Direct Brain Recordings Reveal Impaired Neural Function in Infants With Single-Suture Craniosynostosis: A Future Modality for Guiding Management?

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Background: Patients with single-suture craniosynostosis (SSC) are at an elevated risk for long-term learning disabilities. Such adverse outcomes indicate that the early development of neural processing in SSC may be abnormal. At present, however, the precise functional derangements of the developing brain remain largely unknown. Event-related potentials (ERPs) are a form of noninvasive neuroimaging that provide direct measurements of cortical activity and have shown value in predicting long-term cognitive functioning. The current study used ERPs to examine auditory processing in infants with SSC to help clarify the developmental onset of delays in this population.

Methods: Fifteen infants with untreated SSC and 23 typically developing controls were evaluated. ERPs were recorded during the presentation of speech sounds. Analyses focused on the P150 and N450 components of auditory processing.

Results: Infants with SSC demonstrated attenuated P150 amplitudes relative to typically developing controls. No differences in the N450 component were identified between untreated SSC and controls.

Conclusions: Infants with untreated SSC demonstrate abnormal speech sound processing. Atypicalities are detectable as early as 6 months of age and may represent precursors to long-term language delay. Electrophysiological assessments provide a precise examination of neural processing in SSC and hold potential as a future modality to examine the effects of surgical treatment on brain development.

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The impact of single-suture craniosynostosis (SSC) on intellectual development remains an important concern for craniofacial specialists, pediatricians, and parents. As the methods of neurologic testing have advanced, associations between cranial deformity and cognitive outcomes have gradually evolved. Previously considered by some as a solely cosmetic condition, SSC is now linked to a number of developmental difficulties.[1–4] In particular, studies using long-term neuropsychological testing have demonstrated that individuals previously treated for SSC exhibit normal intelligence but show an increased risk for learning impairments, most notably in language-related areas.[5–7]

Given the growing evidence of long-term intellectual sequelae in SSC, the evaluation of neural functioning in infant patients is critical. Studies examining early development in SSC have often relied on an informative, but limited, standardized measure—the Bayley Scales of Infant Development (BSID).[8–13] The BSID provides a standard series of measurements to score the motor, language, and cognitive development of children between 1 month and 42 months of age. However, although the BSID allows for evaluative scales in early life, it does not offer adequate insight into future intellectual and academic performance. In particular, lower scores in infancy have not shown a strong ability to predict long-term developmental or cognitive delays.[14–16]

Greater understanding of infant brain abnormalities in SSC is needed, as the early detection of neural dysfunction may help to clarify the etiology of long-term delays and, in turn, guide surgical management. Noninvasive neuroimaging provides a safe and efficacious means to gain insight into neural networks. The recording of event-related potentials (ERPs) is one such method that has shown value in predicting long-term outcomes from infant readings.[17–19] ERPs are extracted from continuous electroencephalogram (EEG) recordings and measure voltage changes in the brain in response to external stimuli. Of particular benefit is that ERP recordings do not depend on behavioral responses from participants, greatly facilitating their use in infants. Given their safe application and ability to examine complex patterns of neural functioning, ERPs are well suited to detect developmental abnormalities in very young patients.[20]

Electrophysiological brain recordings have previously demonstrated utility in evaluating neural functioning in craniosynostosis. In particular, auditory brainstem responses have been utilized to identify hearing abnormalities in infants with syndromic craniosynostosis; such measures may provide a means for the early detection of auditory nerve compression.[21]

TABLE 1. Participant Characteristics

	N	Sex (N_{male})	Age (mo)	
			M (SD)	Range
Typically developing	23	15	7.1 (2.7)	3–12
Craniosynostosis	15	9	6.4 (2.2)	3–11

Neural responses to auditory stimuli also represent an important tool in the early identification of language delay. A close connection exists between auditory processing and the intact development of language skills.[22,23] Indeed, ERP studies have demonstrated that neural response to speech sounds show value in predicting rates of dyslexia and other language impairments.[24,25]

The current study examined the cortical response to speech sounds in infants with SSC. ERP analyses focused on segments of the P150–N250–N450 complex, a response pattern that typifies school-age auditory processing and whose precursors are evident in early life.[26] In an earlier study, we implemented this analytic strategy to evaluate cortical response in deformational plagiocephaly, finding normative patterns of language development in affected infants.[27] In the current study, we aimed to identify possible auditory processing anomalies in SSC, which may shed light on the underlying causes of long-term delays.

Given the increased prevalence of learning disabilities in older children and adolescents previously treated for SSC, we hypothesized that affected infants would demonstrate early abnormalities in speech sound processing.

SUBJECTS AND METHODS

Participants

Fifteen infants with untreated SSC and 23 typically developing infant controls without head shape deformity participated in the study (Table 1). The SSC group was comprised of 8 infants with metopic craniosynostosis, 5 infants with sagittal craniosynostosis, and 2 infants with unicoronal craniosynostosis. Cases of SSC were diagnosed at the Craniofacial Center of Yale–New Haven Children's Hospital. Exclusion criteria consisted of pre-existing neurological disorders, a history of hearing difficulties, and a history of prenatal or perinatal complications, such as traumatic head injury or hemorrhage. This study was conducted with written consent from the participants' legal guardians and with approval from the Human Investigations Committee at Yale University.

Experimental Design

The experimental paradigm implemented auditory presentations of the English retroflex phoneme, /Da/. Participants were situated 90 cm from 2 loudspeakers, which delivered stimuli at 80 dB. The Hindi dental phoneme, /da/, was also presented during the paradigm; because the chronological age range of the sample did not permit analysis of how responses to non-native phonemes change over time, the analyses in this initial study focused exclusively on the English phoneme.

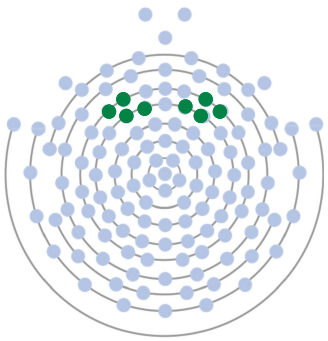

FIGURE 1. Electrode layout showing the frontal scalp regions examined (green).

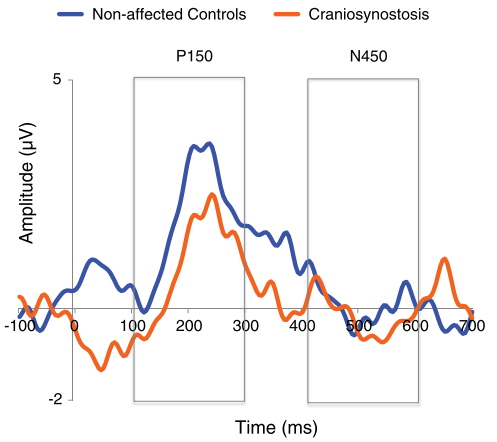

FIGURE 2. Aggregate ERP waveforms from craniosynostosis and non-affected controls over the left frontal scalp illustrating the P150 and N450 components.

Data Collection, Processing, and Analyses

A 128-lead Geodesic Sensor Net Hydrocel (Electrical Geodesics, Inc., Eugene, OR, USA) was used for data collection. Electrical impedances were maintained below 40 kΩ throughout the experiment. EEG data were sampled at a frequency of 250 Hz using NetStation 4.5. The central electrode Cz was used as a reference for all other electrodes. During the experiment, each infant was seated in his or her parent's lap or in an infant highchair. Infants passively viewed bubbles while phonemes were presented.

EEG data processing was completed with NetStation 4.5 software. Frequencies lower than 0.1 Hz or higher than 30 Hz were filtered out to minimize fluctuations in the data. Data were segmented into an epoch from 100 ms before stimulus onset to 700 ms after stimulus onset.

Examination of averaged waveforms revealed an initial positive inflection (P150), followed by a smaller negative deflection (N450). The maximum amplitude and latency of the P150 component were extracted between 100 and 300 ms post-stimulus. The maximum amplitude and latency of the N450 component were

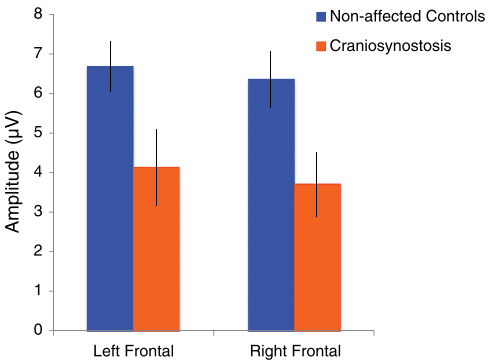

FIGURE 3. Mean P150 amplitudes (±SEM) from infants with craniosynostosis and non-affected controls. The cortical response to language is significantly reduced in infants with craniosynostosis.

extracted between 400 and 600 ms post-stimulus. Data were averaged across electrode clusters over the left (19, 23, 24, 27) and right (3, 4, 123, 124) frontal scalp (Fig. 1).

Analyses of amplitudes and latencies for the P150 and N450 components were completed with separate univariate repeated measures ANOVA using group as a between subjects factor and hemisphere as a within subjects factor. Post hoc independent samples *t* test was performed to examine group differences at specific scalp regions.

RESULTS

Figure 2 presents grand averaged ERP waveforms from infants with SSC and control participants, highlighting the P150 and N450 components.

P150 Component

The maximum amplitude and latency of the P150 component were compared between the 2 groups across the frontal scalp regions of interest. A significant effect of group was identified for the P150 amplitude, with decreased amplitudes observed in SSC patients relative to controls [$F(1, 36) = 6.55$, $P < 0.05$]. Post hoc independent samples *t* test confirmed significantly decreased P150 amplitudes over both the left frontal region ($P < 0.05$) and right frontal region ($P < 0.05$) in patients with SSC (Fig. 3). The latency of the P150 component did not differ between SSC patients and controls.

N450 Component

The maximum amplitude and latency of the N450 component were also compared between SSC patients and non-affected controls. There were no significant effects for either amplitude or latency.

DISCUSSION

Neuropsychological studies have demonstrated that SSC patients face an increased risk of long-term cognitive delay.[4–7] The presence of these adverse outcomes suggests that the early development of neurologic processing follows an abnormal trajectory. However, the precise functional derangements of the infant brain in SSC remain largely unknown.

The current study aimed to address this knowledge gap by evaluating auditory processing in infants with SSC. Decreased amplitudes of the P150 component were observed in affected patients, indicating depressed cortical response to language stimulation. These findings provide the first evidence of impaired speech sound processing in infants with untreated SSC.

Previously, Balan and colleagues[28] conducted auditory ERPs to examine neural functioning in infants with cranial asymmetry. The authors examined cortical response to synthetic tonal stimuli, identifying decreased amplitudes in a composite group that included 3 patients with coronal craniosynostosis and 2 patients with lambdoid craniosynostosis. Our results support these preliminary observations of abnormal auditory processing in SSC and extend their relevance to speech sound stimuli and a larger sample size. Numerous studies have demonstrated the relevance of speech sound stimuli in accurately examining language function.[19,24,25,29]

The presence of impaired speech sound processing in SSC may represent a precursor to long-term learning disabilities. In infants studies, analysis of short latency ERP components has demonstrated that 5-month-olds at high risk for dyslexia exhibit attenuated neural response to speech sounds.[30] In older children and adolescents with severe language impairment, decreased amplitudes of this component have also been observed.[31]

While the current study found abnormal P150 patterns in patients with SSC, no atypicalities were identified in N450 patterns. This dissimilarity may be related to the fact that early ERP components represent lower-order sensory processing of stimuli, whereas later ERP components represent higher-order cognitive interpretation. Given that our stimuli entailed basic phonemes, the study paradigm may not have engaged the neurological centers of higher-order processing to a sufficient degree to distinguish between cases and controls at this level. Alternatively, our findings may indicate that lower-level discriminative processes are impacted whereas subsequent processes are preserved.

A limitation of the current study lies in its inability to provide differentiation between the various forms of SSC. Due to the small sample size of each SSC variant, 3 forms of SSC were combined together for statistical comparison. This analytical strategy limits the ability of the current study to examine the effects that different suture pathology may have on language development. Continued study is needed with larger samples to identify possible correlations between the location of suture pathology and the degree of processing atypicality. It is also important to emphasize that the purview of this investigation was limited to speech sound processing and language development. Given the range of long-term impairments that have been identified in SSC, electrophysiological studies exploring different realms of neural processing will prove informative.

Results from the current study strongly suggest a future role for ERPs in evaluating the effects of surgery on brain development. The role of intervention in ameliorating neuropsychological outcomes remains controversial. Operative treatment has been considered by some as a solely cosmetic procedure that conveys no significant benefit to cognitive functioning.[4,32,33] Previous studies have implemented the BSID to examine the effects of surgical intervention on short-term developmental outcomes in SSC, with results showing little evidence of beneficial effect.[33–36]

The sensitivity of electrophysiological modalities can provide new perspectives, as they allow for the detection of subtle changes in function that behavioral measures may not reveal. Patients from the current study are therefore being followed longitudinally and evaluated postoperatively. The examination of these results may provide insight into the ultimate effects of surgical intervention beyond cosmesis.

In summary, we present novel electrophysiological data demonstrating that speech sound processing abnormalities exist in infants with untreated SSC. The presence of these neurologic derangements can be detected as early as 6 months of age.

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