), and BA21 (MNI: -63,-31,-22) and increased connectivity to the visual association cortex (MNI: -2,-75,26), primary visual cortex (MNI: -12, -84,11), and left BA19 (visual processing) (MNI: -2,-84,29) in ADHD relative to sNSC (p<0.001) (Figure 7). The left BA21 seed had increased connectivity to the visual association cortex (MNI: -2,-80,20), left primary visual cortex (MNI: -2,-76,13), BA19 (MNI: 10,-87,32), left BA7 (visuospatial processing) (MNI: -16,-68,54) and decreased connectivity to left BA20 (MNI: -57,-29,-27) and BA21 (MNI: -65,-33,-17) in ADHD relative to sNSC (p<0.001) (Figure 8).
<table>
<thead>
<tr>
<th>Seed</th>
<th>Area of Altered Connectivity*</th>
<th>MNI (x,y,z)</th>
<th>Connectivity Findings‡</th>
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*Found to be significant at p<0.001
‡ADHD relative to sNSC

Table 5: Results of the network ROI seed to whole-brain connectivity analysis between ADHD and sNSC
Figure 6: Map showing group differences (ADHD vs. sNSC, p<0.001) in connectivity from BA11 seed-to-whole brain analysis. Stronger negative connectivity (anticorrelations) to a different part of BA11 is observed for the ADHD group compared to the sNSC group.
Figure 7: Map showing group differences (ADHD vs. sNSC, p<0.001) in connectivity from the right BA20 and BA21 seed-to-whole brain analysis. Stronger connectivity (correlations) to the visual association cortex, primary visual cortex, and BA19 is observed for the ADHD group compared to the sNSC. Stronger negative connectivity (anticorrelations) to the BA20, and BA21 is observed for the ADHD group compared to the sNSC group.
Figure 8: Map showing group differences (ADHD vs. sNSC, p<0.001) in connectivity from left BA21 seed-to-whole brain analysis. Stronger connectivity (correlations) to the visual association cortex, left primary visual cortex, left BA7 and BA19 is observed for the ADHD group compared to the sNSC. Stronger negative connectivity (anticorrelations) to the left BA20, and BA21 is observed for the ADHD group compared to the sNSC group.
Figure 9: Map showing group differences (sNSC vs. controls, p<0.001) in connectivity from left BA21 seed-to-whole brain analysis. Stronger negative connectivity (anticorrelations) to the visual association cortex and BA19 is observed for the sNSC group compared to the controls group.
Figure 10: Map showing group differences (ADHD vs. controls, p<0.001) in connectivity from left BA21 seed-to-whole brain analysis. Stronger negative connectivity (anticorrelations) to the left BA21 and BA20 is observed for the ADHD group compared to the controls group.
Whole brain-based functional connectivity analyses were done to compare the connectivity of left BA21 seed in ADHD group compared to controls and sNSC group compared to controls (Table 6). Whole brain-based functional connectivity analysis demonstrated decreased connectivity of left BA21 seed to BA19 (MNI: 0, -83,31) and visual association cortex (MNI: 6, -87,19) in sNSC relative to controls (Figure 9). Whole brain-based functional connectivity analysis demonstrated decreased connectivity of left BA21 seed to left BA21 (MNI: -65, -20, -24) and left BA20 (MNI: -63,-27,-24) in ADHD relative to controls (Figure 10).

<table>
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<th>Comparison Groups</th>
<th>Area of Altered Connectivity*</th>
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<th>Connectivity Findings</th>
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<td>Right Visual Association Cortex</td>
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<td>Left BA20</td>
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</table>

*Found to be significant at p<0.001

Table 6: Results of the network Left BA21 seed to whole-brain connectivity analysis as specified on table header
DIFFUSION TENSOR IMAGING

Analysis of the DTI data, demonstrates an increase in anisotropy (i.e. more myelinated pathway detected) in the areas of precuneus area, corpus callosum, posterior limb of the internal capsule, brain stem after surgery (i.e. mature development in myelination) when compared to before surgery (p<0.05). There is also a decrease in anisotropy (i.e. immature development in myelination) in the cingulum after surgery (p<0.05) (Figure 11).

Figure 11: The DTI images show group differences (infants after surgery vs. infants before surgery, p<0.05). Blue colors represent greater anisotropy in the before surgery group (cingulum, A). Warmer colors (orange to yellow) represent greater anisotropy in the after surgery group (corona radiata, includes the precuneus, B).
DISCUSSION

LONGITUDINAL ANALYSIS OF CRANIOSYNOSTOSIS

Earliest Developing Networks

SOMATOSENSORY (SM) AND PRIMARY VISUAL (V1) NETWORKS

The somatosensory system includes the connections between sensory neurons and processing of these stimuli. The somatosensory (SM) and primary visual (V1) networks as the earliest developing networks; make most connections during 0-3 months of age. These are correlated with basic needs for functional survival at early stages of development (i.e. body movements, visual recognition). The SM and V1 networks are very similar to previously published controls of the age range 3-6 months, which includes “before” scans at an average of 5 months. The networks do not have statistically significant differences, before or after surgery, and neither in adolescence, compared to controls. These networks may have developed adequately to withstand negative influences associated with brain maldevelopment.

AUDITORY NETWORK (AN)

The auditory network is also a early developing network, where most of the connections are made within the first 3 months of life. Comparing the “before” AN network to similarly aged controls, the left temporal gyri shows no connectivity to the seed of the AN network. These connections do not correct wholly by 3 months after whole vault surgery. However, as the child develops into adolescence, the bilateral temporal auditory network connection is restored, and there is no difference ultimately between controls and operated adolescents.
Auditory processing has been studied previously by ERP on patients born with sagittal craniosynostosis, and have demonstrated abnormal processing of sounds at age of 8 months of age and before any surgery. Post-operative sagittal patients have also been studied by ERP and there is a return to normal auditory processing by ERP after surgery at age of 15 months. This observation is further corroborated by fMRI connections that return to normal at a later stage of development.

Intermediate Developing Networks

Secondary Visual Cortex (V2) and Third Visual (V3) Networks

The V2 network develops beginning 0-3 months of age but the V3 network extends for a longer period of early development into 12 months of age (i.e. higher order functional network). The before surgery scans demonstrate a decreased connectivity when compared to controls. The V2 and V3 networks have increased connectivity to the insula after surgery compared to the aberrant (decreased) functionality before surgery (p<0.001). Similarly, previous studies have demonstrated that visual evoked potentials are abnormal in some infants before surgery, who were born with craniosynostosis.

DTI analysis demonstrates an increase in anisotropy (improvement), after surgery relative to before surgery, in the precuneus, which is known to have connections to the insula. Therefore, an increase in anisotropy indicates an increase in white matter connections from the precuneus to the insula, and this could be influential in the increase in connectivity to the insula subsequently seen in the V2 and V3 networks.

Operated sagittal craniosynostosis adolescents have no functional differences when compared to controls in these areas. Previous data have demonstrated that
adolescents with repaired craniosynostosis have altered connectivity in visuospatial processing. Therefore, there could be remaining aberrant connections/processing that is not captured by this analysis.

**Late Childhood Developing Networks**

**Default Mode Network (DMN)**

The default mode network (DMN) has been characterized in the baseline state of the brain. This network is considered a higher order network, as it is involved with higher order executive function. It develops synchronously with the visual networks, V2 and V3, in which development occurs throughout the first year of life (0-12 months). Comparing the “before” DMN network of craniosynostosis patients to the DMN network of “same age” controls, there is a rudimentary connection formed, but it does not extend as extensively to more occipital areas, as it does in controls. The connections are stunted 3 months after surgery, but as the child develops into adolescence, (12.1 years of age) the DMN network develops into the same as same-aged controls. Therefore, there are no visible long lasting functional effects post-operatively in the DMN network in patients born with craniosynostosis and treated with a whole vault cranioplasty.

**Salience Network (SA)**

The salience network determines the most relevant processing information from multiple stimuli to guide behavior. The SA network develops quickly during 0-3 months of life into a premature state, and continues beyond 1 year, where it develops into more adult-like connections. The SA network of “before” surgery patients, has increased connections in the temporal areas compared to previously published control infants.
These temporal aberrant connections exist in both “before” and “after” surgery (Figure 3).

Operated patients, postoperatively, have increased connectivity in the left insula compared to controls (p<0.001). Aberrant connections of the insula to the salience network have been well studied in the context of behavior, emotional, and empathic responses. The insula has decreased connectivity in ADHD, and the increase in connectivity after surgery in this region, suggesting at least some surgical modification. These findings could explain some of the emotional deregulation and attention deficit difficulties in children born with craniosynostosis and treated with whole-vault cranioplasty.26

**LEFT FRONTAL AND RIGHT FRONTAL NETWORKS (FPNs)**

The frontoparietal networks organize attention to visual locations in the brain.40 The LFPN and RFPN networks develop quickly during 0-3 months of life into a “premature” state, in which they remain, until at least 1 year age. They then develop into more adult-like connections later in life. Therefore the LFPN network in “before” patients has similar connections to same aged controls.11 The LFPN network “after” surgery however has increased connections in the insula, right putamen, and inferior frontal gyrus when compared to “before” surgery (p<0.001). There is an increase in anisotropy, after surgery relative to before surgery, in the precuneus, and ultimately to the insula via white matter tracts.37 This increase in anisotropy indicates an increase in white matter connections from the precuneus to the insula, however as the child grows, the LFPN network develops to become more like normal controls, (i.e. no statistically significant differences).
The RFPN network in “before” patients has similar expected connections to similar aged control infants. The RFPN network “after” surgery has decreased connections in the left posterior cingulate compared to “before” surgery (p<0.001). Within the context of the RFPN, the posterior cingulate has been correlated with spatial processing.\textsuperscript{41,42} The DTI analysis demonstrates a decrease in anisotropy in the cingulum, from before, to after surgery, associated with a decrease in the white matter tracts. The cingulum, as a collection of white matter fibers, connects at least a portion of the posterior cingulate, to the rest of the brain. This decrease in physical white matter connections between the cingulate and the rest of the brain, could explain the decrease in functional connectivity of the RFPN to the posterior cingulate.\textsuperscript{24} Functionally, the decrease of functional connectivity and white matter tract connections of the posterior cingulate and cingulum, respectively, are linked to a decrease in spatial working memory, memory function, attention (ADHD) and emotional regulation (schizophrenia, autism).\textsuperscript{24}

During adolescence at an average of 12 years of age, the RFPN network of corrected craniosynostosis patients is similar to controls, but there still are decreased connections to the right BA7, the right sensory association cortex, and right primary sensory cortex (p<0.001). The connectivity of BA7 is decreased in craniosynostosis patients, specifying that spatial forms of attention processing are altered in the longer term.\textsuperscript{27,28} The right sensory association and right primary sensory cortex are areas involved in interpretations of outside stimulation such as physical sensations, proprioception, and nociception.\textsuperscript{29} Previous studies following patients into adolescence demonstrate that there remains a residual effect in the frontoparietal networks by fMRI and neurocognitive testing in zones of function related to attention span.\textsuperscript{3,8}
**Comparison of Craniosynostosis and ADHD**

sNSC and ADHD have been thought to have similar functional connectivity in previous fMRI studies and neurocognitive testing. Anecdotally, in clinic many sNSC patients are treated for learning disabilities. The functional connectivity and neurocognitive treatment of ADHD is well established by the literature and child psychologists. This study was undertaken to understand sNSC patients within the context of ADHD, utilizing functional MRI.

ADHD has lower connectivity to BA11, BA20, and BA21 compared to sNSC and controls. The orbitofrontal cortex (BA11) plays a crucial role in the network evaluation of state of mind and perspective, known as cognitive empathy. This is a known deficit for ADHD patients. The inferior temporal gyrus (BA 20) also shows higher connectivity in highly creative subjects, long term and complex memory issues, attention processing of complex auditory and visual stimuli, and emotion. The middle temporal gyrus (BA21) has greater activation in auditory processing, and utilized as a back-up processing area in children that are younger or have lower skill levels in semantic judgments. Therefore, children with ADHD have difficulty with decision making, planning, high level visual processing, and auditory processing, that healthy and sNSC children do not have, at least not to the same extent.

For sNSC patients, there have been findings of a decrease of visuospatial capabilities in neurocognitive testing and with fMRI. Visual and visual spatial deficiencies have also been identified in ADHD patients. When studying functional neural networks, it was found that the visual network in ADHD patients has decreased activation in the visual cortex. Visuospatial memory retrieval is impaired in ADHD.
patients compared to controls.\textsuperscript{48} sNSC patients have a unique visuospatial defect, compared to ADHD, created by decreased connectivity to BA31, BA7, BA19, visual association cortex, and primary visual cortex. BA31 is part of the dorsal posterior cingulate cortex, an area important in attentional focus.\textsuperscript{24} Decreased connectivity to BA7 is characteristic of William’s syndrome’s visuospatial defect.\textsuperscript{49} BA19 is part of visual association cortex, visual association cortex, and primary visual cortex are areas of the brain involved in generating mental images.\textsuperscript{50} Visuospatial and image processing defects are specific to surgically corrected sNSC, and are not seen to the same extent in ADHD. The cause of these neurological differences could be due in part to a genetic difference that cannot be corrected by surgery and/or release of compression that limits blood perfusion and myelination in the womb, before surgery and to an extent that surgery cannot correct.\textsuperscript{1,51,52} Further studies involved the functional and myelination differences will be necessary to answer these questions in more detail.

\textbf{DTI ANALYSIS}

The increase in anisotropy seen in the corpus callosum, precuneus, posterior limb of the internal capsule and brain stem after cranioplasty surgery are most likely due to normal development\textsuperscript{13}, i.e. surgery did not change this, comparing the normal growth in growth in these areas between 6 months to 9 months of age.\textsuperscript{53} However, the cortical area of the brain does not experience large changes in anisotropy normally during the first months of life, therefore the increase in anisotropy in the precuneus, and decrease in the cingulum in operated patients, are likely due to changes developed after (or possibly related to) surgery. The increased anisotropy also signifies increased neural tract connections in the insula and putamen, which could explain the increase in functional connectivity in the
insula and putamen and the rest of the brain. In normal development it has been demonstrated that fractional anisotropy should in fact increase in the cingulum, unlike our results which demonstrate a decrease after surgery, compared to before surgery. The decrease in anisotropy in the cingulum is correlated with lower cognitive ability.\textsuperscript{54,55} Decreased anisotropy in the cingulum, signifies decreased neural tract connections on the cingulate to the rest of the brain, which could explain the decreased functional connections of the posterior cingulate to the multiple other elements of the brain.

In adolescents with repaired sagittal craniosynostosis, the DTI analysis shows no statistical significant difference relative to controls.\textsuperscript{8} Therefore, the differences seen during infancy, correct following surgery, and as the brain matures into adolescence.

In comparison with other studies, this study finds more corroborating evidence toward previous conclusions with stronger statistical power and longer longitudinal data.\textsuperscript{8} Previous work demonstrated that adolescents treated for sagittal craniosynostosis had decreased connectivity in the RFPN network and no differences in the DMN, which is corroborated by our results.\textsuperscript{8} Specifically, there was also decreased connectivity to BA7 that did not reach statistical significance when doing intrinsic analysis.\textsuperscript{8} In comparison, in our seed-based analysis utilizing the seed of the inferior parietal lobule (seed of the RFPN network) demonstrated decreased connectivity to the BA7 as well.

In this study, we present a longitudinal case control study of the neural network development of children born with craniosynostosis and the surgical treatment. Very few conditions that affect cognitive function and psychiatric illness, only schizophrenia and executive function, have been studied in such a longitudinal manner, making this study
unique in this topic area. The limitations of this study are its small sample size, which are caused by the relative uncommon incidence of craniosynostosis and the fact that we cannot utilize sedation for patients in order to obtain shorter term post-operative functional data. We tried to compensate for this by reporting statistically significant differences being judged only at p<0.001. Monetary and time cost consideration, probably select for patients that are actually tested, therefore a broad range of patients of different socioeconomic and educational backgrounds may not have allowed full definition of the spectrum of neurologic dysfunction. Also we cannot define the natural history of untreated craniosynostosis patients because of the unethical withhold of treatment in our clinical context. Also adolescent patients are not the same patients in the “before” and “after” surgery in the infant scans. The adolescents had the same procedure as the infants by the same surgeon; but the true analysis would be longitudinal analysis of the same infants over time. This study is ongoing.
CONCLUSION

Patients born with and uncorrected sagittal craniosynostosis have abnormal connections throughout the neural networks compared to controls. During infancy in controls, and importantly post-operatively, the RFPN network has decreased connectivity in the posterior cingulate cortex (PCC). Decreased functional connectivity to the posterior cingulate can be explained by decreased anisotropy, white matter connections, as seen in DTI analysis. The LFPN has increased connectivity in the insula, putamen, and inferior frontal gyrus, after surgery, compared to before surgery. As the connectivity of the putamen and insula increase, the brain becomes more normal when compared to other conditions that affect executive and emotional regulation, such as ADHD.58

The V2 region has increased connectivity in the inferior frontal gyrus, and left insula, and V3 has increased connectivity in the putamen and insula relative to before surgery. Increased functional connectivity in the insula can be explained by increased anisotropy, that is, white matter connections, as seen in DTI analysis. Therefore, surgery may create positive changes in the brain microstructure, which could lead to changes in neural connectivity in the brains of infants born with craniosynostosis.

However in adolescent operated patients, some aberrancies remain in the SA network. There is decreased connectivity to the right BA7, right sensory association cortex and right primary sensory cortex. In the SA network, there is increased connectivity to the left insula in the post-operative patients relative to controls. Aberrant connectivity of the insula and BA7 has been linked with emotional and executive dysfunction.37,59,60 Therefore, there are remaining aberrancies, which are not as effectively treated by the surgical approach used in this study. These defects may be
treated more effectively possibly by measures, other than surgery (for example employing augmentative learning pathways which may enhance or complement gains achieved by surgery).

Patients born with sagittal nonsyndromic craniosynostosis have different neural connections than children born with ADHD. Patients born with sagittal nonsyndromic craniosynostosis have decreased connections in areas of visual processing and increased connections in areas of attention and auditory processing, when compared to patients with ADHD. Therefore, although children with sagittal craniosynostosis have learning difficulties when compared to ADHD the mechanism and neurologic pathways of involvement differ.
REFERENCES


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