Single-Suture Craniosynostosis: A Review of Neurobehavioral Research and Theory

Matthew L. Speltz, Kathleen A. Kapp-Simon, Michael Cunningham, Jeffrey Marsh, and Geraldine Dawson

Objective To review research and theory regarding the neurobehavioral correlates and outcomes of single-suture, or isolated, craniosynostosis in children. Methods A critical review of 17 studies of the hypothesized association between isolated craniosynostosis and neurodevelopment. Results Isolated craniosynostosis is associated with a three- to fivefold increase in risk for cognitive deficits or learning/language disabilities. The causal basis for this association is unclear. No particular calvarial suture (sagittal, metopic, left or right unilateral coronal) has been associated with higher risk of problems. There is little evidence from quasi-experimental studies that cranioplastic surgery prevents or reduces risk of neurobehavioral impairment. Conclusions Future studies would benefit from larger samples and larger control groups; measures of specific neuropsychological functions (in addition to global cognition); analyses of neuropsychological status in relation to the severity and cortical impact of synostosis; and an examination of interactions between synostosis and social/family risk factors on neurodevelopment. Routine neurodevelopmental screening of young children with isolated craniosynostosis is recommended.

Key words craniosynostosis; neuropsychology; cranioplasty.

Craniosynostosis refers to the premature fusion of one or more of the fibrous joints (sutures) that normally separate the bony plates of the infant’s skull. In typically developing infants, open sutures allow the skull to expand as the brain grows, producing relatively normal head shape. If one or more sutures are prematurely fused, there is restricted growth perpendicular to the fused suture(s) and compensatory growth in the skull’s unfused bony plates, producing abnormal head shape. The etiology and pathogenesis of craniosynostosis are unclear. Multiple factors have been implicated, including genetic processes (monogenic disorders and chromosomal aberrations), teratogens (e.g., nicotine and nitrosatable medications), fetal head constraint, and metabolic and hematologic disorders (Cohen, 1991). Multiple-suture fusions are associated with several well-described genetic syndromes—including Apert, Crouzon, Pfeiffer, Saethre Chotzen, and Carpenter syndromes—which have been associated with elevated rates of mental retardation and learning disabilities (Cohen, 1991).

Single-suture synostosis includes isolated fusions of the sagittal, metopic, and left or right coronal or lambdoid sutures. In Figure 1 (Panel A) these sutures are shown on a three-dimensional CT (computerized tomography) scan of a normal skull. Metopic synostosis (Figure 1, Panel B) produces a triangular head shape (trigonocephaly) that features a forehead midline ridge, frontotemporal narrowing on both sides of the head, and a broad
Speltz, Kapp-Simon, Cunningham, Marsh, and Dawson

Parietal-occipital. Unilateral coronal synostosis (Figure 1, Panel C) is characterized by an asymmetrically skewed head (plagiocephaly) with retrusion of the forehead and brow on the same side as the fused suture and with compensatory “bossing” (bulging) of the forehead on the side opposite of the fused suture. Plagiocephalic head shape is also found in cases of unilateral lambdoid synostosis, characterized by occipital retrusion on the fused side and by bossing in the occipital and frontal areas on the opposite side. Plagiocephaly associated with unilateral coronal or lambdoid synostosis can be distinguished clinically from the relatively common “positional” or “deformational” plagiocephaly, which is believed to result from external forces shaping the infant’s malleable skull (e.g., invariant sleeping position; see Mulliken, Van Der Woude, Hansen, LaBrie, & Scott, 1999). Sagittal synostosis (Figure 1, Panel D) is manifest at birth as a long, narrow head shape (scaphocephaly) with bifrontal and occipital bossing.

The incidence of an isolated suture fusion is about 1 in 2,000 live births (Shuper, Merlob, Grunebaum, &
Moreover, congenital defects involving an infant’s face and skull seem to evoke particularly strong emotional and behavioral difficulties and preventative interventions. Responses from parents, who must contend with a host of pediatric care for early detection of neurodevelopmental problems. This creates opportunities for future studies of isolated synostoses. In recognition of the many psychosocial factors affecting the physical and psychological development of infants and children with craniosynostosis and other craniofacial conditions, the practice parameters of the American Cleft Palate-Craniofacial Association require the provision of psychological assessment and intervention services by hospital-based craniofacial teams (American Cleft Palate-Craniofacial Association, 1993, 1996).

Interrelated Growth of Brain and Cranium

Until recently there has been little study or theoretical discussion of the interrelations between the developing brain and cranium (Kjaer, 1995). Clinical formulations of the relation between calvarial suture fusion and neurodevelopment (e.g., Cohen, 1986) have typically assumed a linear causal pathway in which suture fusion adversely affects brain development. Two specific pathways, operating alone or in combination, have been proposed in this regard: elevated intracranial pressure with hypovascularity (e.g., Renier, Sainte-Rose, Marchac, & Hirsch, 1982) and secondary cerebral deformation resulting from brain growth in an abnormally shaped skull (Fernbach & Feinstein, 1991). Another causal pathway is also possible in which primary brain malformation could lead to both synostosis and neurodevelopmental
difficulties. We next discuss the details of, and empirical support for, each of these possibilities.

**Intracranial Pressure (ICP)**

Elevated ICP is the most frequently cited mediator of the presumed negative effect of suture fusions on brain development (Cohen & Persing, 1998). Elevated ICP is believed to promote hypovascularity in the approximate region of the fused suture, leading to hypoplasia of underlying brain tissue. Clinical formulations often refer to the reduction or prevention of elevated ICP as one of the primary reasons why cranioplasty may reduce the probability of neurodevelopmental delay or deficits in infants with craniosynostosis (e.g., Renier & Marchac, 1988). This hypothesis has been widely communicated to parents, mostly via websites that suggest a causal relation between ICP and subsequent neurobehavioral problems and that surgery may relieve ICP and therefore prevent or lower the risk for “brain damage” and associated neurobehavioral deficits. What is the empirical evidence for such claims, particularly for children having single-suture synostosis?

Thompson et al. (1995) monitored the subdural ICP of 74 children with sagittal, metopic, or unilateral coronal synostosis while they slept. Using a standard criterion for “elevated” ICP (readings above 15 mmHg), they found that nearly half of their sample had normal ICP, over a third had “borderline” readings, and less than 20% had clearly elevated ICP. Among the different types of synostosis, the metopic and sagittal groups had the highest proportions of elevated cases (38% and 24%, respectively). Renier et al. (1982) reported similar findings in their sample of children with single-suture synostosis, using the same criterion for elevation. Few studies have examined associations between ICP and neurobehavioral status. Renier and Marchac (1988) compared the ICP values of children with developmental quotients above and below 90 on standardized cognitive measures. Among the single-suture anomalies included in these analyses (sagittal and unilateral coronal), only those with unilateral coronal synostosis showed the hypothesized inverse relation between cognitive status and ICP; however, it is unclear whether this association was statistically significant (no details of these analyses were reported). Neither Arnaud, Renier, and Marchac (1995) nor Gewalli et al. (2001) found significant associations between ICP and developmental test scores in independent samples of infants with sagittal synostosis.

Cohen and Persing (1998) have discussed the many problems in interpreting ICP data, including the use of differing measurement techniques and patient selection criteria among investigators; and the complete lack of normative data, which are unlikely to become available until there are reliable methods of noninvasive measurement (Mouradian, 1998). In the absence of normative data, the precise threshold for “abnormal” readings is unclear. ICP is also difficult to quantify, as it is a changing value that covaries with an individual’s activities (e.g., coughing or sneezing can produce rapid increases up to 50 or 60 mmHg). ICP therefore needs to be measured over an extended period to obtain a stable representation. The metric most reflective of clinically meaningful intracranial hypertension is still a matter of debate (e.g., mean values or number of elevations above threshold; see Eide, Helseth, Due-Tønnessen, & Lundar, 2002). Cohen and Persing noted the relative infrequency of clinical indicators of increased ICP in cases of single-suture synostosis (e.g., irritability, head banging, retinal changes), even among those with elevated readings. The consequences of elevated ICP in the absence of clinical symptoms are unclear.

Overall, it would appear that the elevated ICP hypothesis is at best modestly supported by available data, with uncertain implications for the causal relation between synostosis and brain growth.

**Secondary Cerebral Deformation**

Radiographic studies of craniosynostosis have revealed abnormalities in the subarachnoid space beneath the region of suture fusion (i.e., a scalloped, or “hammered silver,” appearance apparent on CT scans) and compression of the neighboring ventricular system (e.g., Carmel, Luken, & Aschere, 1981). These observations suggest that cortical or even subcortical brain tissue is compressed or “redirected” in the process of growing within a skull that has limited capacity to accommodate such growth. For example, metopic and sagittal synostoses impose midline restrictions that potentially affect frontal lobe development. In metopic synostosis, the ventral development of the brain may be limited by severely restricted ventral expansion of the anterior cranial fossa and frontal bones. In sagittal synostosis, there are frontal prominences that seem to result from excessive pressure of the growing frontal lobes, presumably due to the inability of the skull to expand sufficiently bi-temporally; in other words, there may be redirection of brain growth toward the frontal lobes because lateral growth is restricted. In unilateral coronal synostosis, the frontal bone ipsilateral to the synostosis is retruded, and the underlying frontal lobe could therefore be compressed and/or hypoplastic.
Evidence for these hypothesized secondary deformations is just beginning to emerge. In a recent study using three-dimensional MRI (magnetic resonance imaging), Marsh and colleagues (Aldridge, Marsh, Govier, & Richtsmeier, 2002) examined preoperative infants with isolated sagittal, metopic, and unilateral coronal or lambdoid synostosis and compared them with unaffected infants. Significant differences in subcortical morphology were found. Sagittal patients displayed anteriorly displaced lateral ventricles (LV) and rostrum of the corpus callosum relative to the unaffected group. In unilateral coronal patients, the anterior LV on the affected side was displaced toward the midline, and the anterior corpus callosum was compressed. In metopic patients, the posterior LV were truncated, and there was midline constriction in the area between the left and right caudate nuclei.

The effects of these observed secondary cerebral deformations on children’s measurable functional abilities are unclear. One complication is the lack of one-to-one correspondence between particular sutures and subcortical brain structures. For example, the sagittal, metopic, and unilateral coronal sutures may all potentially affect frontal lobe growth to some degree. Nevertheless, tentative functional hypotheses can be tendered. If metopic, sagittal, or coronal synostoses have detrimental effects on frontal lobe development, executive functions (e.g., attention, inhibition, working memory, and flexibility) could be more problematic for these children than other neuropsychological functions, as has been hypothesized by Persing, Magge, Westerveld, and Pruizinsky (1999). Similarly, children with unilateral coronal synostosis might experience problems in interhemispheric functions, due to the compression of the corpus callosum, observed by Marsh and colleagues. However, it is important to also consider that 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. All of these factors are likely to moderate the effects of compression or hypoplasia on brain structures occurring in the early months or years of life (Johnson, Halit, Grice, & Karmiloff-Smith, 2002; Spreen, 1989).

**Primary Malformation**

Assumed deformations of the brain (secondary to synostosis) might actually reflect a primary malformation of the central nervous system, which also leads to synostosis. In other words, synostosis and the types of subcortical anomalies observed by Aldridge et al. (2002) may be causally unrelated, with both attributable to underlying neuropathology, perhaps originating early in the course of embryonic development (Kjaer, 1995). This idea is consistent with emerging evidence that elevated risk of craniosynostosis is associated with genetic defects and in utero exposure to environmental toxins such as nicotine or nitrosatable medications (Honein & Rasmussen, 2000; Johnston & Bronsky, 1995). Mutations in the fibroblast growth factor receptor genes have been implicated in most cases of multiple-suture, syndromic synostosis (Gripp, Zackai, & Stolle, 2000; Kan et al., 2002), and mutations in these genes may account for a significant minority of single-suture cases as well. Current data point to isolated unilateral coronal synostosis as the most likely candidate (e.g., Moloney et al., 1997; Schindler, Friedrich, Wagener, Lorenz, & Preising, 2002). This finding has important implications for the study of neurobehavioral outcomes in children with craniosynostosis, as the fibroblast growth factor receptor genes appear to play a role in the early development of the central nervous system (Belluardo et al., 1997; Oh et al., 2003; Sleptsova-Friedrich et al., 2001, Soo et al., 2002; Wilke, Gubels, Schwartz, & Richman, 1997).

**Summary**

Clinical formulations of the potential linkage between synostosis and neurobehavioral functioning have usually assumed a direct, linear pathway in which suture fusion leads to brain deformation and, consequently, neuropsychological impairment (e.g., Arnaud et al., 1995; Renier & Marchac, 1988). However, there are insufficient data and limited theory with which to hypothesize any particular causal pathway. It is not clear whether synostosis is a cause or correlate of neuropathology. Even if single-suture synostosis were shown to directly and independently affect brain structure adversely, compensatory mechanisms and adaptive processes could significantly alter the form and severity of associated functional characteristics. Nevertheless, a necessary first step in the investigative process is to examine whether a measurable association between synostosis and neurobehavioral status exists, understanding that association does not imply causality.

**Measurement Limitations**

In addition to previously noted problems in measuring ICP, the investigation of associations between synostosis and neuropsychological status is complicated by problems and uncertainties in the measurement of both variables. Although the presence and specific location of suture fusions are easily established by clinical diagnosis
Speltz, Kapp-Simon, Cunningham, Marsh, and Dawson

(physical examination confirmed by CT scan), the severity of synostosis and its impact on brain tissue is not so easily assessed. Several aspects of synostosis are potentially quantifiable, including the extent to which the suture is fused or patent (open) and the degree of compression of extraxial cerebrospinal fluid (CSF) spaces in proximity to the fused suture (effacement). Both can be observed on CT scans, but there are no generally accepted or standardized methods of quantifying these potential indicators of severity.

The measurement of neurobehavioral variables is complicated by the early developmental period in which synostosis is initially diagnosed, surgically treated, and followed (typically the first 2 years of life). As we show in the review of neurobehavioral findings, most studies have assessed infants and toddlers before, and at varying intervals after, surgery in large part because surgery is believed to modulate the presumed negative effects of synostosis on neurodevelopment (e.g., reduction of ICP). There are relatively few standardized and well-researched measures of infancy neurodevelopment. Most instruments for this age group focus on global functioning (e.g., the Mental Development index from the Bayley Scales of Infant Development; Bayley, 1969, 1993), with limited assessment of the more specific neuropsychological functions of relevance to hypothesized suture–brain–behavior relations (e.g., executive function deficits). Given the rapidity of brain growth during infancy (Chugani, 1992; Huttenlocher, 1998), the reliability and predictability of scores from infancy assessments have varied depending on the specific functions measured, age of measurement, and the neurodevelopmental status of the child (Aylward, 1997; Hauser-Cram, Warfield, Shonkoff, & Krauss, 2001; Shonkoff & Meisels, 2000). For infants with craniosynostosis, reliable and valid assessment may be further limited by environmental stress and instability associated with the diagnostic process and subsequent hospitalization for and recovery from a potentially life-threatening surgery (e.g., negative effects on the caregiving environment due to parental anxiety; Endriga & Kapp-Simon, 1999).

Review of Neurobehavioral Findings

Table I summarizes the methods and results of 17 studies examining the neurocognitive and/or behavioral development of children with single-suture craniosynostosis. Collectively, these studies have examined well over 1,000 infants, children, or adolescents with single-suture fusions. Despite this relatively large number, most studies have examined relatively small samples, the exception being two very large studies conducted in France that collected patients over several years (Arnaud et al., 1995; Renier & Marchac, 1988). The ages at which cases have been assessed have ranged from 3 months to 16 years, with most cases having participants 8 years or younger at the time of assessment.

Neurocognitive Findings

The results of studies in Table I can be summarized in relation to how outcomes were assessed: either membership in a specific category of adverse outcome (e.g., learning disability, language impairment, “behavioral or cognitive abnormality,” test scores below a defined threshold) or between-group comparisons of average scores on a test or symptom checklist. Among the former, most studies found some type of adverse neurocognitive outcome in about 35–40% of assessed cases (Bottero, Lajeunie, Arnaud, Marchac, & Renier, 1998; Rozzelle, Marty-Grames, & Marsh, 1995; Shimoji, Shimabukuro, Sugama, & Ochiai, 2002; Shipster et al., 2003; Sidoti, Marsh, Marty-Grames, & Noetzel, 1996), although some reports were as high as 50% (classifications of learning disability by Kapp-Simon, 1998; and Magge et al., 2002). As the prevalence of outcomes such as learning disability and behavior problems in the general population of children and adolescents is roughly 10% (at least in the United States; Nietzel, Speltz, McCauley, & Bernstein, 1998), these findings suggest that the risk of poor neurobehavioral outcome in children with single-suture synostosis may be three-to-five times higher than average. This conclusion is tempered by the fact that some studies used imprecisely defined categorical outcomes and/or did not directly assess children but rather relied on clinicians’ reviews of medical or school records. Exceptions include Magge and colleagues’ study (2002) of children with sagittal synostosis (in which learning disability was defined by directly measured IQ–achievement discrepancy scores) and Shipster et al. (2003), who rigorously defined speech and language impairment in terms of standard scores on expressive and receptive language measures and a discrepancy greater than 20 standard score points between language and nonverbal IQ scores. The Magge et al. analysis (2002) revealed one of the highest reported levels of learning disability among cases with synostosis (50%). These investigators also found that verbal IQ was significantly higher than nonverbal IQ, which could indicate specific problems in learning tasks that require visual–spatial abilities or related nonverbal abilities (e.g., perceptual organization and reasoning, visual attention and memory).
<table>
<thead>
<tr>
<th>Authors</th>
<th>Number of cases by diagnosis</th>
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<th>Control group?</th>
<th>Summary of results</th>
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<tbody>
<tr>
<td>Barritt, Brookshank, &amp; Simpson (1981)</td>
<td>44 sagittal (31 without surgical correction)</td>
<td>1–16 yrs</td>
<td>Unspecified psychological assessment and chart review</td>
<td>No</td>
<td>10% with developmental deficits, 7% with learning disability. High psychological distress related to head shape in no surgery group</td>
</tr>
<tr>
<td>Muke (1972; cited in Camfield &amp; Camfield, 1986)</td>
<td>14 sagittal 1 unilateral coronal</td>
<td>7–12 yrs</td>
<td>Unspecified battery of psychological tests</td>
<td>Yes</td>
<td>Group differences favoring control group on each psychological test: synostosis: mean IQ = 79 control: mean IQ = 104</td>
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<tr>
<td>Hunter &amp; Rudd (1976, 1977)</td>
<td>205 sagittal 49 unilateral coronal 13 metopic 23 bicoronal 16 lambdoid 64 multisuture</td>
<td>Not provided</td>
<td>Unspecified intelligence tests given at unknown ages</td>
<td>No</td>
<td>Only retardation rates reported: sagittal: 8.9% unilateral coronal: 0.96% bicoronal: 26% metopic: not reported multisuture: 26%</td>
</tr>
<tr>
<td>Renier &amp; Marchac (1988)</td>
<td>90 sagittal 18 metopic 59 unilateral coronal 28 bilateral coronal 105 other multisuture synostoses</td>
<td>Not provided</td>
<td>Unspecified developmental/intelligence test given at widely varying ages</td>
<td>No</td>
<td>Inferential statistics not reported. For single-suture diagnoses, normal IQ score distribution.</td>
</tr>
<tr>
<td>Kapp-Simon (1994, 1997, 1998; Kapp-Simon et al. (1993)</td>
<td>30 sagittal 19 metopic 35 unilateral coronal sagittal</td>
<td>Mean age at T1 = 8.1 mo T2 = 18.4 mo T3 = 50.2 mo</td>
<td>BSID or BSID-II at T1 and T2, MCA at T3, LD determined by direct assessment and/or chart review at school age</td>
<td>No</td>
<td>Pre- and postsurgery MDI scores unrelated to surgery age (T1 mean = 100, SD = 13; T2 mean = 95, SD = 15) (N = 53). Mental retardation rate: 6.5%; learning disorders rate: 47% (N = 34).</td>
</tr>
<tr>
<td>Arnaud, Renier, &amp; Marchac (1995)</td>
<td>396 sagittal 100 were tested twice (41 without surgical correction)</td>
<td>Mean age at 1st testing = 1 yr 2nd testing = 6.4 yr</td>
<td>Brunet-Lezine scale for children “and younger” 3. Revised Binet-Simon IQ test for older children</td>
<td>No</td>
<td>No group differences by surgery status: No surgery: T1 DQ mean = 105, SD = 8, range = 80–125; T2 IQ mean = 106, SD = 12, range = 76–136; Surgery T1 DQ mean = 101, SD = 12 37% classified as “impaired” in language, articulation, and/or phonology</td>
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<td>Rozzelle, Marty-Grames, &amp; Marsh (1995)</td>
<td>38 sagittal</td>
<td>Preschool to Grade 12</td>
<td>Retrospective chart review focusing on results of speech and language evaluations</td>
<td>No</td>
<td>37.5% identified as having one or more behavioral or cognitive abnormalities</td>
</tr>
<tr>
<td>Sidoti, Marsh, Marty-Games, &amp; Noetzel (1996)</td>
<td>32 metopic</td>
<td>8 yr 3 mo on average</td>
<td>Combination of parent questionnaire and medical chart review targeting behavior, language, and learning problems</td>
<td>No</td>
<td>No group differences at any age. MDI scores and surgery age inversely correlated (r = –0.30).</td>
</tr>
<tr>
<td>Speltz, Endriga, &amp; Mouradian (1997)</td>
<td>19 sagittal</td>
<td>Presurgery, 12 mo, 24 mo</td>
<td>BSID given longitudinally at 3, 12, and 24 mo</td>
<td>Yes: 19 matched for age, gender, SES</td>
<td>No group differences at any age. MDI scores and surgery age inversely correlated (r = –0.30).</td>
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</table>
Table I. Summary of Studies (Continued)

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<tr>
<td>Bottero, Lajeunie, Arnaud, Marchac, &amp; Renier (1998)</td>
<td>76 metopic</td>
<td>Presurgery (before age 3 yr) and “most recent assessment” (mean age 6.5 yr)</td>
<td>Testing same as Arnaud et al., 1995, plus reports from parents, teachers, and clinic team to determine presence/absence of “developmental problems”</td>
<td>No</td>
<td>32% of sample with reported or observed developmental problem. Problem status associated with severity of frontal stenosis, surgery &gt; 1 yr of age, extracranial abnormality.</td>
</tr>
<tr>
<td>Virtanen, Korhonen, Fagerholm, &amp; Viljanto (1999)</td>
<td>18 sagittal</td>
<td>7.8–16.3 yr (mean age 12.2 yr)</td>
<td>Test battery measuring fine motor/visual–spatial skills, reading, language and memory Teacher ratings of achievement, parent ratings of behavior</td>
<td>Yes: 18 matched for age, gender</td>
<td>Group differences favoring the control group found on 3 WISC-R subtests (Similarities, Comprehension, and Digit Span)</td>
</tr>
<tr>
<td>DeLeon, Speltz, &amp; Cunningham (2000)</td>
<td>37 sagittal</td>
<td>Presurgery (before 12 mo) and up to 6 mo postsurgery</td>
<td>BSID No</td>
<td>No</td>
<td><strong>Presurgery PDI,</strong> but not MDI, scores were significantly lower than test norms. No significant pre- or postsurgery change in scores. No relation found between BSID scores and age at surgery.</td>
</tr>
<tr>
<td>Panchal et al. (2001)</td>
<td>21 synostosis</td>
<td>Presurgery (mean age = 11 mo) or prehelmet therapy (mean age = 8.4 mo)</td>
<td>BSID-II No</td>
<td>No</td>
<td><strong>Synostosis group:</strong> PDI, but not MDI, scores lower than test norms. Plagiocephaly group: Both PDI and MDI scores lower than test norms.</td>
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<tr>
<td>Gewalli et al. (2001)</td>
<td>26 sagittal</td>
<td>4–16 mo presurgery; 9–40 mo postsurgery</td>
<td>Griffiths’s Mental Development Scales No</td>
<td>No</td>
<td>No association between DQ and ICP or pre- and postsurgical status.</td>
</tr>
<tr>
<td>Magge Westerveld, Pruzinsky, &amp; Persing (2002)</td>
<td>16 sagittal</td>
<td>6.4–16 yr (mean = 10.3 yr)</td>
<td>Test battery measuring IQ (WISC-R), achievement, attention, and vigilance, executive functions, visual-motor skills, and behavior No</td>
<td>Full scale IQ in normal range but VIQ significantly higher than PIQ. 50% rate of learning disability as defined by IQ–achievement discrepancy scores (approximately 1 SD)</td>
<td></td>
</tr>
<tr>
<td>Shimoji, Shimabukuro, Sugama, &amp; Ochiai (2002)</td>
<td>65 “mild” metopic</td>
<td>Less than 1 yr to 9 yr. Assessed before surgery and 6 mo later</td>
<td>K-Form Developmental Test (yields a developmental quotient) and Japan Child Behavioral Checklist Neurological exam No</td>
<td>94% with language delay before surgery. Some improvement in language following surgery; most remain significantly delayed (37% DQ &lt; 60); behavior improved after surgery. No significant changes in nonsurgery group.</td>
<td></td>
</tr>
<tr>
<td>Shipster et al. (2003)</td>
<td>76 sagittal</td>
<td>9 mo–15 yr</td>
<td>BSID-II, PLS-3, WPPSI-R UK, WISC-III UK, CELF-R’, other tests No</td>
<td>38% with speech and/or language impairment, primarily expressive language problems. No increased rate of global IQ deficit.</td>
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</table>

Abbreviations: BSID = Bayley Scales of Infant Development; BSID-II = Bayley Scales of Infant Development, 2nd edition; CELF-R = Clinical Evaluation of Language Fundamentals–revised; DQ = developmental quotient; (BSID-II); ICP = intracranial pressure; LD = learning disability; MDI = Mental Development index (from the BSID); MSCA = McCarthy Scales of Children’s Abilities; PDI = Psychomotor Development index (from the BSID); PIQ = Performance IQ; PLS-3 = Preschool Language Scale, 3rd edition; SES = socioeconomic status; VIQ = Verbal IQ; WISC-III = Wechsler Intelligence Scale for Children–third edition; WISC-R = Wechsler Intelligence Scale for Children–revised; WPPSI-R = Wechsler Preschool and Primary Scale of Intelligence, revised.
Few studies have reported actual rates of mental retardation (typically defined as standardized test scores below 70). Hunter and Rudd (1976, 1977), Kapp-Simon (1998), and Sidoti et al. (1996) reported slightly increased rates of mental retardation (from 6.5 to 12%). This compares to an expected rate of approximately 2.2% in the population.

Among studies that focused on or included analyses of average group performance, two used a matched control group, and the others compared the performance of cases with test norms (i.e., essentially comparison with the test's standardization group). One of the two control-group studies found that children with sagittal synostosis scored significantly lower than controls on 3 subtests of the WISC-R (Wechsler Intelligence Scale for Children–revised; Virtanen, Korhonen, Fagerholm, & Viljanto, 1999), although these differences might not have reached statistical significance had the data been analyzed more conservatively (i.e., controlling for the number and intercorrelation of variables analyzed). The other study using a matched control group (Speltz, Endriga, & Mouradian, 1997) found no differences between infants with and without sagittal synostosis tested at three age points (3, 12, and 24 months).

Nearly all studies comparing average test scores to test norms examined infants and toddlers with the well-known Bayley Scales of Infant Development (BSID; Bayley, 1969), using the BSID Mental Development index (MDI) and Psychomotor Developmental index (PDI). Kapp-Simon's studies (1994, 1997, 1998; Kapp-Simon, Figueroa et al. (1993)) did not find that cases performed worse than test norms on average. However, Kapp-Simon did not administer the PDI, which in two other studies revealed lower-than-average scores among cases than did the mean of the BSID standardization group (DeLeon, Speltz, & Cunningham, 2000; Panchal et al., 2001). In both studies, MDI scores did not distinguish cases from test norms. Although it is therefore tempting to speculate that motor functions are more affected by synostosis than purely cognitive functions, this is an unreliable distinction during infancy, given the highly integrated and reciprocal development of cognition and motor skills at this age (Bremner, 1993). However, the PDI findings may have some importance, as studies involving other high-risk groups (e.g., premature infants) have found that infancy PDI scores are more predictive of children's subsequent language and intellectual abilities than are MDI scores (Siegel, 1989) and are therefore believed by some investigators to better index central nervous system integrity (Aylward, Verhulst, Bell, & Guyrke, 1995).

**Behavior and Social Adjustment**

Few studies of craniosynostosis have included measures of children's behavior and social–emotional characteristics. Speltz, Morton, Goodell, and Clarren (1993) found that children with various craniofacial anomalies—including those with craniosynostosis—were more than twice as likely as children in a matched control group to have teacher- and parent-reported behavior problems at school entry. However, small numbers precluded analysis by craniofacial diagnosis.

The Bottero et al. study (1998) of metopic synostosis used a categorical outcome measure based in part on clinicians' judgments regarding the presence or absence of "behavior problems"; however, there was no specification of the nature of these problems or how they were assessed. Investigators of three other studies in Table I included a concurrent measure of behavioral adjustment or conducted follow-ups of their samples that included assessment of children's behavioral–social status. In the Finnish sample of school-age sagittal cases studied by Virtanen et al. (1999), no significant differences between cases and controls in maternal ratings of child behavioral adjustment were found. Subsequent analyses of the infants with sagittal synostosis examined by Speltz et al. (1997) indicated that these children at 7 years old showed higher levels of parent- and teacher-reported behavior problems than did a matched group of normal children. Using a normed behavior checklist, Kapp-Simon and Dawson (1998) examined the behavior and social adjustment of 29 children with single-suture synostoses at age 7 and found that parental ratings of problem behavior were roughly equivalent to those obtained in the standardization sample.

**Surgery and Neurobehavioral Status**

The assertion that cranioplastic surgery prevents or mitigates neurobehavioral delays or deficits (e.g., Arnaud et al., 1995) has provoked considerable controversy, raising the question of whether the effects of surgery are "merely" aesthetic or functional as well (Hayward, Jones, & Evans, 1999; Kapp-Simon, 1994, 1998; Posnick, 1998; Rozelle et al., 1995). To our knowledge, there have been no randomized trials of cranioplasty for craniosynostosis, given the ethical constraints of this approach. Investigators have therefore been forced to rely on quasi-experimental designs and measures of association to draw inferences about the effects of surgery on neurodevelopment. As noted, age of surgery and neurobehavioral status are hypothesized to show an inverse relation because increased ICP in the absence of...
surgery is expected to affect brain development adversely (Arnaud et al., 1995). Several studies have therefore examined the developmental scores of infant groups distinguished by surgery before or after a specified age point, or they simply computed correlations between surgery age and outcome measures among operated children. Most of these studies have been conducted in Europe. In a French cohort, Renier and Marchac (1988) found that 88% of children having surgery before 1 year of age (with various synostoses) scored above 90 on a standardized test of infancy development, whereas only 76% of children having surgery after 1 year exceeded this criterion. The investigators concluded that surgery lowered ICP and therefore prevented cognitive decline. The same investigative group found in a later study (Arnaud et al., 1995) that ICP among cases of sagittal synostosis was unrelated to cognitive functioning, although age of surgery was nevertheless correlated inversely with mental function. This finding is difficult to interpret, as ICP is believed to be the primary mediator of the relation between surgery age and neurodevelopment. In yet another study by these investigators, Bottero et al. (1998) found that age of surgery was one of four variables in a multifactorial model accounting for about half of the variance in neurobehavioral measures of children with metopic synostosis (in order of contribution, the predictors were severity of frontal stenosis, family environment, age of surgery, and extracranial malformations).

Virtanen et al. (1999) compared cases of sagittal synostosis having surgery after 1 month of age with those having surgery at or before 1 month of age. Although no significant differences emerged, the direction of mean group differences favored the early surgery group on most measures, and the investigators concluded that “an early operation seems to be justified not only for correction of the skull shape but also to allow unrestricted development for the brain” (p. 791). In a Swedish sample, Gewalli et al. (2001) evaluated the cognitive effects of cranioplasty on 26 infants with sagittal synostosis. No significant pre- or postsurgery differences in developmental scores were observed, and there was no association between developmental scores and increased cranial pressure.

The few studies conducted in the United States have generated less-positive findings regarding surgery effects. Speltz et al. (1997) found that MDI scores (based on the BSID) and surgery ages inversely correlated \( r = -0.30 \) in a small sample of infants with sagittal synostosis, but no presurgery-to-post surgery change in scores was evident when assessed twice and up to a year following surgery. In subsequent analyses of a larger cohort of infants with sagittal synostosis drawn from the same hospital program (DeLeon et al., 2000), the correlations between BSID scores (MDI and PDI) and surgery age were near zero. Similarly, there were no significant relations found between MDI scores and surgery age in Kapp-Simon's (1994, 1997, 1998; Kapp-Simon, Figueroa et al. (1993)) samples of infants with various single-suture synostoses.

**Methodological Critique**

In the interpretation of data regarding surgery age, it is important to consider two methodological vulnerabilities that commonly limit the inference of causality from correlational data. Correlation is sensitive to the range of values of the variables measured in a particular sample (e.g., restricted range produces lower correlation in the sample than in the general population). The range of surgery ages included in studies of craniosynostosis may be affected by factors unrelated to the etiology of synostosis and its neurobehavioral correlates (e.g., regional practice parameters, study duration, and subject enrollment procedures). Second, age of surgery may be confounded with other variables that affect neurobehavioral status. For example, infants with synostosis who first come to the attention of a craniofacial specialist well into their second year of life may represent a somewhat different sample of infants from those first diagnosed in early life; for example, early-diagnosed infants may have better medical care, closer proximity to services, more vigilant or concerned parents, parents less ambivalent about surgery, and so on. Factors such as these could affect neurobehavioral development in subtle ways. We are unaware of studies that have been able to disentangle the effects of age of detection (i.e., diagnosis) from age of surgery, as this would require varying intervals of time between initial testing and surgery—typically, cases have been tested at the time of their initial diagnosis, with surgery immediately following. It is also possible that surgical timing could have an effect on cognition that is independent of ICP or synostosis (e.g., early surgeries might be better tolerated by infants in terms of initial trauma or recovery). Other reviewers have noted similar problems in the ascertainment and segregation of cases based on surgery age or occurrence, and they have urged caution in the interpretation of these data (Hayward et al., 1999; Kapp-Simon, 1994; Posnick, 1998).

In addition to these issues specific to the study of surgical effects, nearly all the studies in Table 1 have been limited by the methodological problems commonly
found in studies of rare disorders. Sample sizes have been typically small, limiting statistical power and precluding analyses of outcome by specific sutural diagnosis. Little is known about the effects of different synostoses on neurodevelopment (e.g., sagittal vs. metopic), comparisons that are critical to a better understanding of specific suture–brain–behavior associations. Another problem is the use of nonstandardized age and assessment points in case series. Cases have been initially tested at widely differing ages (this has usually been necessary to recruit a large enough sample), with extremely variable follow-up assessment intervals that likely reflect various clinical care exigencies (e.g., surgical dates, scheduling convenience). Seldom has the selection of assessment ages reflected investigators’ consideration of critical developmental milestones or the optimal ages at which certain functions can be assessed. Widely differing assessment ages can also introduce unwanted test score variation due to varying levels of reliability and validity in assessment instruments across age periods. For example, Aylward (1992) has noted that standard scores from the BSID tend to decline with age. To our knowledge, only one of the longitudinal studies in this area (Speltz et al., 1997) assessed all cases at the same age points (3, 12, and 24 months), but this study had one of the smallest samples reviewed (n = 19), reflecting the logistical difficulty of recruiting a large sample of cases and assessing them all at the same age points.

Another methodological issue is the inclusion/exclusion criteria by which cases are selected, particularly with respect to the co-occurrence of associated intracranial or extracranial anomalies. Bottero et al. (1998) found that nearly 20% of their sample of children with metopic synostosis had one or more extracranial malformations, including finger deviations and/or extra digits, ear anomalies, maxillofacial abnormalities, and cardiac defects. Such children had higher rates of developmental problems (57%) than those without associated anomalies (26%), and the relation between age of surgery and subsequent developmental outcome was mediated by this variable. In contrast, Kapp-Simon and colleagues (1993) found no differences in mental development as a function of various risk factors, including extracranial malformations. Although Posnick (1998) argues that the presence of associated anomalies in children with single-suture synostosis raises the probability of genetic defects and therefore may increase the probability of neurodevelopmental problems, most studies in Table I have provided no information about the presence or absence of associated anomalies.

Most studies in this area have ascertained cases strictly through large hospital-based programs, an approach that can introduce sample bias influencing the range and variance of neurobehavioral score distributions. The sources of such bias include regional practice parameters that may over- or undertarget urban or rural families, or families with particular socioeconomic backgrounds. Furthermore, hospital programs may be more likely to see and retain more severe or complicated patients than community practices, especially if the sample is recruited in relatively late childhood or adolescence. In the absence of population-based epidemiological data, the extent is unknown to which any of the study samples in Table I represents the larger population of children with single-suture craniosynostosis. Ascertainment bias may compromise the external validity of the research—for example, to whom can the results of the study be appropriately generalized?—as well as internal validity, particularly when test scores or categorical outcomes are compared only to test norms or known base rates of particular outcomes—for instance, samples containing a disproportionate number of low-income families would produce spuriously low estimates of neurodevelopmental status in the broader population of cases.

**Directions for Future Research**

**Multisite Investigations**

Two obvious directions for future research are to incorporate control groups and to develop strategies for increasing sample size. Larger samples would address several of the methodological shortcomings listed here, including low statistical power, corresponding limitations on diagnostic subgroup comparisons, and problems associated with extended case recruitment (e.g., widely varying ages of assessment). Given the low prevalence of isolated synostoses, multisite investigations will almost certainly be necessary to recruit samples of adequate size. Multisite studies also offer the advantages of a broader range of surgery ages, greater demographic heterogeneity among cases, and some protection against program-specific ascertainment bias.

**Selection and Specificity of Neurobehavioral Measures**

With few exceptions (e.g., Magge et al., 2002; Shipster et al., 2003; Virtanen et al., 1999), the neurobehavioral assessment of craniosynostosis has been narrowly focused on a single index of global functioning (e.g., the BSID’s MDI and PDI). Global indexes are less likely to
detect current and future aberrant development than is the assessment of multiple domains of functioning, including expressive and receptive language, executive functioning and attention, memory, fine- and gross-motor functioning, and visual perception (Aylward, 1997; Spreen, Risser, & Edgell, 1995). Although the reliable assessment of separate domains of function in infants and very young children is challenging, future studies of craniosynostosis can benefit from recent developments in standardized testing and experimental paradigms for assessing fundamental processes. Reznick, Corley, and Robinson (1997), for example, have developed a model for distinguishing theoretically relevant subsets of BSID items pertaining to receptive language, expressive language, and nonverbal problem solving, which can be used to supplement or replace global index scores (Speltz et al., 2000). Experimental tasks that assess specific brain–behavior relations in primates and other animals have been recently adapted for use in young humans. One example is the A not B task, which requires both working memory and response inhibition and has been consistently linked to the dorsolateral prefrontal cortex in primates and humans as young as 18 months (Braver et al., 1997; Diamond & Goldman-Rakic, 1986, 1989). Lesions to the medial temporal lobe and parietal cortex do not disrupt performance on this task, suggesting relative specificity of linkage to the frontal lobe (Diamond & Goldman-Rakic, 1989; Diamond, Zola-Morgan, & Squire, 1989). Similar tasks—suitable for infants and derived from animal studies—have been associated with the medial temporal lobe and parietal cortex and assess visual working memory (e.g., Bachevalier & Mishkin, 1986; Squire, Zola-Morgan, & Chen, 1988).

Another strategy for targeting relevant domains of functioning in future studies is to identify the precursors or emerging forms of later, fully developed skills. One example of relevance to young children with craniosynostosis is the well-demonstrated association between reading ability at school age and phonological processing skills in preschool children (e.g., Leitao, Hogben, & Fletcher, 1997; Webster, Plante, & Couvillion, 1997). Preschool phonological processing is in turn predicted by still earlier measures of rhyming and alliteration (Bryant, MacLean, Bradley, & Crossland, 1990; MacLean, Bryant, & Bradley, 1987). Simple rhyming tasks given to children as young as 3 years old have predicted effective word decoding at school age, after controlling for general IQ, receptive vocabulary, memory, and sociometric status (Whitehurst & Lonigan, 1998). In light of findings suggesting language and/or phonological deficits in school-age children with isolated synostosis (Rozzelle et al., 1995; Shipster et al., 2003), future longitudinal studies should examine the use of these measures as predictors of school-age verbal learning disabilities.

**Neurobehavioral Functioning and Severity of Synostosis**

Most previous studies have examined neurobehavioral status in relation to the presence or absence of diagnosis, with little consideration of severity level or degree of impact on brain tissue. Analysis of the interrelations among measures of neurobehavioral functioning, severity of synostosis, and degree of compression of brain structures would help to clarify and refine causal hypotheses. For example, if severity (or degree of) suture fusion and compression of underlying brain tissue were highly intercorrelated and predictive of neurobehavioral status, it would strengthen (although not prove) the hypothesis that these processes are causally related to neurodevelopment. As noted, a limiting factor has been the lack of standardized methods for assessing severity and impact of synostosis from CT scans, which are routinely given to infants with synostosis as part of the diagnostic process (MRI is rarely used at this age, due to the risks of sedation). However, future neurodevelopmental studies could develop relatively simple measures in this regard.

The percentage of suture patency could be obtained from CT scan by linear measurement of the proportion of native suture remaining open, or “unfused” (i.e., the proportion of total suture length unobstructed). Severity of secondary calvarial deformation could be estimated by measuring the deformation of skull shape that has been produced by the fused suture. For fusions of the sagittal suture, skull deformation could be estimated by calculating the ratio of the biparietal and sagittal dimensions of the skull. Severity of brain tissue compression could be rated or classified by examination of the amount and symmetry of extraxial (subarachnoid) CSF visible on CT film. For example, it should be possible to reliably distinguish between subarachnoid space diminished to the point of direct contact of the brain with the inner table of the skull—but still showing preserved gyri and sulci—versus complete absence of discernible gyri and sulci. Given large enough sample sizes, these measurements and ratings could be correlated with neuropsychological data, both within and across groups of children with different isolated synostoses.

**Effects of Family Environment**

There has been surprisingly little investigation of the potential interaction between craniosynostosis and family
risk factors on neurodevelopment. Only one study among those reviewed included a measure of family or other social risk factors (Bottero et al., 1998). Family risks such as single parenting, low socioeconomic status, family or marital conflict, and parenting stress may exacerbate the adverse effects of synostosis on neurodevelopment—such factors have been shown to influence the developmental trajectories of children with other types of chronic medical conditions or disability (e.g., Britner, Morog, Pianta, & Marvin, 2003; Hauser-Cram et al., 1999; Kapp-Simon, 2002; Speltz et al., 1994). Parenting stress may be particularly influential, as few events are as devastating for parents as learning that their newborn has a serious or chronic medical condition or disability (e.g., Britner, Morog, Pianta, & Marvin, 2003; Hauser-Cram et al., 1999; Kapp-Simon, 2002; Speltz et al., 1994). In our clinical work with families of infants with craniosynostosis, we have encountered many parents who seem confused about the diagnosis and—for reasons already discussed—uncertain about the medical necessity of surgery, particularly with respect to surgery's role in preventing cognitive impairment (Speltz et al., 2003). The style and effectiveness of parental adaptation and coping responses during this stressful period are likely to vary widely but have been largely unstudied in this population. Future studies of craniosynostosis would benefit from assessment of the family environment, including measures of parental adjustment to the diagnosis and its impact on infant-caregiving routines (e.g., Parenting Stress Index, Abidin, 1995; Reaction to Diagnosis Interview, Pianta & Marvin, 1992).

**Facial Appearance**

Infants with single-suture craniosynostosis have visibly altered craniofacial appearance, which varies in relation to the location and extent of suture involvement. The possibility of permanent abnormality in facial or cranial appearance seems to greatly affect parents' decisions to have their infant undergo cranioplastic surgery. Many surgeons believe that the primary indication for cranioplasty in isolated synostosis is cosmetic rather than functional (Hayward et al., 1999). Even after corrective surgery, mild residual differences in appearance persist for some children, particularly those with unilateral coronal synostosis. However, this is a clinical impression that has not been studied empirically in this population. As there is clear evidence in other groups of children that even mild deviations from typical facial appearance can have significant impact on psychological adjustment (Endriga & Kapp-Simon, 1999; Macgregor, 1982, 1990; Richman, 1978), future studies of infants with single-suture craniosynostosis should include ratings of appearance both before and after cranioplastic surgery, including comparisons with age- and gender-matched controls.

**Summary and Conclusions**

The majority of studies reviewed in this paper found at least modestly elevated risk of neurobehavioral problems among infants or children with single-suture synostosis, as compared with standardized test norms, estimated population base rates of problems, or (rarely) control groups. This research suggests that the degree of impairment associated with synostosis is mild to moderate on average. Learning and language disorders and other categories of academic difficulty (“low average”) are the most anticipated problem areas. Quasi-experimental studies have found little support for the hypothesis that cranioplastic surgery prevents or reduces risk of these outcomes. Behavior and social problems may also occur at elevated levels among children with isolated synostosis, but there are too few studies of this issue to offer even tentative conclusions.

It remains unclear whether single-suture craniosynostosis is a cause or correlate of neurobehavioral impairment. Future studies looking more closely at the relation between neurobehavioral status and the severity and cortical impact of synostosis are needed to clarify etiological pathways. It is also possible that the probability of neurobehavioral impairment depends in part on the co-occurrence and severity of other risk factors, including adversity and stress in the family environment. This hypothesis has yet to be investigated.

Conclusions drawn from the reviewed literature are tentative, given the methodological limitations described, which could either minimize or accentuate the neurobehavioral differences between children with and without single-suture synostosis, particularly within the range of dysfunction suggested thus far. Furthermore, the majority of studies in this area have examined children during early childhood, when the reliable assessment of mild-to-moderate neurodevelopmental deficits is a challenge. The full range of deficits associated with these disorders may not be revealed until there is opportunity to assess a sizable number of children in their middle-to-late elementary school years. Only at this age can different types of learning disorders and subtle patterns of neuropsychological deficit (e.g., verbal versus nonverbal, reading versus math or visual spatial) be unequivocally established.

From a clinical perspective, the studies reviewed suggest that the outcomes of most children with isolated synostosis are as devastating for parents as learning that
synostosis (slightly more than half) are indistinguishable from those of typical children. However, a sizable minority (perhaps 30% to 40%) is likely to have problems in need of intervention. This tentative estimate of risk suggests that routine neurodevelopmental screening and referral would benefit children with synostosis, especially preschool-age children for whom the benefits of early assessment and intervention have been well demonstrated (Shonkoff & Meisels, 2000).

Acknowledgment
Dr. Marsh is now in private practice in St. Louis.

Received September 29, 2003; revisions received February 5, 2004; accepted March 29, 2004.

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