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Attention and executive function in children with and without single-suture craniosynostosis

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Abstract

Children with single suture craniosynostosis have higher rates of learning disabilities and related neurocognitive problems than unaffected peers. Executive function and attention are thought to be areas of particular vulnerability, though studies to date have been limited by small sample sizes and a lack of control groups. We evaluated 179 school-aged children with single suture craniosynostosis (cases) and 183 unaffected controls at an average age of 7 years using clinician-administered and parent and teacher report measures of executive function and attention. Among children with craniosynostosis, we examined differences as a function of suture location (sagittal, metopic, unicoronal, or lambdoid) and age of corrective surgery. We used linear regression analyses, adjusted for potential confounders, to compare the two groups on all outcome measures. Cases scored lower than controls on most measures, though the magnitude of these differences was small and most were statistically insignificant. The largest relative deficit was on a measure of

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inhibitory control. Results changed little in sensitivity analyses adjusting for potential attrition bias and for the effects of developmental and academic interventions. Among cases, there were few differences in relation to the location of suture fusion or timing of surgery. Overall, we found limited evidence of broad deficits in executive function or attention in children with single suture craniosynostosis relative to unaffected controls. Neurocognitive development for children with SSC appears to be variable, across affected children and outcomes assessed. Further research is needed to understand the potential sources of this variability.

Keywords

Executive function; attention; craniosynostosis; inhibition

Single-suture craniosynostosis (SSC) involves premature fusion of one of the cranial sutures (sagittal, metopic, coronal or lambdoid). Approximately 3 to 6 children per 10,000 live births are affected by SSC (Boulet et al., 2008). Prevalence varies by suture site, ranging from <1 per 10,000 births for lambdoid synostosis to approximately 2 per 10,000 births for sagittal synostosis. In the United States, the vast majority of children with SSC undergo surgery in the first year of life to release the fused suture, capitalizing on brain growth to round the skull with development (Warren et al., 2012). In addition to the cosmetic benefits, it has been proposed that surgery for children with SSC attenuates the risk of neurodevelopment problems by expanding the cranial vault and reducing the possibility of elevated intracranial pressure and/or reducing constriction on brain growth (e.g., Patel et al., 2014). Earlier surgery is generally thought to promote better neurocognitive outcomes, though findings on this topic are mixed (Kapp Simon et al., 2007; Speltz et al., 2004) and complicated by clinically important variations in surgical approach (Hashim et al., 2014; Panchal et al., 1999).

In a recent review, Knight and colleagues (2014) identified 33 studies of neurodevelopment in children with SSC. Most of the reviewed studies assessed children 5 years old, used broad measures of development, and relied on test norms for comparison. Among the few studies of school-aged children and adolescents, most focused on intellectual ability rather than specific neuropsychological skills. Knight et al. (2014) concluded that children with SSC score slightly behind age expectations on measures of development and intellectual ability. A small number of studies of more detailed neuropsychological assessment have reported deficits in speech and language (Becker et al., 2005; Shipster et al., 2003; Virtanen et al., 1999), visual-spatial skills (Chieffo et al., 2010), and memory and attention (Bolthausen et al., 2003; Chieffo et al., 2010; Virtanen et al., 1999). However, these studies evaluated small patient samples (i.e., most $N < 50$) and rarely included unaffected controls or adjustment of potential demographic confounders (e.g., socioeconomic status).

In one of the largest case-control studies to date, we assessed the neurodevelopment of children with and without SSC in early childhood (pre-surgery through approximately age 36 months) and again at age 7 years. In early childhood, children with SSC consistently scored lower than unaffected controls on standardized measures of development, with differences of 0.25 to 0.5 standard deviations (SD) (Speltz et al., 2007; Starr et al., 2012).

Similarly, at age 7 years, children with SSC continued to score below unaffected controls on intellectual ability and academic achievement measures (Speltz et al., 2015). Case versus control group differences were largest on measures of global IQ and math achievement. Further, there was a ‘downward shift’ in the distribution of scores among cases relative to test norms, with cases more likely than controls to score below average relative to test norms and less likely to score in the above average or superior range. In addition to these broad measures, at age 18 months we completed experimental tasks based on the A not B paradigm (Toth et al., 2008) to assess early executive function (EF) and inhibition. Group differences on these tasks were negligible, though fewer children with SSC than controls were able to complete the most challenging tasks, possibly indicating problems with EF under more demanding conditions. We also found slightly greater attention problems in children with SSC versus controls at age 36 months based on parent, but not teacher reports (Kapp-Simon et al., 2012).

In this study, we examined EF and attention in school-aged children with SSC versus unaffected controls. We used standardized, clinician-administered measures of sustained attention, working memory, and inhibitory control. We also collected parent and teacher report measures of attention and EF in daily activities. These higher order cognitive skills are thought to be more vulnerable to early insult during brain development (e.g., Anderson et al., 2014), and we therefore hypothesized worse performance in all domains for children with SSC versus controls. Among cases, we also explored differences as a function of location of suture fusion and age at corrective surgery.

Methods

Study design

As part of a multi-center longitudinal study of children with SSC (“cases”) and unaffected children (“controls”), we sought to enroll all eligible cases seen at participating centers between January, 2002 and September, 2006. Participants were recruited from the following sites: Seattle Children's Hospital; the Cleft Lip and Palate Institute and Northwestern University in Chicago; Children's Heath Care of Atlanta; and St. Louis Children's Hospital. We also approached eligible children diagnosed with SSC at Children's Hospital of Philadelphia starting in January, 2006. Unaffected controls were recruited by each site and frequency-matched to cases at the time of recruitment on the basis of sex, age at enrollment, race/ethnicity, and socioeconomic status (SES). Participants were assessed 4 times: a “baseline” assessment prior to surgery (mean age = 7.4 months) and on average at ages 18 months, 36 months and 7 years. The current study focuses on assessments completed at the age 7 visit. The study was approved by the institutional review boards (IRB) at each of the participating centers.

Cases—Infants with SSC were referred to the project at the time of diagnosis by a treating physician. Cases were eligible for participation if they: (1) had SSC (sagittal, metopic, unilateral coronal, or unilateral lambdoid synostosis), confirmed by computed tomography scans; (2) had not yet had cranial vault surgery; and (3) were 30 months of age at recruitment. Exclusions were: (1) prematurity (<34 weeks gestation); (2) major medical or

neurological conditions (e.g., cardiac defects, seizure disorders, significant health conditions requiring surgical correction, etc.); (3) presence of three extracranial minor malformations (Leppig et al., 1987); or (4) presence of other major malformations.

For a subsample of 178 cases whose parents gave consent, we collected biospecimens and analyzed genetic data by array CGH and candidate and gene re-sequencing (for details see Cunningham et al, 2011). Children with SSC who had a genetic variant (including a known or probable causal mutation for craniosynostosis) were eligible if they had no phenotypic features of a known syndrome and otherwise met all inclusion criteria.

We enrolled 270 cases (84% of those eligible), four of whom were later found to be ineligible (for details regarding ascertainment, see Starr et al., 2012). We also excluded from all analyses 3 children with SSC who did not receive surgery for SSC. Among the 266 infant cases seen at baseline, 179 children (67%) were re-assessed at age 7.

Controls—Control group participants were recruited through pediatric practices, birthing centers, and announcements in publications of interest to parents of newborns. Control infants were eligible if they had no known craniofacial anomaly and met none of the exclusionary criteria for cases. Controls were frequency-matched to cases on factors related to neurodevelopmental performance that may also be related to craniosynostosis risk (i.e., potential confounders): 1) age at enrollment (within ± 3 weeks); 2) sex; 3) family SES within the same Hollingshead category (Hollingshead, 1978); and 4) race/ethnicity.

We enrolled 76% of all interested, eligible controls who were matched to enrolled cases (Starr et al., 2012). Among the 259 controls seen at baseline, 183 (71%) were seen at age 7.

Measures

Caregiver Interview—Children's primary caregivers completed a semi-structured interview to collect information on child medical history, including diagnosis of attention deficit hyperactivity disorder (ADHD), learning problems, and other developmental concerns (e.g., speech/language delay). When relevant, we collected information on interventions that children received in the community, including medications (e.g., stimulant medication for ADHD), behavioral interventions, developmental interventions (e.g., speech/language therapy), and special education.

Wonderlic Personnel Test (WPT; Wonderlic, 1999)—The WPT is a timed, norm-referenced screening measure to assess general intelligence in adolescents and adults. The WPT has good reliability, and correlates well with clinician administered measures (e.g., the Wechsler scales). The WPT was administered to mothers of participating children, allowing us to control for maternal IQ in analyses of differences between cases and control group participants.

Test of Everyday Attention in Children (TEA-Ch; Manly et al., 1999)—The TEA-Ch is a norm-referenced, clinician administered test of attentional control. We administered selected sub-tests, including: Sky Search, Score!, Sky Search DT, and Score DT. The Sky Search task is a timed task requiring the child to find as many target spaceships as possible

on a sheet filled with targets and distractors. During the Score! subtest, children listen to an audio tape and are asked to count the number of 'scoring' sounds that they hear. The Sky Search DT task is a combination of these first two sub-tests, requiring the child to simultaneously identify target spaceships and keep a count of scoring sounds heard on audio tape. Finally, the Score DT task requires the child to count scoring sounds and listen for an animal name spoken during a news report. Reliability and validity data support the use of the TEA-Ch in school-aged children. For all sub-scales, we used scaled scores as dependent variables in analyses.

NEPSY-II: A Developmental Neuropsychological Assessment (NEPSY-II; Korkman, Kirk, & Kemp, 2007)—The Inhibition subtest, which is based on the Stroop task (Stroop, 1935), was used as a measure of children's inhibitory control. During the Inhibition task the child looks at a series of black or white shapes or arrows and names as quickly as possible the shape, direction, or an alternate response depending on the color of the shape or arrow. The Inhibition task has good evidence of reliability for children in this age range, and evidence of convergent and discriminant validity (Brooks et al., 2010). We used scaled scores for the Total Errors (regardless of time) and the Total Score (combines time and errors) as dependent measures.

Wechsler Intelligence Scale for Children – IV (WISC-IV; Wechsler, 2004)—The WISC-IV is a widely used measure of cognitive ability for children ages 6-16 years. In this study, we utilized scores from the Working Memory Index, which assesses auditory attention, verbal recall (e.g., ability to recall a series of orally-presented digits), the ability to manipulate information in short term memory, and the ability to formulate a verbal response. Scores on the Working Memory Index have been found to be highly reliable and correlate well with other measures of working memory and EF (Wechsler, 2004).

Parent and Teacher Questionnaires—Participating children's parents and teachers were asked to complete scales from the *Achenbach System of Empirically Based Assessment (ASEBA; Achenbach and Rescorla, 2001)* and the *Behavioral Rating Inventory of Executive Function (BRIEF; Gioia et al., 2000)*. We used the Attention Problems sub-scale from the parent and teacher versions of the ASEBA. Items included in this sub-scale assess hyperactivity-impulsivity and inattention as manifest at home or in the classroom. We used composite scores for Behavioral Regulation, Metacognition, and the Global Executive Function composite (Total score) from the BRIEF. The ASEBA and BRIEF are normed for school-aged children and adolescents, including separate norms for males and females. Reliability estimates are excellent, and both measures have well-established validity.

Procedures

Parents were contacted by telephone six months prior to their child's 7th birthday and screened to determine their willingness to participate in a follow-up assessment. We obtained informed consent following the IRB-approved protocols of each participating institution. Families were offered \$100 compensation for the study visit. Parents who so desired were mailed a summary of their child's test results and they were encouraged to share this information with their child's pediatrician or teacher.

Data Analysis

The distributions of demographic characteristics and EF and attention scores were calculated for cases and controls, as well as the number and percentage of children with a diagnosis of attention deficit hyperactivity disorder (ADHD) or the use of stimulants or other related medications for ADHD. To explore factors associated with attrition, we examined the characteristics of children lost to follow-up with those assessed at age 7.

Norm-referenced scores (T-scores, scaled scores, or standard scores) were used for all outcome measures, both for ease of interpretation and because in preliminary analyses these scores provided a more normal distribution than raw scores. Differences in EF and attention scores were estimated using linear regression with corresponding 95% confidence intervals and robust standard error estimates. To examine whether cases were more likely than controls to be ‘at risk’ for problems with EF and attention relative to test norms, we used logistic regression to compare the proportion of cases versus controls who scored more than 1 standard deviation (SD) below the normative mean (or 1 SD above the mean, on tests where higher scores indicated greater impairment). All estimates were adjusted for age at assessment (in months, continuous), sex, maternal IQ (continuous), and family socioeconomic status (SES) using the Hollingshead composite score (continuous).

Due to small sample sizes, we were unable to control for all potential confounders in a single model. We therefore repeated our analyses using propensity score matching (Abadie, 2004; Rosenbaum, 1983). Propensity scores were estimated using a logit model which predicted case status based on all covariates included in the primary analyses plus race/ethnicity, and study site. Cases were matched to controls using 1:1 nearest neighbor matching with replacement. A large proportion of subjects (49%) received intervention services prior to the 7 year study visit, including speech/language therapy, occupational/physical therapy, psychiatric medication treatment, or special education services. We therefore used censored normal regression (Tobin et al., 2005) to account for the effects of interim intervention on subsequent scores. This approach assumes that the scores of children who received intervention services would be at least as low as those observed in the absence of intervention, i.e. that they are “left-censored.” We also examined case versus control group differences after excluding cases with a known or probable causal mutation for SSC.

Within cases, we conducted exploratory analyses to determine whether EF and attention scores differed by the site of the affected suture (sagittal, metopic, unicoronal, and lambdoid) using linear regression with robust standard errors and examined overall group differences using Wald tests. Sagittal cases were considered the referent category. We also evaluated the association between age at surgery and EF and attention. Because the optimal age for surgery varies by suture location (e.g., surgery tends to be performed at younger ages for children with sagittal SSC, and older for children with unicoronal SSC), we calculated the median age at surgery within each suture group. We then compared outcomes for children who were younger than the median versus those who were older than the median age at the time of surgery using linear regression.

We evaluated the impact of attrition over time by repeating our analyses using inverse probability weighting (IPW) (Robins et al., 1994). This method places greater weight on

observations from subjects seen at age 7 who are similar in terms of baseline characteristics to children lost to follow-up. Weights were estimated based on factors observed at baseline in all subjects, including date of birth, sex, race/ethnicity, delivery at < 38 weeks gestation (coded yes/no), case status, suture diagnosis, parents' marital status, maternal IQ, study site, and scores from the Bayley Scales of Infant Development-2 (Psychomotor Development Index [PDI]) and the Preschool Language Scale-3 (auditory comprehension [PLS-AC]) completed at baseline (see Starr et al., 2012). We also repeated our analyses after excluding 19 children with SSC in whom known or probable causal mutations for craniosynostosis were detected through array CGH and candidate and gene re-sequencing (Cunningham 2011).

All analyses were performed using Stata version 12 (StataCorp, 2011).

Results

We assessed 175 and 183 controls at an average age of 7.5 years for cases (range 6.9-9.5 years) and 7.4 years for controls (range 7.0-11.1 years). Nearly all subjects had completed first or second grade (98%). Subjects in both groups were predominantly male (62%), white (77%), and of middle to upper SES (Hollingshead categories I-II, 76%) (Table 1). The frequency of any intervention service was 49% for cases and 37% for controls. Of particular relevance in this study, 13% of cases and 19% of controls were reported by a parent to have received mental health or psychiatric interventions (e.g., behavioral interventions, stimulant medications for attention problems). Most children with SSC (74%) received surgery by age 10 months, with the median age at surgery ranging from approximately 5 months for children with sagittal SSC to 10 months for children with unicoronal SSC. Thirty-one percent of cases and 29% of controls from the original cohort were lost to follow-up. Compared to participants, these non-participants were more likely to be of lower SES (44% Hollingshead categories III-V versus 24% in participating subjects) and had lower Bayley PDI scores and lower maternal IQ scores at baseline.

Average scores for cases and controls were similar to test norms for most of the tests administered (Table 2). Scores on the TEA-Ch were an exception, with both groups scoring lower than expected on average relative to test norms. Cases consistently scored lower than controls on clinician administered and parent and teacher report measures, though differences were small in magnitude (Table 3). Adjusted differences on clinician administered measures ranged from 0.05 to 0.30 SD (p values = 0.03 to 0.67). Group differences were largest for measures assessing inhibitory control: NEPSY Inhibition Combined Score and Total Errors (adjusted group differences = 0.23 and 0.30 SD, respectively). We also observed a case deficit on Score DT, a measure of divided attention (adjusted group difference = 0.23, p = 0.04). Parent and teacher report measures revealed small group differences (0 to 0.15 SD, p -values = 0.06 to 0.96). When examining outcomes using categorical analyses, cases were more likely than controls to score below average relative to test norms on NEPSY Total Errors (adjusted OR = 2.08, p = 0.02) and Inhibition Combined Score (adjusted OR = 1.64, p = 0.08).

Estimates using propensity-score matching to adjust for additional confounding, using IPW to examine attrition bias, and after exclusion of 19 children with known or probable causal genetic mutations for craniosynostosis were of similar magnitude (data not shown). A higher proportion of controls received a diagnosis of ADHD (6.6% in controls versus 3.9% in cases), although cases were more likely to have a present or past history of stimulant or other ADHD medication use (5.5% in controls vs. 5.6% in cases). Eighty-seven cases (49%) and 68 controls (37%) received intervention services at some point from infancy to the age 7 study visit. After accounting for the presumed positive benefit of such intervention using censored normal regression, case deficits increased by 0.3 to 0.7 points. However, differences between cases and controls remained modest (data not shown).

Among cases, attention and EF scores were similar across diagnostic groups, and there was no evidence for effect modification by site of suture fusion (*P* values for overall group differences ranged from 0.08 to 0.92) (Table 4). Effects related to age at surgery were negligible for most outcomes. However, scores on the WISC-IV Working Memory sub-tests were inversely associated with age at surgery (Digit Span: adjusted difference = -0.88, *p* = 0.02; Letter-Number Sequencing: adjusted difference = -0.91, *p* = 0.044). Specifically, children with SSC who underwent surgery later than average relative to other children with the same diagnosis scored lower than those who received surgery earlier than average.

Discussion

To our knowledge, this is the first large case-control study to examine EF and attention in school-aged children with SSC versus unaffected controls. An advantage of the study was the assessment of these skills using both clinician administered measures and parent and teacher report. Additionally, we controlled for potential confounds (e.g., demographic characteristics) through inclusion of unaffected control children and we examined possible effects of attrition bias and treatment effects. Children with SSC scored lower than unaffected controls on all measures, though most of these differences were small in magnitude. Measures of inhibitory control and divided attention were exceptions, with cases scoring significantly lower than controls. The significance of these findings should be interpreted cautiously given the number of group comparisons made and the possibility of spurious results. However, a deficit in inhibitory control among cases is consistent with our previous finding that cases also had poor math skills in relation to controls (Speltz et al., 2015) and studies showing an association between inhibition and math performance in typically developing children (e.g., Espy et al., 2004).

Nevertheless, aside from inhibitory control and divided attention, the measures in this study showed scant evidence of broader case deficits in EF and attention. These findings, which were relatively unaffected by attrition, potential confounding variables, and the presumed effects of intervention, stand in contrast with clinical impressions (Kapp-Simon et al., 2007) and two earlier studies. In the first, Bolthausen et al. (2003) assessed 30 individuals with uncorrected sagittal synostosis at ages 2.5 to 25.5 years. Seventeen siblings served as a control group. A high percentage (40%) of cases exhibited problems with selective and sustained attention; however, the rate of attention problems was similar among unaffected siblings, suggesting the possibility of shared vulnerability that may not have been

attributable to SSC. In the second study, involving the same cohort of children studied here, Kapp-Simon et al. (2012) evaluated behavior problems in children ages 18 and 36 months. In that study, children with SSC had slightly higher parent-reported attention problems scores than unaffected controls, but did not differ on teacher/daycare provider report measures (Kapp-Simon et al., 2012). A third study is more consistent with the findings reported here: Hashim et al. (2014) examined the neurodevelopmental status of patients ages 5 to 25 with sagittal craniosynostosis who underwent one of two types of corrective surgery during infancy. Included in the tests given by these investigators was the BRIEF, which generated mean scores for cases in both surgery groups within the average range relative to test norms.

The emerging findings from this cohort suggest highly variable neuropsychological outcomes in children with SSC, both among affected individuals and across outcome measures. For example, as noted previously, we found differences in intellectual ability and math achievement between children with SSC and controls, but these groups performed similarly in reading and spelling (Speltz et al., 2015). The underlying sources of this variability are unclear. Suture location is one possibility and we have previously shown that global neurodevelopmental outcomes are better in preschool children with sagittal synostosis versus other sutures (Starr et al., 2012). However, we did not observe this effect in the current study of attention and executive functions at school age. Similarly, timing of surgery has been hypothesized to affect neurocognitive outcomes for children with SSC, with some evidence to suggest that earlier surgery is better (e.g., Patel et al., 2014), though in our sample this effect was modest at best. Other potential sources of variability include surgical approach (endoscopic vs. open methods including whole vault remodeling), duration of surgery and associated exposures (e.g., anesthesia, blood loss), other medical comorbidities, or characteristics of the home environment that are not readily captured by measures of SES and maternal IQ. Although ours' is the largest cohort studied to date, we did not have adequate statistical power to examine many of these possibilities.

Limitations of our study include attrition, particularly among children from lower SES backgrounds. ADHD has been found to be more common in lower SES populations (e.g., Froehlich et al., 2007), which may explain why the rate of ADHD was lower among both cases and controls in this sample relative to the prevalence reported in population-based studies (Akinbami et al., 2011). Although attrition was similar for cases and controls, and findings did not differ when adjusting for the effects of attrition bias, the resulting sample was predominately middle to upper SES and the findings may not generalize to other populations. For example, the effects of a condition like SSC might be more pronounced in children who are at higher risk for poor neurodevelopmental outcomes by virtue of their demographic characteristics. Further, many aspects of EF and attention continue to develop through adolescence (Anderson, 2002), and some of the subtle deficits observed in this study may become more apparent with maturation. Follow-up studies of older adolescents and young adults are needed to evaluate differences that emerge with maturation. Analyses comparing outcomes as a function of location of suture fusion, in particular, were limited by low sample sizes for some sub-groups, making these findings tentative pending further replication. Finally, scores on the TEA-Ch in our sample were lower than expected relative to test norms, with average scores for both cases and unaffected controls approximately 1

SD lower than the normative mean. The TEA-Ch was given in the middle of a long test battery (approximately 4.5 hours, including time for breaks) and scores may have been affected by fatigue. Although fatigue may have affected children's scores relative to test norms, test order was standardized for cases and controls, making it unlikely that this would have affected group comparisons.

Conclusions

On average, children with SSC showed few differences in attention or EF relative to unaffected controls. Inhibitory control and divided attention were exceptions, and these appear to be areas of weakness for children with SSC that warrant further study. Location of suture fusion appears unrelated to attention and executive functions. Similarly, we found only modest associations between these outcomes and age at surgery. Accumulating data suggest that neurocognitive outcomes are highly variable among children with SSC. Future research to identify the demographic and clinical sources of this variability is likely to be helpful in identifying subgroups of children with SSC who might warrant developmental screening and early intervention. Clinically, our findings suggest that children with SSC, on average, do not show substantial deficits in EF or attention. This may be useful when discussing the neurocognitive implications of SSC with families of affected children and clinicians in the community who may have limited experience with this condition.

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Table 1

Demographics of children with and without single-suture craniosynostosis (SSC).

Characteristic	Unaffected Controls (N=183)		SSC Cases (N=179)	
	N	%	N	%
Age (in years)				
<7.5	144	78.7	122	68.2
7.5	39	21.3	57	31.8
Grade ^a				
<1	3	1.6	3	1.7
1-2	171	93.4	164	91.6
3	9	4.9	9	5.0
Sex				
Female	69	37.7	66	36.9
Male	114	62.3	113	63.1
Race/ethnicity				
Hispanic or Non-white ^b	47	25.7	37	20.7
White, Non-Hispanic	136	74.3	142	79.3
SES				
I (highest)	54	29.5	42	23.5
II	102	55.7	82	45.8
III	14	7.7	33	18.4
IV	10	5.5	20	11.2
V (lowest)	3	1.6	2	1.1
Site				
Seattle	71	38.8	74	41.3
Chicago	76	41.5	63	35.2
St. Louis	9	4.9	18	10.1
Atlanta	27	14.8	24	13.4
Age at Surgery				
<5 Months	--	--	43	24.0
5-10 Months	--	--	89	49.7
11-15 Months	--	--	32	17.9
>15 Months	--	--	15	8.4
Intervention Services				
Speech/Hearing	38	20.8	46	25.7
Physical/Occupational Therapy	24	13.1	44	24.6
Special Education	17	9.3	29	16.2
Mental Health Therapy	29	15.8	19	10.6
Stimulant medications	10	5.5	10	5.6
Any Intervention	68	37.2	87	48.6

^aGrade level missing for 3 SSC cases.

^bIncludes Hispanic/Latino, Asian/Pacific Islander, Black/African American, and Mixed Races/Ethnicity.

^cInterventions are not mutually exclusive, and include any interventions before the age 7 assessment. Intervention data were missing for 3 SSC cases and 1 control

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Table 2

Distribution of attention and executive function scores for children with and without single suture craniosynostosis (SSC).

Outcome	Controls			All SSC Cases			Sagittal		Metopic		Unicoronal		Lambdoid	
	N	Mean (SD)		N	Mean (SD)		N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
TEA-Ch^a														
Sky Search	180	7.1 (2.5)		174	7.3 (2.6)		76	6.9 (2.6)	44	7.7 (3.0)	42	7.8 (2.1)	12	7.5 (2.3)
Score!	180	8.2 (3.1)		175	7.9 (3.3)		75	8.3 (3.3)	45	7.4 (3.4)	43	7.7 (3.3)	12	7.1 (2.2)
Sky Search DT	180	7.1 (4.5)		173	6.4 (4.5)		75	6.7 (4.5)	43	5.9 (4.5)	43	6.2 (4.9)	12	6.8 (3.5)
Score DT	180	9.1 (3.1)		174	8.2 (3.2)		75	8.3 (2.7)	44	8.1 (3.7)	43	8.3 (3.4)	12	8.4 (3.9)
WISC-IV^a														
Digit Span	183	10.5 (2.8)		178	10.0 (2.7)		76	10.0 (2.5)	45	9.8 (3.1)	45	10.2 (2.8)	12	9.7 (2.6)
Letter-Number Sequencing	182	11.3 (3.3)		178	10.9 (3.3)		76	11.1 (3.4)	45	10.9 (3.6)	45	10.8 (3.0)	12	10.7 (1.7)
NEPSY^a														
Inhibition Combined	179	9.7 (3.2)		174	8.8 (3.3)		75	9.0 (3.0)	43	9.0 (3.7)	44	8.6 (3.4)	12	7.9 (4.0)
Inhibition Total Errors	174	10.1 (3.4)		165	8.9 (4.1)		72	9.6 (3.9)	41	8.4 (4.5)	40	8.3 (4.0)	12	8.4 (4.0)
BRIEF:Parent^b														
Behavioral Regulation	177	50.4 (10.6)		163	50.6 (10.3)		71	49.9 (10.3)	40	53.0 (10.8)	41	50.6 (10.4)	10	45.5 (7.3)
Meta-Cognition	177	51.6 (10.3)		162	52.3 (9.9)		70	51.3 (9.6)	40	54.4 (9.7)	41	52.8 (10.9)	10	48.8 (7.2)
Global Executive Function	177	51.5 (10.4)		162	52.1 (10.0)		70	51.1 (9.8)	40	54.4 (10.1)	41	52.3 (10.8)	10	47.7 (5.6)
BRIEF:Teacher^b														
Behavioral Regulation	137	48.3 (8.3)		126	50.0 (10.3)		57	48.0 (7.9)	31	52.3 (14.1)	28	52.4 (10.1)	9	47.4 (7.5)
Meta-Cognition	137	48.4 (9.6)		126	50.7 (10.7)		57	48.1 (9.3)	31	53.3 (12.1)	28	53.1 (10.7)	9	50.2 (11.9)
Global Executive Function	137	48.3 (8.9)		126	50.4 (10.4)		57	47.9 (8.5)	31	52.9 (12.7)	28	52.9 (10.4)	9	49.2 (10.6)
ASEBA:Parent^b														
Attention	172	54.6 (6.0)		172	55.4 (7.1)		74	54.7 (6.9)	42	56.5 (6.8)	43	55.8 (8.1)	12	54.5 (6.1)
ASEBA:Teacher^b														
Attention	135	53.1 (5.3)		131	55.0 (7.1)		62	53.3 (4.5)	31	57.3 (8.7)	27	56.3 (9.3)	10	54.9 (6.2)

^aThe TEA-Ch, WISC-IV, and NEPSY subscales use scaled scores (norm-referenced mean=10, standard deviation=3).

^bThe BRIEF and ASEBA use T-scores (norm-referenced mean=50, standard deviation=10).

Table 3

Mean differences in executive function and attention scores for children with and without single suture craniosynostosis (SSC).

Outcome	Unadjusted SSC Case v. Control Differences		Adjusted ^a SSC Case v. Control Differences	
	Mean Difference (95% CI)	p-value	Mean Difference (95% CI)	p-value
TEA-Ch^b				
Sky Search	0.25 (-0.28, 0.78)	0.36	0.31 (-0.24, 0.85)	0.27
Score!	-0.38 (-1.04, 0.29)	0.27	-0.31 (-0.98, 0.37)	0.38
Sky Search DT	-0.69 (-1.63, 0.26)	0.16	-0.51 (-1.45, 0.44)	0.30
Score DT	-0.85 (-1.51, -0.20)	0.01	-0.68 (-1.34, -0.02)	0.04
WISC-IV^b				
Digit Span	-0.53 (-1.09, 0.04)	0.07	-0.19 (-0.73, 0.35)	0.49
Letter-Number Sequencing	-0.39 (-1.06, 0.29)	0.265	0.14 (-0.49, 0.76)	0.67
NEPSY^b				
Inhibition Combined	-0.85 (-1.54, -0.17)	0.02	-0.68 (-1.38, 0.01)	0.06
Inhibition Total Errors	-1.25 (-2.05, -0.44)	0.003	-0.91 (-1.71, -0.11)	0.03
BRIEF:Parent^c				
Behavioral Regulation	0.19 (-2.05, 2.42)	0.87	-0.06 (-2.43, 2.31)	0.96
Meta-Cognition	0.69 (-1.46, 2.85)	0.53	0.18 (-2.02, 2.39)	0.87
Global Executive Function	0.56 (-1.62, 2.74)	0.61	0.16 (-2.11, 2.43)	0.89
BRIEF:Teacher^c				
Behavioral Regulation	1.63 (-0.65, 3.92)	0.16	1.12 (-1.21, 3.45)	0.35
Meta-Cognition	2.26 (-0.21, 4.73)	0.07	1.21 (-1.35, 3.77)	0.36
Global Executive Function	2.08 (-0.28, 4.44)	0.08	1.18 (-1.26, 3.62)	0.34
ASEBA:Parent^c				
Attention	0.79 (-0.61, 2.19)	0.27	0.42 (-0.98, 1.82)	0.56
ASEBA:Teacher^c				
Attention	1.94 (0.43, 3.45)	0.01	1.49 (-0.07, 3.04)	0.06

^aAdjusted for age (continuous), sex, SES (continuous), maternal IQ (continuous).

^bThe TEA-Ch, WISC-IV, and NEPSY subscales use scaled scores (norm-referenced mean=10, standard deviation=3).

^cThe BRIEF and ASEBA use T-scores (norm-referenced mean=50, standard deviation=10).

Table 4

Mean differences in executive function and attention scores for children with sagittal (reference group), metopic, unicoronal, and lambdoid synostosis.

Outcome	Metopic vs. Sagittal		Unicoronal vs. Sagittal		Lambdoid vs. Sagittal		Group difference p-value
	Mean Difference ^a (95% CI)	p-value	Mean Difference ^a (95% CI)	p-value	Mean Difference ^a (95% CI)	p-value	
TEA-Ch^b							
Sky Search	0.91 (-0.16, 1.98)	0.10	0.84 (-0.07, 1.76)	0.07	0.30 (-1.24, 1.83)	0.71	0.20
Score!	-0.76 (-2.03, 0.50)	0.24	-0.45 (-1.79, 0.88)	0.51	-1.36 (-3.00, 0.28)	0.11	0.35
Sky Search DT	-0.48 (-2.15, 1.20)	0.58	-0.19 (-2.02, 1.64)	0.84	-0.15 (-2.45, 2.15)	0.90	0.96
Score DT	0.03 (-1.23, 1.29)	0.96	-0.04 (-1.20, 1.13)	0.95	-0.83 (-2.96, 1.30)	0.45	0.90
WISC-IV^b							
Digit Span	-0.04 (-0.97, 0.89)	0.93	0.18 (-0.88, 1.25)	0.74	-0.51 (-2.33, 1.32)	0.59	0.92
Letter-Number Sequencing	-0.01 (-1.16, 1.15)	0.99	-0.67 (-1.84, 0.50)	0.26	-0.40 (-1.84, 1.04)	0.59	0.66
NEPSY^b							
Inhibition Combined	0.16 (-1.14, 1.46)	0.81	-0.72 (-1.99, 0.55)	0.27	-1.58 (-3.94, 0.78)	0.19	0.41
Inhibition Total Errors	-1.03 (-2.56, 0.51)	0.19	-1.83 (-3.38, -0.28)	0.02	-1.62 (-4.35, 1.10)	0.24	0.10
BRIEF:Parent^c							
Behavioral Regulation	3.00 (-1.19, 7.18)	0.16	1.19 (-3.01, 5.39)	0.58	-4.47 (-10.12, 1.17)	0.12	0.10
Meta-Cognition	3.17 (-0.57, 6.91)	0.10	1.83 (-2.32, 5.97)	0.39	-1.88 (-7.38, 3.62)	0.50	0.24
Global Executive Function	3.25 (-0.67, 7.16)	0.11	1.68 (-2.44, 5.80)	0.43	-2.89 (-7.73, 1.95)	0.24	0.11
BRIEF:Teacher^c							
Behavioral Regulation	3.93 (-1.51, 9.37)	0.16	4.35 (-0.31, 9.02)	0.07	-1.70 (-8.41, 5.02)	0.62	0.12
Meta-Cognition	5.13 (0.32, 9.94)	0.04	4.98 (-0.01, 9.98)	0.05	1.96 (-7.21, 11.13)	0.68	0.09
Global Executive Function	4.86 (-0.12, 9.85)	0.06	5.00 (0.18, 9.82)	0.04	0.80 (-7.69, 9.30)	0.85	0.08
ASEBA:Parent^c							
Attention	1.57 (-1.07, 4.21)	0.25	1.44 (-1.68, 4.56)	0.37	-1.17 (-4.91, 2.57)	0.54	0.41
ASEBA:Teacher^c							
Attention	3.46 (0.23, 6.69)	0.04	2.83 (-1.43, 7.09)	0.20	1.84 (-2.98, 6.65)	0.46	0.09

^a Adjusted for age (continuous), sex, SES (continuous), maternal IQ (continuous).

^b The TEA-Ch, WISC-IV, and NEPSY subscales use scaled scores (norm-referenced mean=10, standard deviation=3).

The BRIEF and ASEBA use T-scores (norm-referenced mean=50, standard deviation=10).

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Table 5

Mean differences in executive function and attention scores for children with single suture craniosynostosis (SSC) receiving surgery younger versus older than the median age.^a

Outcome	< median age at surgery	median age at surgery	median age vs. < median age	
	N	N	Mean Difference ^b (95% CI)	p-value
TEA-Ch^c				
Sky Search	81	91	0.61 (-0.24, 1.46)	0.16
Score!	82	91	0.16 (-0.88, 1.19)	0.76
Sky Search DT	82	89	0.57 (-0.90, 2.04)	0.45
Score DT	82	90	-0.72 (-1.64, 0.19)	0.12
WISC-IV^c				
Digit Span	83	93	-0.88 (-1.61, -0.15)	0.02
Letter-Number Sequencing	83	93	-0.91 (-1.79, -0.03)	0.04
NEPSY^c				
Inhibition Combined	82	90	0.15 (-0.87, 1.18)	0.77
Inhibition Total Errors	76	87	-0.74 (-1.96, 0.49)	0.24
BRIEF:Parent^d				
Behavioral Regulation	78	82	2.32 (-0.95, 5.60)	0.17
Meta-Cognition	78	81	2.29 (-0.91, 5.49)	0.16
Global Executive Function	78	81	2.48 (-0.74, 5.70)	0.13
BRIEF:Teacher^d				
Behavioral Regulation	58	65	1.76 (-2.00, 5.52)	0.36
Meta-Cognition	58	65	0.61 (-3.29, 4.52)	0.76
Global Executive Function	58	65	1.12 (-2.72, 4.96)	0.57
ASEBA:Parent^d				
Attention	81	88	-0.07 (-2.21, 2.08)	0.95
ASEBA:Teacher^d				
Attention	61	67	-1.16 (-3.61, 1.29)	0.36

^aMedian age at surgery was 5.1 months for sagittal cases and 9.1, 9.7, and 9.5 months for metopic, unicoronal, and lambdoid cases, respectively.

^bAdjusted for age (continuous), sex, SES (continuous), maternal IQ (continuous), and suture location (categorical).

^cThe TEA-Ch, WISC-IV, and NEPSY subscales use scaled scores (norm-referenced mean=10, standard deviation=3).

^dThe BRIEF and ASEBA use T-scores (norm-referenced mean=50, standard deviation=10).