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REVIEW PAPER

Neurodevelopment of children with single suture craniosynostosis: a review

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Abstract
Introduction Rates of neurocognitive risk range from 35–50% of school-aged children with isolated single suture craniosynostosis (SSC). It has been hypothesized that early surgical intervention to release suture fusion reduces risk for increased intracranial pressure (ICP) and the corresponding risk to neurodevelopment. However, studies assessing children with SSC have been inconsistent in finding an association between neurocognitive development, age of surgery, and ICP.
Review SSC produces notable distortion of the cranial vault and underlying brain mass. Although a linear relationship between skull distortion, ICP, and neurocognitive deficits has generally been assumed, recent studies have postulated an interactive process between the skull and developing brain that results in neuroanatomical changes that are not limited to areas directly beneath the fused suture. The specific neuropsychological deficits identified in children with SSC including problems with attention and planning, processing speed, visual spatial skills, language, reading, and spelling may be related to the anatomic differences that persist after correction of suture fusion.
Conclusions Available literature on neurocognitive development of children with SSC is suggestive of mild but persistent neuropsychological deficits, which become more significant as cognitive demands increase at school age. Anatomical studies of children without SSC are beginning to identify particular groups of brain structures that if disrupted or malformed, may be associated with specific cognitive deficits. Controlled research investigating the relationship between persistent anatomical changes and neurocognitive functioning of school-aged children with SSC is needed.

Keywords Single suture craniosynostosis · Neurodevelopment · Cognition · Increased cranial pressure · Neuroimaging

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Introduction

In recent years, there has been considerable discussion regarding the neurodevelopment of children with single

suture craniosynostosis (SSC). Much of this dialogue has centered on the timing and relationship of reconstructive surgery to increased cranial pressure and ultimately, neurocognitive outcomes. However, as of present, there is little evidence supporting the contribution of these factors to neurodevelopment, and testable hypotheses regarding the links among these variables have yet to be clearly developed. In this paper, we focus on these issues, first by briefly providing an overview of SSC and its etiology, treatment, and effects on neuroanatomy. Next, we review studies of the neuropsychological correlates of SSC. We conclude by offering tentative hypotheses about the neuropsychological outcomes of the different suture fusions.

Overview of SSC

SSC refers to an isolated premature fusion of one cranial suture: the metopic, sagittal, and right or left coronal and right or left lambdoid. The overall incidence of SSC is approximately 1 in 2,000 live births, although estimates vary [29, 108, 112]. Sagittal synostosis is most common with an incidence of 1 in 5,000 live births, whereas lambdoid is least common with an incidence of 1 in 200,000 [29]. Metopic synostosis occurs at a rate of approximately 1 in 15,000 and unilateral coronal at a rate of 1 in 11,000 [29].

Specific types of SSC result in clinically recognizable characteristic skull malformations (Fig. 1). Premature synostosis of the sagittal suture results in an increased sagittal growth at the expense of its transverse width with varying degrees of occipital and frontal prominence clinically described as scapholcephaly. With the premature closure of the metopic suture, the normal growth of the frontal cranial vault is restricted with secondary compensatory growth of the parietal width, resulting in trigonocephaly. The central metopic ridge is characterized with a constriction of the lateral aspect of the frontal bones. The lateral supraorbital rims are recessed with elevation of the medial orbital roof. Unilateral coronal synostosis results in anterior plagiocephaly with restricted forward growth of the anterior cranial vault on the affected side. The frontal bone and orbital rim are recessed with elevation of the lateral orbital roof on the involved side, compensatory prominence of the frontal bone on the uninvolved side, and a temporal prominence on the ipsilateral side. Additionally, the asymmetry ultimately affects the facial development with deviation of the nasal axis and differential in the zygomatic arch lengths. Posterior synostotic plagiocephaly that occurs with lambdoid synostosis is characterized by the flattening of the occipital bone and prominence of the mastoid bone on the involved side. Compensatory growth then occurs in the occipital and parietal regions of the uninvolved side resulting in a trapezoidal-shaped cranial vault [30, 42, 118]. Historically, skull radiography [49] and computerized tomography (CT) [70, 123, 124] have been used to confirm a clinically derived diagnosis of SSC; however, recently, some researchers have suggested that the various synostoses can

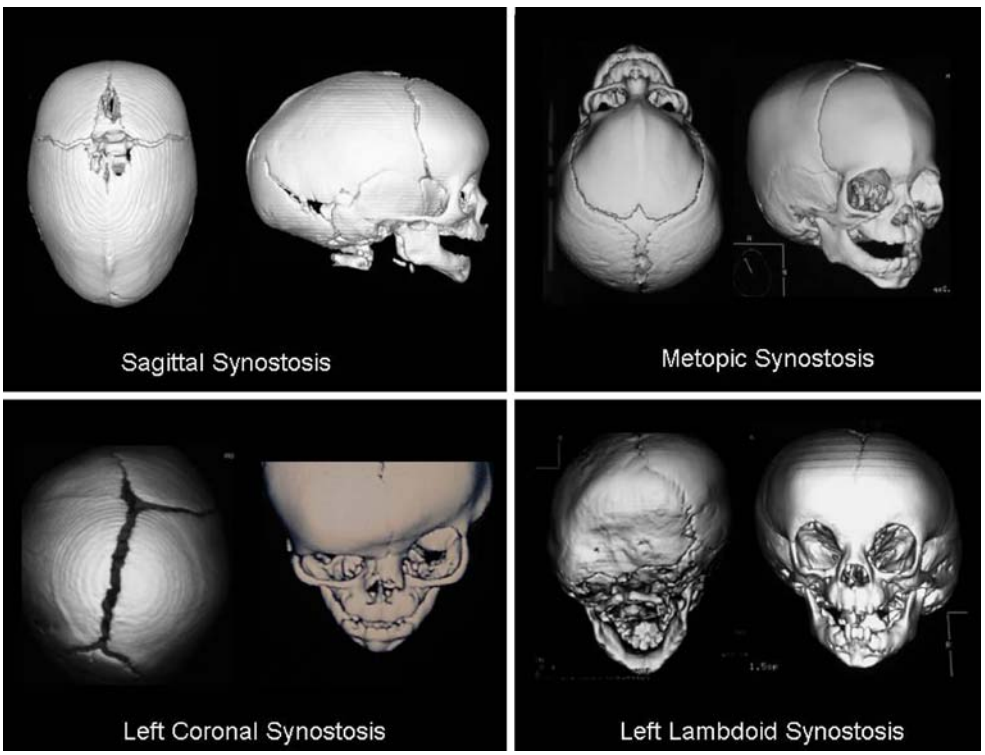

Fig. 1 Representative CT scans showing location of premature suture fusions for sagittal, metopic, left unilateral coronal, and left lambdoid craniosynostosis

be reliably diagnosed with physical exam alone, thus minimizing radiation exposure to infants [2, 24].

Etiology The etiology of SSC is variable. Basic science research has identified multiple potential causes of suture closure including biomechanical, environmental, vascular, hormonal, and genetic. It is likely that there is more than one mechanism involved [30]. Fetal head constraint has been postulated as a cause of some cases of SSC, particularly in the case of multiple births [51, 52, 54]. There have been few epidemiologic studies on craniosynostosis; however, there are some evidences relating maternal smoking and maternal exposure to nitrosatable drugs to craniosynostosis [3, 4, 47, 48, 56, 64, 86]. The majority of the cases of SSC are non-familial, and mutations have been identified infrequently in individuals with isolated synostosis who have no other medical problems. Coronal synostosis (bilateral more often than unilateral) has been associated with a known mutation, most often involving *FGFR3* and *Twist* and has a familial rate of 6 to 11% [29, 83]. Metopic synostosis has a familial rate of approximately 5.6%, whereas the rate for sagittal is 6%. Metopic synostosis, in conjunction with other problems, has been associated with several chromosomal abnormalities [73]. Until recently, however, no mutations had been identified for isolated metopic or sagittal synostosis [72, 73]. In 2000, Kress et al. [71] identified an unusual FGFR1 mutation in a girl with an isolated metopic synostosis. More recently, Seto et al. [104] identified a Twist1 mutation in a boy with isolated sagittal synostosis.

Surgical treatment The primary goal in surgical management of SSC is to allow normal cranial vault development to occur by removing the growth restriction caused by the particular fused suture. The cranial volume triples within the first year of life, and rapid growth continues until age 3 as it begins to decelerate until age 6 when the cranial vault reaches 90% of its adult size. Without surgical intervention, the deformity progressively worsens until growth is complete [70]. Thus, early surgical release of the fused suture is critical to restore the normal growth pattern of the cranial vault directed by early brain development and to minimize the secondary compensatory development of the craniofacial structures that is abnormal [77, 78]. In general, the surgical outcome from a morphologic perspective is excellent in SSC, with the need for revision surgery minimal in contrast to multi-sutural synostosis and syndromic cases. Historically, surgery has evolved from limited strip craniectomy to increasingly more extensive cranio-orbital surgery to improve morphologic outcome. However, it should be emphasized that comparative studies that evaluate morphologic appearance with normal unaffected population are limited. Studies that do exist have almost exclusively focused on measurement of the cranial index [11, 65, 87] or cranial volume changes for sagittal synostosis [93], with subjective judgment in many of the other SSC suffering from methodological errors [78].

Although surgical intervention for morphologic reasons alone is clear, surgical intervention for minimization of cognitive deficits, which may result from constricted brain growth as a result of abnormal cranial vault development, is unclear. The assumption is that intracranial pressure (ICP) increases with restricted cranial growth and, in turn, adversely influences mental development [9, 94, 95, 114]. Although this is likely in multi-sutural synostosis, with SSC, the patency of the remaining sutures in theory should allow 'decompression' of any increased pressure. Whether there is a localized increase in pressure in the region of the fused suture in SSC and whether it can be decompressed globally remains unknown. Thus, at this time, surgical intervention on morphologic grounds remains the only absolute indication.

Hypothesized effects on brain structure SSC produces notable distortion of the cranial vault and underlying brain mass. Restricted intracranial volume due to constriction on skull growth has been described frequently [20], but there are also data suggesting that brain volume in these cases is within [92] or exceeds [93] normal limits. These discrepancies may relate to measurement issues as well as to non-existent or poor normative data [20].

Brain shape is also important to consider because it is independent of volume, and the shape of brain structures (and the spatial relations among them) provide information about neural organization [5]. Historically, researchers have believed that the structure of the brain was normal in SSC, with the component parts present but misshapen. With that in mind, the major goal of cranial remodeling has been to restore the normal anatomy of the cranial vault, with the expectation that the shape of the brain would then also normalize [96]. This view of normal morphology in SSC has been held in sharp contrast to the well-known structural brain anomalies associated with multi-suture craniosynostosis such as ventriculomegaly, Chiari malformation, corpus callosum abnormalities, and abnormalities of the septum pellucidum [28, 96]. However, recent studies using CT and magnetic resonance imaging (MRI) scanning technology have identified morphologic differences between the brains of healthy children and those with SSC. Patients with metopic synostosis have been found to display frontal subdural space distention, corpus callosum anomalies, abnormally small frontal lobes, and widened precentral sulci [18, 78]. Evidence of Chiari malformation in children with metopic ridging has been presented [122]. The CT analysis of SSC has revealed enlargement of the subarachnoid space in the areas of compensatory bone expansion likely due to

constriction in the area of fusion and compensatory fluid shift [25]. The MRI has identified cortical and subcortical differences in the relative location of brain structures in children with SSC not limited to areas under the fused sutures [5–7]. Furthermore, although the linear distances between and among brain structures were altered after corrective surgery, these relations were still abnormal in comparison to individuals without craniosynostosis.

Neurocognitive issues: theoretical considerations

The idea that single suture fusions might compromise neuropsychological functions, including global intelligence (IQ), has been discussed for many years [8, 16, 95]. Historically, the association between SSC and neurodevelopment has been conceptualized as a linear pathway in which suture fusion leads to abnormal brain development, creating measurable deficits in neuropsychological functions [114]. Two factors have been most often cited as the causal links between SSC and impaired function: (1) elevated ICP with hypovascularity [94, 96] and (2) secondary cerebral deformation resulting from brain growth in an abnormally shaped skull [44].

Current reviews suggest that the incidence of clinically significant increases in ICP for infants with SSC ranged from about 4 to 20% [19, 119]. Recently, there is evidence that increased ICP is more likely to occur in children with a diagnosed $FGFR3^{P250R}$ mutation [121]. However, these findings are complicated by the fact that there is no universally agreed upon scale for determining "normal" versus "abnormal" ICP in children. In addition, there is a lack of consistency in the methods for assessing ICP (see [19, 119] for reviews), which makes interpretation of the available data extremely difficult. The few studies of SSC that have included measures of both ICP and neurodevelopmental status have failed to find reliable associations between the two [9, 50]. Pinpointing the correlation between ICP and neurodevelopment is complicated by the fact that ICP seems to fluctuate with age, independent of any surgical effect that may exist. For example, there is evidence that ICP levels in children with SSC decrease with advancing age, possibly due to accommodations in the brain including cerebral atrophy [20, 61, 94]. Animal models also suggest that a decrease in ICP with age may be related to cerebral atrophy [43].

There has been little study of the secondary cerebral deformation hypothesis. As noted above, preliminary evidence using MRI suggests that SSC is associated with cerebral dysmorphology [6], although the direction of causality between skull and brain is unclear [97]. Aldridge et al. [6, 7] found that the shape of the brain did mirror the general shape of the skull in each of the SSC conditions; however, they also found that dysmorphology was not limited to areas directly under the fused suture, occurring as well in structures deep within the cortex. The significant localized differences in the distances between major cortical and subcortical brain structures were reasonably consistent within suture type but varied among the three types of SSC evaluated (metopic, sagittal, and right unilateral coronal). Although this line of research did not examine neurodevelopment, it is theoretically possible that abnormally long or short distances between major brain structures could cause small perturbations in cortical connectivity, eventually producing functional changes in the way the brain processes information. Indeed, evidence from cognitive neuroscience research suggests that small variations in neural organization can lead, over time, to significant changes in cognitive functioning [27, 80, 84].

In summary, the potential mediating effects of ICP and secondary cerebral deformity on the link between SCC and neurodevelopment are largely theoretical at this stage of research. Given this uncertainty, it is important to consider another possibility: SSC and its expected neuropsychological deficits may both stem from a primary malformation of the brain rather than—or in addition to—secondary deformation [69]. If this were true, suture fusion may serve as an indicator of neurodevelopmental concern but may have fewer direct effects on neurodevelopment.

Research on neurobehavioral outcomes

Speltz et al. [114] reviewed 17 studies examining the neuropsychological status of infants, children, and/or adolescents with SSC completed between 1972 and 2003. The majority of children in these studies demonstrated global developmental or IQ scores within the normal range. However, approximately 35 to 40% of assessed cases demonstrated some types of adverse neurodevelopmental outcome such as a learning disability, language impairment, or a less precisely defined "behavioral or cognitive abnormality" [66, 76, 107]. These data suggest that SSC is associated with a three to fivefold increase in risk for cognitive or motor deficits or learning/language disabilities. No particular suture among those studied (sagittal, metopic, and left or right unilateral coronal) was associated with relatively higher risk of problems, although such comparisons were typically limited by the very small numbers of cases in all diagnostic categories except sagittal. Among the several quasi-experimental studies of cranioplastic surgery reviewed by Speltz et al. [114], there was little evidence that surgery either prevented or reduced risk of neurobehavioral impairment. The authors concluded that the level of risk for neuropsychological problems among

infants with SCC warranted routine neurodevelopmental screening in the interest of early identification and prevention.

Since the Speltz et al. [114] review, an additional eight studies addressing neurodevelopmental functioning have been published, five involving infants and three examining school-aged children (see Table 1 for a summary of these studies).

Infancy studies In US studies of SSC, the most widely used standardized test of infancy development is the Bayley exam, specifically the Bayley scales of infant development, first edition (BSID-I [12]) and second edition (BSID-II [13]). Both editions yield norms for a mental development index (MDI), which primarily represents the infant's problem-solving skills (as well as verbal/vocal and fine-motor behaviors required to solve such problems), and a psychomotor development index (PDI), which targets a range of gross and fine motor abilities.

Three of the infant studies published since Speltz et al. [114] lacked control groups and therefore compared the BSID scores of SSC cases with published test norms. Using the BSID-II, Cohen et al. [31] examined 22 infants with SSC before surgical correction and 15 of the same infants after surgery (about half were sagittal cases and the remainder were metopic and unilateral coronal). These investigators found that more than half of their SSC cases had MDI and PDI scores within the mildly to severely delayed categories of development when tested before surgery (64 and 55%, respectively). There was little change in performance after surgery (67 and 40% showed delayed functioning on the MDI and PDI scales, respectively). Warschausky et al. [125] examined 22 infants with isolated metopic synostosis before surgery using the BSID-I or II MDI. Average MDI scores in this study were within the normal range. Scores were positively correlated with maternal education but unrelated to perinatal risk factors, infant age when tested, and severity of frontal stenosis [125].

Kapp-Simon et al. [67] reported data on the first 100 infant cases of SSC enrolled in a prospective longitudinal study that will eventually recruit 250 cases and an equal number of controls. Among these 100 participants were 49 sagittal, 24 metopic, 18 unilateral coronal, and 9 lambdoid cases, ranging from about 2 to 30 months of age (Mean=7.3 months). The infants were assessed using the BSID-II MDI and PDI scales as well as the preschool language scale-3 expressive and receptive scales. On all measures given, infants with SSC had scores significantly lower than test norms, a finding that was unaffected by diagnostic subgroup. MDI scores were two thirds of a standard deviation below average and PDI scores more than a full standard deviation below the normative mean. Contrary to the maternal education finding reported by Warschausky et al. [125], test scores were unrelated to maternal intelligence (measured by an IQ test) and family socioeconomic status (including parents' level of education).

The comparisons in the foregoing three studies of test scores with test norms are typical of research in this area, given the relative absence of control groups. This is a questionable strategy, as cases drawn from clinical programs may differ substantially from the samples used to develop test norms. Moreover, test norms may become invalid over time due to changes in population characteristics and/or environmental factors that affect the assessment of development [46]. The Bayley [13] and other standardized infant tests may be particularly vulnerable to this effect as a result of the American Academy of Pediatrics' Back to Sleep campaign [1]. Several investigators have documented transitory motor delays in otherwise typically developing infants who were positioned frequently in supine for sleep [35, 39, 62]. Test norms for instruments developed before Back to Sleep—including both the BSID I and II—may therefore lead to inaccurate comparative impressions about the developmental status of infants with SSC and other index groups. For example, the developmental delays suggested by Cohen et al. [31] and Kapp-Simon et al. [67] could in part reflect the comparison of SSC data with norms established before the advent of Back to Sleep.

This possibility is supported by more recent data from Speltz et al. [115] who compared a larger number of cases from the same longitudinal sample with 125 case-matched healthy infants (62 infants with sagittal, 27 with metopic, 28 with unilateral coronal, and 8 with lambdoid). Statistically significant differences favoring the control group were found on both MDI and PDI scores, but average scores for both cases and controls were below BSID test norms: Cases were about two thirds of a standard deviation (MDI) to a full standard deviation below test norms (PDI), whereas controls were about one third to half a standard deviation below norms for the MDI and PDI, respectively. When compared with test norms, BSID-II motor scores appeared to be more affected by SSC in the Kapp-Simon et al. [67] study than the magnitude of the case–control group differences obtained by Speltz et al. [115].

Several other infant studies [15, 31, 36, 88] have reported that SSC samples performed significantly worse than normative data on the psychomotor scale of the BSID. In recent studies of infants without other medical problems who were positioned frequently in supine for sleep, motor delays on the BSID present at 7 months were no longer evident at 15 months of age [35, 39]. The long-term significance of the clinically small but statistically significant group differences in development reported by Speltz et al. [115] remains uncertain.

Table 1 Summary of studies examining neurodevelopment since Speltz et al. 2004 [114]

Authors	Number of cases by diagnosis	Age(s) at evaluation	Neurobehavioral measures	Control group?	Summary of results
Boltshauser et al. [17]	30 Sagittal (all without surgical correction)	2.5–25.5 years	Neuropsychological battery; CBCL[a]; quality of life	Yes, siblings	No differences in mean IQ; K-ABC[b] cases: 106.7; K-ABC[b] siblings: 107.9; WISC[c]/WAIS[d] cases: 112.5; WISC[c]/WAIS[d] siblings: 113.3; more cases delayed in attention and processing speed; more cases displayed impaired global positive emotional functioning
Cohen et al. [31]	10 Sagittal; 7 unilateral coronal; 5 metopic	T1 Pre-surgery, mean: 5.9 months; T2 1 year post-surgery	BSID-II[e]	No	Mild or severe delays; pre-surgery: MDI[f] 14/22 (64%), PDI[g] 12/22 (55%); post-surgery: MDI[f] 10/15 (67%), PDI[g] 6/15 (40%)
Bellew et al. [15]	43 Sagittal (28 surgery, 13 no surgery); 28 controls	T1 Surgery: 7 months, no surgery: 26 months, control: 7 months; T2 surgery: 15 months, no surgery: 35 months	Griffiths mental development scales	Yes	T1 Sagittal surgery vs control; surgery significantly lower motor; T1 pre/T2 post surgery; significantly increased motor score; T1/T2 no surgery; all scales within normal limits on both occasions
Warschausky et al. [125]	22 Metopic	11.6 months (SD 4.8)	BSID-I or II[e]	No	No significant difference in MDI scores by severity of synostosis; language low for both groups
Kapp-Simon et al. [67]	49 Sagittal; 24 metopic; 10 right unilateral coronal; 11 left unilateral coronal; 9 lambdoid	7.3 months (range 1.7 to 30.6)	BSID-II[a]; PLS-III[h]; maternal IQ; parenting stress index	No	Mean MDI[f]=91.9*; mean PDI[g]=83.5*; mean PLS-AC[i]=90.4*; mean PLS-EC[j]=95.8
Da Costa [33] and Da Costa et al. (in press)	13 Syndromic, 3 Apert synd, 3 Crouzon Synd, 3 Crouzon synd, 5 Saethre–Chotzen, 1 Pfeiffer synd, 1 Witkop; 18 Nonsyndromic, 6 unioronal, 6 sagittal, 3 metopic, 3 multisutural	7 to 16 years	WISC-III; Leiter-R; neuropsychological; battery; CBCL[a]	No	IQ significantly higher for nonsyndromic group, full scale IQ (SD): syndromic, 83.1 (21.9); non-synd, 104.7 (15.8); significant deficits in attention skills and executive functioning identified in both groups
Speltz et al. [115]	62 Sagittal; 27 metopic; 16 right unilateral coronal; 12 left unilateral coronal; 8 lambdoid	6.5 months(SD 3.9)	BSID-II[e]; PLS-III; Maternal IQ	Yes, case matched by age, gender, SES, and race	Synostosis subjects significantly lower on MDI[f], PDI[g] but not on PLS-AC[h], PLS-EC[i] or maternal IQ. Effect size was small

[a] Child behavior checklist
[b] Kaufman assessment battery for children
[c] Wechsler intelligence scale for children-III
[d] Wechsler adult intelligence scale-revised
[e] Bayley scales of infant development I or II
[f] Mental development index from the BSID-II
[g] Psychomotor development index from the BSID-II
[h] Preschool language scale-III
[i] Preschool language scale-III, auditory comprehension
[j] Preschool language scale-III, expressive language
*Significantly lower than test norms

The Bellew et al. [15] infant study conducted in Great Britain used the Griffiths mental development scales (GMDS), which was published in 1986 before Back to Sleep. The Bellew et al. study also included an unaffected control group at the initial assessment. Twenty-eight infants with sagittal synostosis scheduled for surgery were compared to 28 unaffected controls [group matched by age and socioeconomic status (SES)] as well as to a group of older children with sagittal synostosis who did not have surgical correction. Follow-up GMDS data (7 months post-surgery) were also reported for some of the children from the two sagittal groups but not the control group. Among the five subscales of the GMDS, only the gross motor scale (locomotor scale) revealed differences between matched cases and controls before surgery. Post-surgery scores for sagittal cases showed significant improvement in average GMDS scores, driven primarily by improving motor scale scores. Mean motor scores for the "no surgery" sagittal group were 99 and 100, respectively, at the two assessments, which was an insignificant change; however, infants in the "no surgery" group were old enough at initial assessment (time 1, mean age=26 months) so that the development lags potentially associated with "back to sleep" would no longer have been evident.

Studies involving older children, adolescents, and young adults Boltshauser et al. [17] assessed 30 individuals with ages 2.5 to 25.5 years (mean=9.25 years), all with unoperated sagittal synostosis. Seventeen siblings were used as controls. There were no differences in intelligence between the cases and siblings, and scores for both groups were higher than norms. Despite high average intelligence, neuropsychological processing deficits were evident in 40% of cases for selective and sustained attention, with smaller proportions displaying deficits in processing speed and tasks assessing learning, memory, or memory span. The siblings also displayed a high rate of deficits on selective attention and alertness. There were more frequent parental concerns about emotional adjustment and behavior problems among the cases than in the siblings, although self-reported quality of life was similar in the two groups. The results of this study are difficult to interpret, given the very broad ages of the individuals examined, the possibility of parental report bias, and the fact that not all tests could be given to all participants (because of age constraints). Moreover, the use of siblings as a comparison group potentially controls for a number of environmental influences such as family SES and parenting style but introduces possible bias due to the high inheritability of many types of learning disabilities [90].

Using a similar neuropsychological battery as Boltshauser et al. [17], Da Costa et al. [34] assessed 21 children and adolescents with various nonsyndromic craniosynostoses (including 18 with SSC) and compared their performance with that of 13 cases with syndromic, multiple-suture craniosynostosis. SSC cases had normal intelligence with equivalent levels of performance on verbal and nonverbal IQ subtests. SSC scores were significantly higher on average than children with syndromic craniosynostosis. However, both groups showed lower-than-expected performance of tasks assessing sustained attention, visual–spatial planning ability, and planning/problem solving; all are skills associated with the frontal lobe. Neuropsychological processes that are deficient across various levels of disorder severity (in this case, syndromic, nonsyndromic, and SSC) and mental ability may represent the 'core deficits' of the specific medical condition [37]. Consistency of deficits across suture types would add some credence to the hypothesis that SSC and neuropsychological deficits may both stem from a primary malformation of the brain raised earlier.

Becker et al. [14], using retrospective chart review, examined speech, cognitive, and behavioral outcomes for 214 patients with nonsyndromic craniosynostosis (175 with SSC). The majority of patients (96.7%) had undergone calvarial surgery. "Abnormal functioning" was defined as performance more than 1 SD below the normative mean on the assessment instrument used. Forty-five percent of the children were categorized as either functioning abnormally in one or more of these areas or having a documented learning disability, special education placement, or identified behavioral problem; 23% had a documented speech/language problem. Nearly half of all patients with SSC displayed a problem in one or more of the measured areas, a figure consistent with the estimated base rate of neurobehavioral problems suggested by the Speltz et al. [114] review.

Summary Several trends can be discerned from both the new studies reviewed here and those reviewed previously by Speltz et al. [114]. First, the design and methods of research in this area continue to improve. For example, several of the studies included control groups of some type [15, 17, 115]. Several assessed the impact of variables likely to affect cognitive development including family SES, maternal IQ, and factors related to condition severity [67, 115, 125]. Studies of school-aged children have begun to investigate the broader spectrum of neurobehavioral functioning rather than limiting outcome to presence or absence of retardation [14, 17, 33].

Second, regardless of age, global measures of intelligence and developmental status mostly point to average to low average levels of performance. There is little evidence that SCC is associated with mental retardation or significant global deficits in cognitive functions.

Third, among infants with SSC, there is relatively consistent support for reliable but clinically modest developmental delays, mostly demonstrated by studies using

matched control groups or a more current version of the BSID with updated norms [13].

Such comparisons tentatively suggest that early delays are more likely to manifest as problems in psychomotor development rather than problems in problem-solving or early vocal/verbal abilities, although this could partially reflect the greater challenge of testing the latter functions at a young age. These findings may be of importance for predicting later outcomes, given the evidence linking problems in early motor development with subsequent problems in cognition [10, 40].

Fourth, there is no evidence yet that surgery affects the presence or trajectory of early developmental delays, which may largely reflect the absence of well-designed studies of pre–post-surgery change (e.g., tracking change over the same time interval in demographically matched controls).

Fifth, among the relatively few studies of school-age and older children with SCC, there is growing evidence of deficits in neuropsychological functions including attention and planning, processing speed, and visual spatial skills, with related problems in language, reading, and spelling.

Cognitive processing and suture-specific functional deficits

Studies of SSC to date have not had sufficient numbers within each diagnostic group to identify a suture-specific impact on neuropsychological processing, and there are no studies that have used imaging techniques in conjunction with neuropsychological data to assess relationships between cognitive functioning and anatomical changes. However, anatomical studies of children without SSC are beginning to identify particular groups of brain structures that, if disrupted or malformed, may be associated with specific cognitive deficits. For example, there is broad consensus that disruption of the neural pathways located in the left temporo-parietal cortex is linked with dyslexia [74, 105, 110, 111, 120]. Deutsch et al. [38] identified changes in the direction of white matter fiber tracks of the left temporo-parietal region, which discriminated between good and poor readers. A constellation of anatomic measures including marked right cerebral and left anterior lobe cerebellar asymmetries, asymmetry of specific areas of the Sylvian fissure, and duplications of the left Heschl's gyrus distinguished children with phonological dyslexia from children who were normal readers and from those with more global reading comprehension and language problems. Conversely, classification of children with global language delays and reading comprehension deficits was predicted by smaller cerebral volume and perisylvian symmetry rather than asymmetry. Normal phonology, reading comprehension, and language skills were predicted by moderate asymmetry and size [74, 75]. It has been postulated that deviant asymmetry of cortical areas may be related to abnormalities of the corpus callosum [60].

Problems with executive functioning including working memory, impulse control, and planning have been associated with the dorsolateral frontal regions of the brain [53, 98, 105, 117]. Differences in brain morphology for children with attention deficit–hyperactivity disorder (ADHD) include size reduction of the total cerebrum, with the greatest reduction visible in the right hemisphere [101], although not all studies support these differences [45, 58]. Smaller volumes of some portion of either right or left dorsolateral prefrontal cortex have been found in the majority of imaging studies that have investigated ADHD in children [21–23, 41, 45, 55, 58, 68, 81, 103], whereas Sowell et al. [113] identified bilateral size reduction in both the inferior aspects of the dorsolateral cortex and the lateral aspects of the anterior and midtemporal cortices. Corpus callosum abnormalities have also been identified in children with ADHD, particularly in the area of the genu and splenium [59, 102]. Sowell et al. [113] hypothesized that increased bilateral density of gray matter in more posterior aspects of the temporal lobes and the inferior aspects of the parietal lobes may be related to corpus callosum differences.

Structural and functional abnormalities in the dorsal and medial prefrontral cortex and premotor cortex—often more evident in right brain areas—have been implicated in social attention impairments and visual-motor-functioning in children with autism [32, 79, 82, 91], schizophrenia [26], and nonsyndromic cleft lip and palate [85]. Nonverbal learning disorders, which share some characteristics with autism, have been associated with white matter disturbance of the right hemisphere [89, 99, 126].

These findings suggest that if a specific isolated synostosis produces a consistent type of brain deformation, different suture fusions may be associated with different neuropsychological deficits. However, the plausibility of this hypothesis must be judged in the context of several potentially limiting factors. First, research on neuropsychological deficits does not consistently support a direct relation between a single anatomic anomaly or change and cognitive functioning; rather, there appears to be cumulative risk in relation to multiple structure changes [74]. Second, clear models of cognitive strengths and weaknesses have not been identified for specific suture fusions. Third, the research of Aldridge et al. [5–7] suggests that morphologic changes in the brain of children with SSC, although reasonably consistent within suture type, are not limited to the areas directly beneath the fused suture, either before or after surgical correction. Cortical and subcortical abnormalities in the shape of brain structures [5–7], *only some of which reflect the synostotic shape of the skull*, are present in each

SSC type. Structural abnormalities that occur in areas of the skull that are not directly under the area of synostosis raise the possibility noted earlier that isolated synostosis and the neurodevelopmental deficits with which it is associated both result from primary brain malformation rather than secondary deformation. Fourth, the current evidence implicates multiple etiologic pathways for the development of SSC. Different etiologies may produce different types of cognitive sequelae. Finally, neuropsychological functions may have limited relation to the affected suture and associated structural deficits due to the effects of neural plasticity, compensatory processes, behavioral adaptation, and environmental factors that potentially mediate the effects of any cerebral insult in early life [37, 63, 100, 116].

Tentative hypotheses Despite the above caveats, it is heuristically useful to consider hypotheses regarding the potential relations between different isolated suture fusions and specific types of neuropsychological profiles:

1. Sagittal synostosis: Infants and children with sagittal synostosis have, by far, been studied the most extensively, with cumulative evidence pointing to early speech and language problems and subsequent literacy issues and problems in related functions such as working memory, attention, and planning. Clinical impressions suggest that children with sagittal synostosis often resemble children who have developmental reading disorders, often with ADHD. Consequently, we might expect bilateral abnormalities in the occipital parietal area including the Sylvian fissure and possibly the dorsolateral prefrontal cortex due to elongation of the skull and related prominence of the forehead and occiput. Future studies of case–control differences could be designed to test this hypothesis by comparing neuropsychological profiles with imaging-based analyses of brain structures.
2. Metopic synostosis: Neurobehavioral studies of children with metopic synostosis are far less common and less precise. There is limited evidence of increased learning and/or behavior problems [14, 106, 109]; however, there have been no studies of school-aged metopic cases using comprehensive neuropsychological testing batteries. In a review of children with metopic synostosis, Bottero et al. [18] identified severity of frontal stenosis as the primary predictor of poorer neurobehavioral outcomes (lower mental ability, learning, or behavior problems). These authors also suggested that MRI studies may reveal more frequent corpus callosum abnormalities than previously reported. Based on a study of institutionalized children, Shimoji et al. [106] theorized that even mild forms of metopic ridging may be associated with significant developmental delay, language problems, and hyperactivity. We can speculate that the abnormally low frontal lobe volume associated with frontal stenosis and/or corpus callosum abnormalities would elevate risk for language delays, ADHD, or lower general intelligence among children with metopic synostosis.
3. Unilateral coronal synostosis: To our knowledge there are no studies of children with unilateral coronal synostosis using comprehensive neuropsychological testing batteries. In an older study of children with unilateral coronal synostosis looking only at global intelligence, Hunter and Rudd [57] found that 10% were mentally retarded and 11% were of borderline intelligence, proportions higher than expected in the population. These authors did not report the side of synostosis, nor did they assess for specific learning disorders. In the retrospective study reviewed earlier, Becker et al. [14] reported that 52% of children with left unilateral coronal and 61% of children with right unilateral coronal synostosis demonstrated a developmental problem related to intelligence, speech, learning, or behavior. Regardless of side, unilateral coronal synostosis may affect neurodevelopment of visual–perceptual skills due to changes in vision. Furthermore, the constriction on brain growth associated with left unilateral coronal synostosis may result in more language-based learning disorders including developmental reading disorder. Right-sided unilateral coronal synostosis, on the other hand, may increase risk for nonverbal learning disorders including problems with social perception and functioning.
4. Lambdoid synostosis: To our knowledge there are no studies that focus exclusively on neurodevelopment of children with unilateral lambdoid synostosis. This is a rare condition; consequently, it is difficult to obtain samples of sufficient size for research purposes.

Conclusions

There is growing evidence that SSC is associated with mild to moderate neurobehavioral impairment in a significant number of children, particularly as they approach school age. These impairments occur in the presence of normal intelligence and may be most evident during tasks that are more challenging. As previously noted, Dennis [37] suggests that failure to maintain skill competence under increasingly challenging cognitive conditions (e.g., increased speed of performance, multi-tasking, or distraction) is a sensitive sign of neurocognitive disability and provides a truer measure of the impact of a medical condition on the central nervous system.

The research identifying changes in brain morphology provides some clues as to the possible etiology of these impairments. There is a continued need for suture-specific research investigating the broad spectrum of neuropsychological functioning in a larger number of children. Our understanding of the relationship between changes in brain morphology and neurobehavioral functioning will be enhanced by the use of imaging studies that investigate correlations between neurocognitive skills thought to be affected in SSC, such as focused attention, visual spatial planning, or other aspects of executive functioning, and brain structure and function.

Clinically, a greater understanding of the neural functional implications of SSC is critical in the clinician's discussion with parents who must make the difficult decision of whether to surgically intervene for their child beyond morphologic reasons alone.

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References

1. American Academy of Pediatrics Task Force on Infant Positioning and SIDS (1992) Positioning and SIDS. Pediatrics 89:1120–1126
2. Agrawal D, Steinbok P, Cochrane DD (2006) Diagnosis of isolated sagittal synostosis: are radiographic studies necessary? Child's Nerv Syst 22:375–378
3. Alderman BW, Lammer EJ, Joshua SC, Cordero JF, Ouimette DR, Wilson MJ, Ferguson SW (1988) An epidemiologic study of craniosynostosis: risk indicators for the occurrence of craniosynostosis in Colorado. Am J Epidemiol 128:431–438
4. Alderman BW, Bradley CM, Greene C, Fernbach SK, Baron AE (1994) Increased risk of craniosynostosis with maternal cigarette smoking during pregnancy. Teratology 50:13–18
5. Aldridge K, Marsh JL, Govier D, Richtsmeier JT (2002) Central nervous system phenotypes in craniosynostosis. J Anat 201:31–39
6. Aldridge K, Kane AA, Marsh JL, Panchal J, Boyadjiev SA, Yan P, Govier D, Ahmad W, Richtsmeier JT (2005) Brain morphology in nonsyndromic unicoronal craniosynostosis. Anat Rec A Discov Mol Cell Evol Biol 285:690–698
7. Aldridge K, Kane AA, Marsh JL, Yan P, Govier D, Richtsmeier JT (2005) Relationship of brain and skull in pre- and postoperative sagittal synostosis. J Anat 206:373–385
8. Anderson FM, Geiger L (1965) Craniosynostosis: a survey of 204 cases. J Neurosurg 22:229–240
9. Arnaud E, Renier D, Marchac D (1995) Prognosis for mental function in scaphocephaly. J Neurosurg 83:476–479
10. Aylward GP, Verhulst SJ, Bell S, Gyurke JS (1995) Cognitive and motor score differences in biologically at-risk infants. Infant Behav Dev 18:43–52
11. Barritt J, Brooksbank M, Simpson D (1981) Scaphocephaly: aesthetic and psychosocial considerations. Dev Med Child Neurol 23:183–191
12. Bayley N (1969) Manual for the Bayley scales of infant development. The Psychological Corporation, Berkeley
13. Bayley N (1993) Manual for the Bayley scales of infant development. The Psychological Corporation, San Antonio
14. Becker DB, Petersen JD, Kane AA, Cradock MM, Pilgram TK, Marsh JL (2005) Speech, cognitive, and behavioral outcomes in nonsyndromic craniosynostosis. Plast Reconstr Surg 116:400–407
15. Bellew M, Chumas PD, Mueller R, Liddington M, Russell J (2005) Pre- and postoperative developmental attainment in sagittal synostosis. Arch Dis Child 90:346–350
16. Bertelsen TI (1958) The premature synostosis of the cranial sutures. Acta Ophthalmol 51(Suppl):87–117
17. Boltshauser E, Ludwig S, Dietrich F, Landolt MA (2003) Sagittal craniosynostosis: cognitive, development, behavior, and quality of life in unoperated children. Neuropediatrics 34:293–300
18. Bottero L, Lajeunie E, Arnaud E, Marchac D, Renier D (1998) Functional outcome after surgery for trigonocephaly. Plast Reconstr Surg 102:952–958
19. Bristol RE, Lekovic GP, Rekate HL (2004) The effects of craniosynostosis on the brain with respect to intracranial pressure. Semin Pediatr Neurol 11:262–267
20. Camfield PR, Camfield CS Jr, CMM (2000) Neurologic aspects of craniosynostosis. In: Cohen MM Jr, MacLean RE (eds) Craniosynostosis: diagnosis, evaluation, and management. Oxford Press, New York, pp 177–183
21. Castellanos FX, Giedd JN, Marsh WL, Hamburger JD, Vaituzis AC, Dickstein DP (1996) Quantitative brain magnetic resonance imaging in attention deficit hyperactivity disorder. Arch Gen Psychiatry 53:607–616
22. Castellanos FX, Giedd JN, Berquin PC, Walter JM, Sharp W, Tran T (2001) Quantitative brain magnetic resonance imaging in girls with attention-deficit hyperactivity disorder. Arch Gen Psychiatry 58:289–295
23. Castellanos FX, Lee PP, Sharp W, Jeffries NO, Greenstein DK, Clasen LS (2002) Developmental trajectories of brain volume abnormalities in children and adolescents with attention-deficit/hyperactivity disorder. JAMA 288:1740–1748
24. Cerovac S, Neil-Dwyer JG, Rich P, Jones BM, Hayward RD (2002) Are routine preoperative CT scans necessary in the management of single suture craniosynostosis? Br J Plast Surg 16:348–354
25. Chadduck WM, Chadduck JB, Frederick A (1992) The subarachnoid spaces in craniosynostosis. Neurosurgery 30:867–871
26. Chemerinski E, Nopoulos P, Crespo-Facorro B, Andreasen NC, Magnotta V (2002) Morphology of the ventral frontal cortex in schizophrenia: relationship with social dysfunction. Biol Psychiatry 52:1–8
27. Churchill JD, Grossman AW, Irwin SA, Galvez R, Klintsova AY, Weiler IJ, Geenough WT (2002) A converging-methods approach to fragile X syndrome. Dev Psychobiol 40:323–338
28. Cinalli G, Spennato P, Sainte-Rose C, Arnaud E, Aliberti F, Brunelle F, Cianciulli E, Renier D (2005) Chiari malformation in craniosynostosis. Child's Nerv Syst 21:889–901
29. Cohen MM Jr (2000) Epidemiology of craniosynostosis. In: Cohen MM Jr, MacLean RE (eds) Craniosynostosis: diagnosis, evaluation, and management. Oxford Press, New York, pp 112–118
30. Cohen MM Jr, MacLean RE (2000) Anatomic, genetic, nosologic, diagnostic, and psychosocial considerations. In: Cohen MM Jr, MacLean RE (eds) Craniosynostosis: diagnosis, evaluation and management. Oxford, New York, pp 119–143
31. Cohen SR, Cho DC, Nichols SL, Simms C, Cross KP, Burstein FD (2004) American Society of Maxillofacial Surgeons Outcome Study: preoperative and postoperative neurodevelopmental findings in single-suture craniosynostosis. Plast Reconstr Surg 114:841–847
32. Courchesne E, Pierce K (2005) Why the frontal cortex in autism might be only talking to itself: local over-connectivity but long distance disconnection. Curr Opin Neurobiol 15:225–230

33. Da Costa AC (2004) Neuropsychological profiles of children and adolescents with craniosynostosis. Dissertation, Victoria University, School of Psychology, Melbourne, Victoria
34. Da Costa AC, Walters I, Savarirayan R, Anderson VA, Wrennall J, Meara JG (2006) Intellectual outcomes in children and adolescents with syndromic and nonsyndraomic craniosynostosis. Plast Reconstr Surg 118(1):175–181
35. Davis BE, Moon RY, Sachs HC, Ottolini MC (1998) Effects of sleep position on infant motor development. Pediatrics 102:1135–1140
36. DeLeon MR, Speltz ML, Cunningham ML (2000) Does sagittal synostosis adversely affect early psychological development? In: Annual meeting of the UW Star-Bridges Program. Seattle, WA
37. Dennis M (2000) Childhood medical disorders and cognitive impairment: Biological risk, time, development, and reserve. In: Yeates KO, Ris MD, Taylor HG (eds) Pediatric neuropsychology: research, theory, and practice. Guilford, New York, pp 3–22
38. Deutsch GK, Dougherty RF, Bammer R, Siok WT, Gabrieli JDE, Wandell B (2005) Children's reading performance is correlated with white matter structure measured by diffusion tensor imaging. Cortex 41:354–363
39. Dewey C, Fleming P, Golding J (1998) Does the supine sleeping position have any adverse effects on the child? II. Development in the first 18 months. ALSPAC Study Team. Pediatrics 101:E5
40. Diamond A (2000) Close interrelation of motor development and cognitive development of the cerebellum and prefrontal cortex. Child Dev 71:44–56
41. Durston S, Hulshoff Pol HE, Schnack HG, Buitelaar JK, Steenhus MP, Minderaa RB (2004) Magnetic resonancy imaging of boys with attention-deficit/hyperactivity disorder and their unaffected siblings. J Am Acad Child Adolesc Psych 43:332–340
42. Ehret FW, Whelan MF, Ellenbogen RG, Cunningham ML, Gruss JS (2004) Differential diagnosis of the trapezoid-shaped head. Cleft Palate Craniofac J 41:13–19
43. Fellows-Mayle WK, Mitchell R, Losken HW, Bradley J, Siegel MI, Mooney MP (2004) Intracranial pressure changes in craniosynostosis rabbits. Plast Reconstr Surg 113:557–565
44. Fernbach SK, Feinstein KA (1991) Radiologic evaluation of children with craniosynostosis. Neurosurg Clin N Am 2:569–586
45. Filipek PA, Semrud-Clikeman M, Steingard RJ, Renshaw PF, Kennedy DN, Biederman J (1997) Volumetric MRI analysis comparing subjects having attention-deficit hyperactivity disorder with normal controls. Neurology 48:589–601
46. Flynn JR (1999) Searching for justice: the discovery of IQ gains over time. Am Psychol 54:5–20
47. French LR, Jackson IT, Melton LJ (1990) A population-based study of craniosynostosis. J Clin Epidemiol 43:69–73
48. Gardner JS, Guyard-Boileau B, Alderman BW, Fernbach SK, Greene C, Mangione EJ (1998) Maternal exposure to prescription and non-prescription pharmaceuticals or drugs of abuse and risk of craniosynostosis. Int J Epidemiol 27:64–67
49. Gellad FE, Haney PJ, Sun JC (1985) Imaging modalities of craniosynostosis with surgical and pathological correlation. Pediatr Radiol 15:285–290
50. Gewalli F, Guimaraes-Ferreia JP, Sahlin P, Emanuelsson I, Horneman G, Stephensen H (2001) Mental development after modified pi procedure: dynamic cranioplasty for sagittal synostosis. Annals Plast Surg 46:415–420
51. Graham J, DeSaxe M, Smith D (1979) Sagittal craniostenosis: fetal head constraint as one possible cause. J Pediatr 95:747–750
52. Graham JJ, Badura R, Smith D (1980) Coronal craniostenosis: fetal head constraint as one possible cause. Pediatrics 65:995–999
53. Happaney K, Zelazo PD, Stuss DT (2004) Development of orbitofrontal function: current themes and future directions. Brain Cogn 55:1–10
54. Higginbottom M, Jones K, James H (1980) Intrauterine constraint and craniosynostosis. Neurosurgery 6:39–44
55. Hill DE, Yeo RA, Campbell RA, Hart B, Vigil J, Brooks W (2003) Magnetic resonancy imaging correlates of attention-deficit/hyperactivity disorder in children. Neuropsychology 17
56. Honein MA, Rasmussen SA (2000) Further evidence for an association between maternal smoking and craniosynostosis. Teratology 62:145–146
57. Hunter AG, Rudd NL (1977) Coronal synostosis: its familial characteristics and associated clinical findings in 109 patients lacking bilateral polysyndactyly or syndactyly. Teratology 15:301–310
58. Hynd GW, Semrud-Clikeman M, Lorys AR, Novey ES, Eliopulos D (1990) Brain morphology in developmental dyslexia and attention-deficit hyperactivity. Arch Neurol 47:919–926
59. Hynd GW, Semrud-Clikeman M, Lorys AR, Novey ES, Eliopulos D, Lytinen H (1991) Corpus callosum morphology in attention-deficit hyperactivity disorder: morphometric analysis of MRI. J Learn Disabil 24:141–146
60. Hynd GW, Hall J, Novey ES, Eliopulos D, Black K, Gonzalez JJ, Edmonds JE, Riccio C, Cohen M (1995) Dyslexia and corpus callosum morphology. Arch Neurol 52:32–38
61. Jane JA, Persing JA (2000) Neurosurgical treatment of craniosynostosis. In: Cohen MM Jr, MacLean RE (eds) Craniosynostosis: diagnosis, evaluation, and management. Oxford Press, New York, pp 209–227
62. Jantz JW, Blosser CD, Fruecting LA (1997) A motor milestone change noted with a change in sleep position. Arch Pediatr Adolesc Med 151:565–568
63. Johnson MH, Halit H, Grice SJ, Karmiloff-Smith A (2002) Neuroimaging of typical and atypical development: a perspective from multiple levels of analysis. Dev Psychopathol 14: 521–536
64. Kallen K (1999) Maternal smoking and craniosynostosis. Teratology 60:146–150
65. Kapp-Simon KA (1994) Mental development in infants with nonsyndromic craniosynostosis with and without cranial release and reconstruction. Plast Reconstr Surg 94:408–410
66. Kapp-Simon KA (1998) Mental development and learning disorders in children with single suture craniosynostosis. Cleft Palate Craniofac J 35:197–203
67. Kapp-Simon KA, Leroux B, Cunningham ML, Speltz ML (2005) Multi-site study of infants with single-suture craniosynostosis: preliminary report of pre-surgery development. Cleft Palate Craniofac J 42:377–384
68. Kates WR, Frederikse M, Mostofsky SH, Folley BS, Cooper K, Mazur-Hopkins P (2002) MRI parcellation of the frontal lobe in boys with attention deficit hyperactivity disorder or Tourette syndrome. Psychiatry Res 116:63–81
69. Kjaer I (1995) Human prenatal craniofacial development related to brain development under normal and pathologic conditions. Acta Odontol Scan 53:135–143
70. Kreiborg S (2000) Postnatal growth and development of the craniofacial complex in premature craniosynostosis. In: Cohen MMJ, MacLean RE (eds) Craniosynostosis: diagnosis, evaluation, and management. University Press, New York
71. Kress W, Petersen B, Collmann H, Grimm T (2000) An unusual FGFR1 mutation (fibroblast growth factor receptor 1 mutation) in a girl with non-syndromic trigonocephaly. Cytogenet Cell Genet 91:138–140
72. Lajeunie E, LeMerrer M, Bonaiti-Pellie C, Marchac D, Renier D (1996) Genetic study of scaphocephaly. Am J Med Genet 62:282–285
73. Lajeunie E, Le Merrer M, Marchac D, Renier D (1998) Syndromal and nonsyndromal primary trigonocephaly: analysis of a series of 237 patients. Am J Med Genet 75

74. Leonard CM, Eckert MA, Lombardino LJ, Oakland T, Kranzler J, Mohr CM, King WM, Freeman A (2001) Anatomical risk factors for phonological dyslexia. Cereb Cortex 11:148–157
75. Leonard CM, Lombardino LJ, Walsh K, Eckert MA, Mockler JL, Rowe LA, Williams S, DeBose CB (2002) Anatomical risk factors that distinguish dyslexia from SLI predict reading skill in normal children. J Commun Disord 35:501–531
76. Magge SN, Westerveld M, Pruzinsky T, Persing JA (2002) Long-term neuropsychological effects of sagittal craniosynostosis on child development. J Craniofac Surg 13:99–104
77. Marsh JL, Jenny A, Galic M, Picker S, Vannier MW (1991) Surgical management of sagittal synostosis. A quantitative evaluation of two techniques. Neurosurg Clin N Am 2:629–640
78. Marsh JL (2000) Surgical research on Craniosynostosis in. In: Cohen MM, Jr, MacLean RE (eds) Craniosynostosis: diagnosis, evaluation, and management, pp 292–306
79. McPartland J, Dawson G, Webb SJ, Panagiotides H, Carver LJ (2004) Event-related brain potentials reveal anomalies in temporal processing of faces in autism spectrum disorder. J Child Psychol Psychiatry 45:1235–1245
80. Morton JB, Munakata Y (2005) What's the difference? Contrasting modular and neural network approaches to understanding developmental variability. J Dev Behav Pediatr 26:128–139
81. Mostofsky SH, Cooper K, Kates WR, Denckla MB, Kaufmann W (2002) Smaller prefrontal and premotor volumes in boys with attention-deficit/hyperactivity disorder. Biol Psychiatry 52:785–794
82. Mueller R-A, Cauich CC, Rubio MA, Mizuno A, Courchesne E (2004) Abnormal activity patterns in premotor cortex during sequence learning in autistic patients. Biol Psychiatry 56:323–332
83. Mulliken JB, Gripp KW, Stolle CA, Steinberger D, Muller U (2004) Molecular analysis of patients with synostotic frontal plagiocephaly (unilateral coronal synostosis). Plast Reconstr Surg 113:1899–1909
84. Munakata Y, Casey BJ, Diamond A (2004) Developmental cognitive neuroscience: progress and potential. Trends Cogn Sci 8:122–128
85. Nopoulos P, Choe I, Berg S, Van Demark D, Canady J, Richman LC (2005) Ventral frontal cortex morphology in adult males with isolated orofacial clefts: relationship to abnormalities in social function. Cleft Palate Craniofac J 42:138–140
86. Olshan AF, Faustman EM (1989) Nitrosatable drug exposure during pregnancy and adverse pregnancy outcome. Int J Epidemiol 18:891–899
87. Panchal J, Marsh J, Kaufman B, Pilgram TK, Huang SH (1999) Sagittal craniosynostosis outcomes assessment for two methods and timings of intervention. Plast Reconstr Surg 103:1574–1584
88. Panchal J, Amirsheybani H, Gurwitch R, Cook V, Francel P, Neas B, Levine N (2001) Neurodevelopment in children with single-suture craniosynostosis and plagiocephaly without synostosis. Plast Reconstr Surg 108:1492–1498, discussion 1499–1500
89. Pennington BF (1991) Diagnosing learning disorders: a neuropsychological framework. Guilford, New York
90. Pennington BF (2002) The development of psychopathology. Guilford, New York, pp 32–63
91. Pierce K, Haist F, Sedaghat F, Courchesne E (2004) The brain response to personally familiar faces in autism: findings of fusiform activity and beyond. Brain 127:2703–2716
92. Polley JW, Charbel GT, Kim D, MaFee MF (1998) Nonsyndromal craniosynostosis: longitudinal outcomes following cranio-orbital reconstruction in infancy. Plast Reconstr Surg 102:619
93. Posnick JC, Armstrong D, Bite U (1995) Metopic and sagittal synostosis: intracranial volume measurements prior to and after cranio-orbital reshaping in childhood. Plast Reconstr Surg 96:299–309
94. Renier D, Sainte-Rose C, Marchac D, Hirsch JF (1982) Intracranial pressure in craniostenosis. J Neurosurg 57:370–377
95. Renier D, Brunet L, Marchac D (1987) IQ and craniosynostosis: Evolution in treated and untreated cases. In: Marchac D (ed) Craniofacial surgery. Springer, Berlin Heidelberg New York, pp 114–117
96. Renier D, Lajeunie E, Arnaud E, Marchac D (2000) Management of craniosynostosis. Child's Nerv Syst 16:645–658
97. Richtsmeier JT, Aldridge K, Deleon VB, Panchal J, Kane AA, Marsh JL, Yan P, Cole TM 3rd (2006) Phenotypic integration of neurocranium and brain. J Exp Zoolog B Mol Dev Evol 306 (4):360–378
98. Romine CB, Reynolds CR (2004) Sequential memory: a developmental perspective on its relation to frontal lobe functioning. Neuropsychol Rev 14:43–64
99. Rourke BP (1987) Syndrome of nonverbal learning disabilities: the final common pathway of white-matter disease/dysfunction? Clin Neuropsychol 1:209–234
100. Scerif G, Karmiloff-Smith A (2005) The dawn of cognitive genetics? Crucial developmental caveats. Trends Cogn Sci 9:126–135
101. Seidman LJ, Valera EM, Makris N (2005) Structural brain imaging of attention-deficit/hyperactivity disorder. Biol Psychiatry 57:1263–1272
102. Semrud-Clikeman M, Filipek PA, Biederman J, Steingard R, Kennedy DN, Renshaw P, Bekken K (1994) Attention-deficit hyperactivity disorder: Magnetic resonance imaging morphometric analysis of the corpus callosum. J Am Acad Child Adolesc Psych 33:875–881
103. Semrud-Clikeman M, Steingard R, Flipek P, Biederman J, Bekken K, Renshaw P (2000) Using MRI to examine brain-behavior relationships in males with attention deficit disorder with hyperactivity. J Am Acad Child Adolesc Psych 39:477–484
104. Seto ML, Hing AV, Chang J, Hu M, Kapp-Simon KA, Patel PK, Burton BK, Kane A, Smyth MD, Hopper R, Ellenbogen RG, Stevenson K, Speltz ML, Cunningham ML (2006) Isolated sagittal and coronal craniosynostosis associated with TWIST Box mutations. Am J Med Genet (in press)
105. Shaywitz BA, Shaywitz SE, Pugh KR, Mencl WE, Fullbright RK, Skudlarski P, Constable RT, Marchione KE, Fletcher JM, Lyon GR, Gore JC (2002) Disruption of the posterior brain systems for reading in children with developmental dyslexia. Biol Psychiatry 52:101–110
106. Shimoji T, Shimabukuro S, Sugama S, Ochiai Y (2002) Mild trigonocephaly with clinical symptoms: analysis of surgical results in 65 patients. Child's Nerv Syst 18:215–224
107. Shipster C, Hearst D, Somerville A, Stackhouse J, Hayward R, Wade A (2003) Speech, language, and cognitive development in children with isolated sagittal synostosis. Dev Med Child Neurol 45:34–43
108. Shuper A, Merlob P, Grunebaum M, Reisner SH (1985) The incidence of isolated craniosynostosis in the newborn infant. Am J Dis Child 139:85–86
109. Sidoti EJ Jr, Marsh J, Marty-Grames L, Noetzel MJ (1996) Long-term studies of metopic synostosis: frequency of cognitive impairment and behavioral disturbances. Plast Reconstr Surg 97:276–281
110. Simos PG, Breier JI, Fletcher JM, Bergman E, Papanicolaou AC (2000) Cerebral mechanisms involved in word reading in dyslexic children: a magnetic source imaging approach. Cereb Cortex 10:809–816
111. Simos PG, Breier JI, Fletcher JM, Foorman BR, Bergman E, Fishbeck K, Papanicolaou AC (2000) Brain activation profiles in dyslexic children during non-word reading: a magnetic source imaging study. Neurosci Lett 290:61–65

112. Singer S, Bower C, Southall P, Goldblatt J (1999) Craniosynostosis in Western Australia, 1980–1994: a population-based study. Am J Med Genet 83:382–387
113. Sowell ER, Thompson PM, Welcome SE, Henkenius AL, Toga AW, Peterson BS (2003) Cortical abnormalities in children and adolescents with attention-deficit hyperactivity disorder. Lancet 362:1699–1707
114. Speltz ML, Kapp-Simon KA, Cunningham M, Marsh J, Dawson G (2004) Single-suture craniosynostosis: a review of neurobehavioral research and theory. J Pediatr Psychol 29:651–668
115. Speltz ML, Kapp-Simon KA, Collett B, Keich Y, Gaither R, Cradock MM, Buono L, Cunningham M (2006) Neurodevelopment of infants with single-suture craniosynostosis: pre-surgery comparisons with case-matched controls. Plast Reconstr Surg (in press)
116. Spreen O (1989) The relationship between learning disabilities, emotional disorders, and neuropsychology; some results and observations. J Clin Exp Neuropsychol 11:117–140
117. Stuss DT, Levine B (2002) Adult clinical neuropsychology: lessons from the frontal lobes. Annu Rev Psychol 53:401–433
118. Sze RW, Hopper RA, Ghouzzi VE, Gruss JS, Ellenbogen RG, King D, Hing AV, Cunningham ML (2005) MDCT Diagnosis of the child with posterior plagiocephaly. Am J Roentgenol 185:11342–11346
119. Tamburrini G, Caldarelli M, Massimi L, Santini P, Di Rocco C (2005) Intracranial pressure monitoring in children with single suture and complex craniosynostosis: a review. Child's Nerv Syst 21:913–921
120. Temple E, Poldrack RA, Salidis J, Deutch GK, Tallal P, Merzenich MM (2001) Disrupted neural responses to phonological and orthographic processing in dyslexic children: An fMRI study. Neuroreport 12:299–307
121. Thomas GPL, Wilkie AOM, Richards PG, Wall SA (2005) FGFR3 P250R Mutations increases the risk of reoperations in apparent 'nonsyndromic' coronal craniosynostosis. J Craniofac Surg 16:347–352
122. Tubbs RS, Elton S, Blount JP, Oakes WJ (2001) Preliminary observations on the association between simple metopic ridging in children without trigonocephaly and the Chiari I malformation. Pediatr Neurosurg 35:136–139
123. Vannier MW, Hildebolt CF, Marsh JL, Pilgram TK, McAlister WH, Shackelford GD, Offutt CJ, Knapp RH (1989) Craniosynostosis: diagnostic value of three-dimensional CT reconstruction. Radiology 173:669–673
124. Vannier MW, Pilgram TK, Marsh JL, Kraemer BB, Rayne SC, Gado MH, Moran CJ, McAlister WH, Shackelford GD, Hardesty RA (1994) Craniosynostosis: diagnostic imaging with three-dimensional CT presentation. Am J Neuroradiol 15:1861–1869
125. Warschausky S, Angobaldo J, Kewman D, Buchman S, Muraszko KM, Azengart A (2005) Early development of infants with untreated metopic craniosynostosis. Plast Reconstr Surg 115:1518–1523
126. Woods SP, Weinborn M, Ball JD, Tiller-Nevin S, Pickett TC (2000) Periventricular leukomalacia (PVL): an identical twin case study illustration of white matter dysfunction and nonverbal learning disability (NLD). Child Neuropsychol 6:274–285