Normalization of Speech Processing After Whole-Vault Cranioplasty in Sagittal Synostosis

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Background: Neurocognitive studies have found impairments in language-related abilities in nonsyndromic craniosynostosis, highlighting clinical importance of early language processing. In this study, neural response to speech sounds in infants with nonsyndromic sagittal craniosynostosis (NSC) is compared, preoperatively and postoperatively, using event-related potentials (ERPs) to objectively characterize development in language processing.

Methods: Electroencephalogram was recorded while 39 infants (12 NSC and 27 controls; ages 73–283 days) listened to the Hindi dental /d̪a/ and retroflex /ɖa/ phonemes (non-native phonemic discrimination task). The mismatch negativity (MMN) ERP was extracted as the peak amplitude of the largest negative deflection in the difference wave over 80 to 300 milliseconds poststimulus. Differences in MMN were analyzed using repeated measures analysis of variance.

Results: The MMN amplitude was attenuated in the infants with NSC preoperatively compared with controls ($P = 0.047$). A significant region by group interaction ($P = 0.045$) was observed, and infants with NSC displayed attenuated MMN in the frontal electrodes compared with controls ($P = 0.010$). Comparing the preoperative and postoperative MMN, a time by group interaction trend ($P = 0.070$) was observed. Pair-wise comparisons showed a trend for increase in MMN amplitude from preoperatively to postoperatively in the infants with NSC ($P = 0.059$). At the postoperative time point, infants with NSC showed no significant difference in MMN from controls ($P = 0.344$).

Conclusion: Infants with NSC demonstrated atypical neural response to language preoperatively. After undergoing surgery, infants with NSC showed increased MMN amplitude which was not significantly different from controls. These findings support the idea that whole vault cranioplasty may improve neurocognitive outcomes in sagittal craniosynostosis.

Key Words: Craniosynostosis, event-related potential, language processing, neurocognitive outcome, sagittal synostosis

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Previous studies of children with craniosynostosis have found neurologic sequelae, including elevated intracranial pressure and suboptimal neurocognitive outcome,[1–3] potentially due to constraint of brain growth and development secondary to the fused suture and associated skull deformity.[4] There is increasing evidence of poor neurocognitive outcomes in school-age children with craniosynostosis, even in children who have undergone surgical correction. Specifically, compared with population norms and their typically developing (TD) peers, children with craniosynostosis perform more poorly on measures of general cognitive function (IQ and memory), language, reading, and spelling.[5–7] Children with craniosynostosis also have increased frequency of individualized educational program utilization.[8] A goal of surgical correction is to reduce potential deleterious neurocognitive effects of craniosynostosis. However, impact of cranial vault remodeling surgery on neurocognitive outcome is difficult to study due to lack of patients with nonsyndromic sagittal craniosynostosis (NSC) who do not undergo correctional surgery, as few families decline surgical treatment for this condition.

Neurocognitive deficits associated with craniosynostosis in infancy are poorly characterized. Even with sophisticated neurocognitive testing, validated measures of outcome are not truly stable until years after surgical intervention.[9] Previously, the Bayley Scales of Infant Development (BSID) have been used to assess neurocognitive outcome in infants with craniosynostosis.[10,11] However, this measure demonstrates only modest correlation with long-term neurocognitive functioning.[12–15] As such, better methods for measurement of neurocognitive functioning (or neurocognitive potential, associated with future neurocognitive functioning) in infancy are needed to enable evaluation before and after surgery to assess neurocognitive outcome and how it changes with surgery. Furthermore, such measures could be used preoperatively in children with craniosynostosis to evaluate which patients are at higher risk for neurocognitive deficits and would more likely benefit from surgery from a neurocognitive standpoint. The resulting models from these studies could frame the subsequent recommendation for treatment with knowledge of which children are most likely to benefit most from a particular type or timing of treatment.

Early language processing is of particular importance in craniosynostosis because neurocognitive studies of school-age children with craniosynostosis reveal impairments in language-related abilities (eg, reading and spelling).[5,16] In a previous study, we used a technique to detect neural response to speech sounds in infants,

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known as auditory event-related potentials (ERPs).[17] ERPs are small voltages generated in cortical structures in response to specific events/stimuli, derived from averaged electroencephalograms (EEGs) with repeated stimuli and multiple participants.[18] Many types of sensory, cognitive, and motor events generate ERPs. In this study, we focus on auditory ERPs, which are time-locked to the onset of specific auditory stimuli. Auditory ERPs have been found to correlate with language abilities in school-aged children.[19,20] Our previous work demonstrated that infants with craniosynostosis have attenuated P150 responses to speech sounds compared with TD controls.[17] The P150 reflects neural processes related to recognition of the acoustic features of auditory stimuli, such as a fundamental frequency, which modulates perception.[21] The auditory mismatch negativity (MMN) component is another ERP that has been found to be highly associated with language processing via auditory memory and attention to auditory input.[21,22] The MMN reflects both acoustic and higher level preattentive perceptual processes that may be more closely related to language outcomes, compared with the P150. The MMN and related tasks in infancy have been found to be associated with language ability later in life, such as word understanding, word production, and phrase understanding.[23] In the present study, the use of the MMN expands on our previous work by examining an auditory ERP reflecting speech discrimination, a higher-order measure of language development. We studied language processing changes in the MMN ERP preoperatively to postoperatively in NSC.

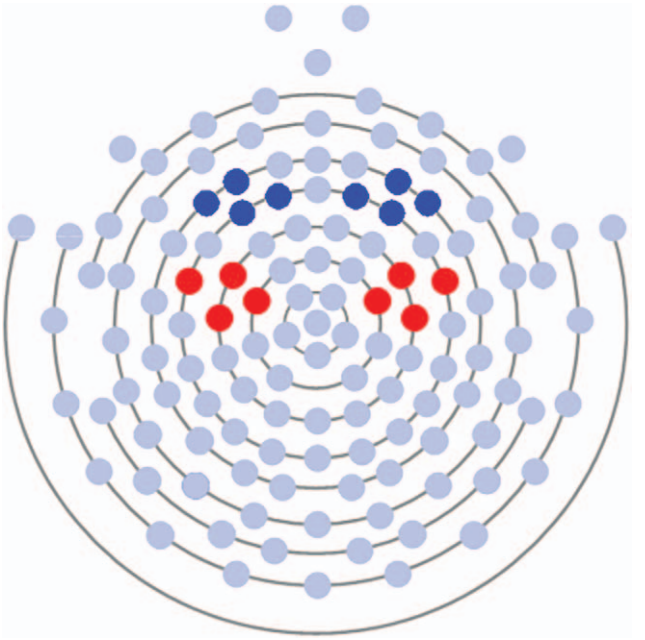

FIGURE 1. Central (red) and frontal (blue) electrodes used for analysis of the mismatch negativity.

METHODS

Participants

This study was approved by the Yale University institutional review board, and written informed consent was obtained for each participant. Twelve infants with NSC and 27 TD infants participated in the study. The initial visit occurred at age 60 to 300 days, and the second visit occurred at age 210 to 480 days. The visits corresponded with preoperative and postoperative timing for the sagittal craniosynostosis group, although the control group was also assessed at these 2 time points. No statistical differences in gender were observed between groups. Mean age at the initial (preoperative) time point was 133 days (SD 45 days) in the NSC group and 171 days (SD 50 days) in the TD group. The NSC group was significantly younger than the TD group ($P < 0.05$) at the initial time point. Mean age at the second (postoperative) time point was 359 days (SD 78 days) in the NSC group and 366 days (SD 56 days) in the TD group. There was no statistical difference in age at the second time point. Exclusionary criteria included any known neurologic disorder (eg, brain malformations, microcephaly), prenatal and perinatal complications, intracranial hemorrhage, or hearing impairment. For all participants, English was the only language spoken in the home.

Experimental Design

In the current experiment, we used a non-native phoneme discrimination task. The experimental paradigm implemented equiprobable presentations of consonant vowel stimuli containing the Hindi retroflex /ɖ/ or Hindi dental /d̪/ speech sounds (/ɖa/ or /d̪a/, respectively). For native English speakers, these speech sounds are not-distinct variants of an English /da/. The stimuli were presented in 5 blocks, with 20 trials per block. Each phoneme was presented 10 times per block in random order. An equiprobable design was used instead of an oddball paradigm because the participants were infants with limited ability to tolerate a lengthy experimental paradigm. Previous work has shown phonemic discrimination in the MMN time range in both equiprobable and oddball paradigms.[24] The stimulus duration was 250 milliseconds with a constant interstimulus interval of 610 milliseconds. Block duration was 17.2 seconds with total experiment duration of 86 seconds. A trained research associate administered a neuropsychologic assessment, the BSID, to assess general infant developmental function.[25]

Data Acquisition and Analysis

The EEG was recorded with an Electrical Geodesics, Inc, Net Amps 300 system using a 124-channel HydroCel Geodesic Sensor Net, and data were sampled at 250 Hz. The EEG was segmented into an epoch from 100 milliseconds prestimulus to 700 milliseconds poststimulus, baseline-corrected, filtered (0.1–30 Hz), and corrected for artifacts (eg, eye blink, eye movement, bad channels with 200 μV difference over entire segment with no moving average) using NetStation 4.5.4 (EGI, Eugene, OR). Two clusters of electrodes, 1 central and 1 frontal (Fig. 1) were selected for analysis based on previous studies that have identified a frontocentral topographic distribution for the MMN.[26] The MMN was computed as the largest negative amplitude in the difference wave (obtained by subtracting the dental from the retroflex response) between 80 and 300 milliseconds. This time window was selected based on previous literature describing the MMN.[26]

RESULTS

Preoperative/initial time point BSID assessment scores were available for 13 TD infants and 9 infants with NSC. Mean cognitive score on the BSID was 111 (standard deviation [SD] 11) in the NSC group and 107 (SD 13) in the TD group ($P = 0.551$). Mean language score on the BSID was 103 (SD 15) in the NSC group and 98 (SD 15) in the TD group ($P = 0.502$). The BSID cognitive and language scores were not significantly different between groups.

Statistical analysis of the MMN ERP was performed using a $2 \times 2 \times 2 \times 2$ mixed model, repeated measures analysis of variance with group as a between-subjects factor and preoperative or postoperative visit, brain region, and hemisphere as within-subjects factors.

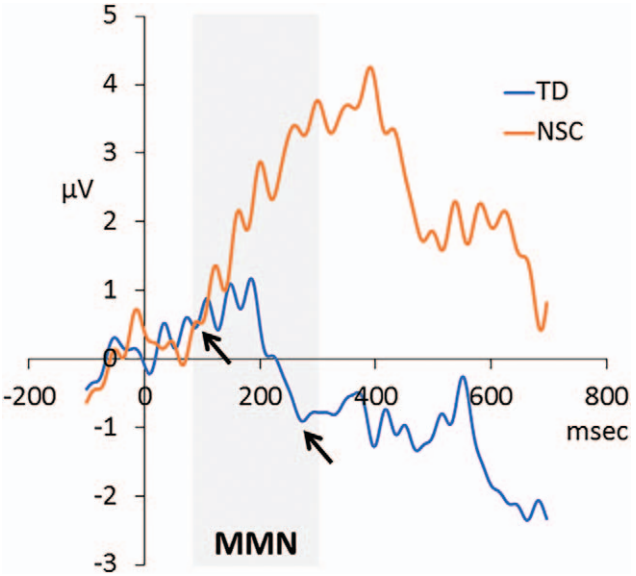

FIGURE 2. Grand averaged difference wave in the TD infants versus infants with NSC preoperatively. Arrows indicate location of the MMN on the difference wave. MMN, mismatch negativity; NSC, nonsyndromic sagittal craniosynostosis; TD, typically developing.

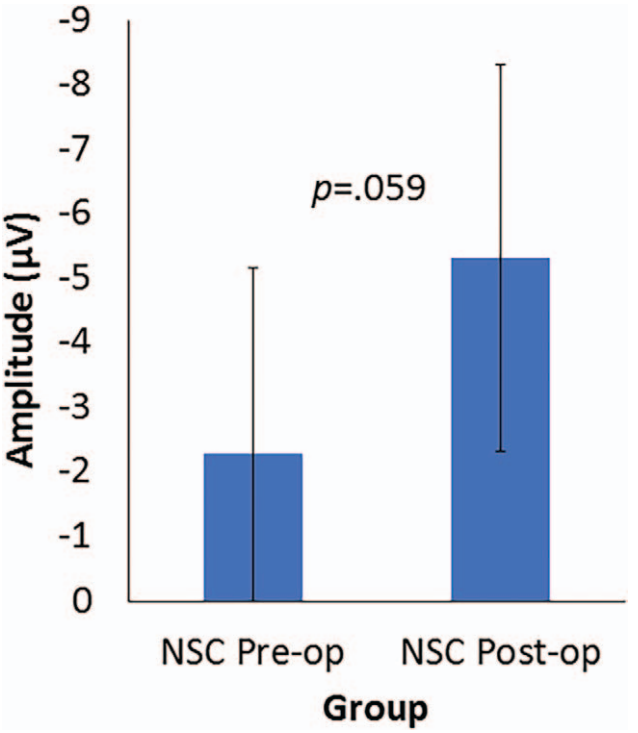

FIGURE 4. Comparison of mismatch negativity amplitude preoperatively versus postoperatively in infants with NSC. NSC, nonsyndromic sagittal craniosynostosis.

The grand averaged difference waves for the NSC and TD groups at the initial time point are shown in Figure 2. At the initial time point (n = 39; 27 TD, 12 preoperative NSC), a significant effect of group was observed ($P = 0.047$) such that infants with NSC displayed attenuated MMN compared with TD infants (Fig. 3A). A significant region by group interaction was also observed ($P = 0.045$), and pair-wise comparisons revealed preoperative infants with NSC displayed attenuated MMN compared with TD infants in the frontal region ($P = 0.010$). This was not significant in the central region. A significant region by hemisphere interaction was observed ($P = 0.012$) with pair-wise comparisons showing a trend of higher MMN amplitude in the frontal region compared with the central region ($P = 0.074$) in the left hemisphere. No other interactions were significant.

For participants who were assessed at both time points (n = 24; 16 TD and 8 NSC), a trend of time by group ($P = 0.070$) was observed. Pair-wise comparisons revealed a marginal increase in the MMN amplitude from the preoperative to postoperative time points in the infants with NSC ($P = 0.059$), shown in Figure 4. The TD infants showed no significant change in MMN amplitude ($P = 0.641$). At the second time point, no significant difference in MMN amplitude was observed between the infants with NSC and TD infants ($P = 0.344$, Fig. 3B). The grand averaged difference waves for the infants with NSC and TD infants at the second time point are shown in Figure 5.

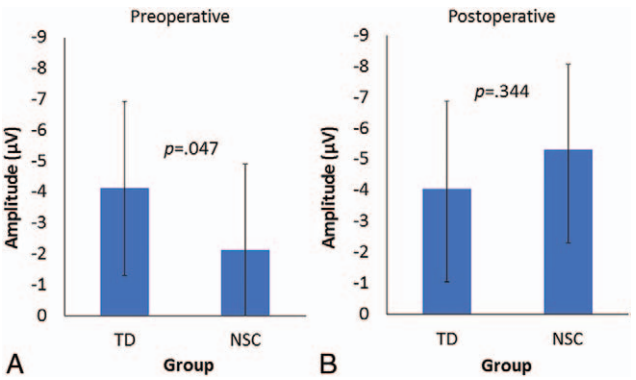

FIGURE 3. (A) Significant difference of MMN amplitude between TD infants and infants with NSC preoperatively. (B) Nonsignificant difference of MMN amplitude between TD infants and infants with NSC postoperatively. MMN, mismatch negativity; NSC, nonsyndromic sagittal craniosynostosis; TD, typically developing.

DISCUSSION

We measured infants' response to speech using auditory ERPs, a methodology shown previously to correlate with future language outcomes in school-age children.[19,20] Infants with NSC demonstrated atypical speech sound processing, as evidenced by reduced MMN response in frontal regions, compared with control infants prior to surgery. After undergoing surgery, response to speech normalized in infants with NSC such that they showed no difference from TD infants. This suggests that skull remodeling surgery was associated with a normalization of language processing.

This study is consistent with our previous work that identified abnormal language processing in infants with craniosynostosis[17] and expands upon and further refines our previous work in several ways. Critically, this study examined ERP response to speech both preoperatively and postoperatively to measure the impact of surgery on language processing. Our findings reveal a marginal change in ERP between these 2 time points, suggesting normalization of response to speech. In addition, we studied a different ERP component called the MMN, a neural measure of discrimination which is analyzed as a difference wave, which represents the subtraction of the average response to 2 different stimuli. Using an ERP difference waveform as the dependent variable may reduce the impact of some infant-specific factors on the ERP such as skull thickness, because

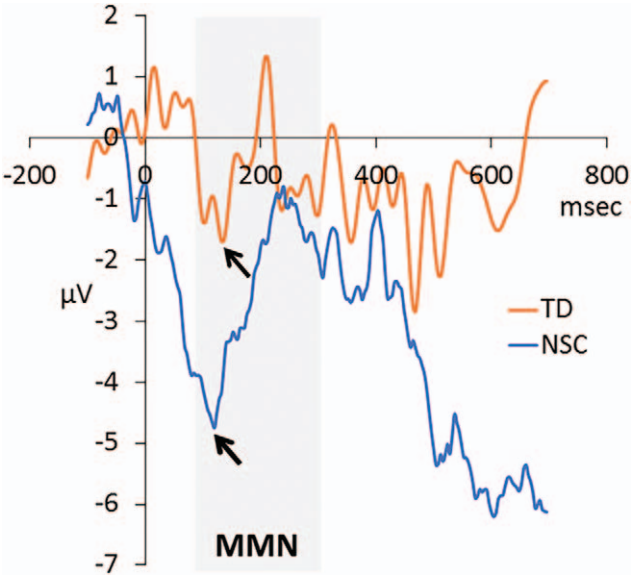

FIGURE 5. Grand averaged difference wave in the TD infants versus infants with NSC postoperatively. Arrows indicate location of the MMN on the difference wave. MMN, mismatch negativity; NSC, nonsyndromic sagittal craniosynostosis; TD, typically developing.

absolute differences in magnitude cancel out when subtracting responses to the 2 phonemes. This is particularly useful for studying a population with craniosynostosis in which skull thickness variation is common both before and after skull remodeling surgery. In addition, the MMN reflects discrimination of distinct auditory stimuli, involving auditory sensory memory.[21] Thus, the MMN reflects an ability to perceive different acoustic sounds in speech and is thought to influence later language skills through various mechanisms. With speech discrimination developing over time, differential ability in initial phonetic perception may impact language acquisition. Phonetic perception skills in infancy are important for identifying words in ongoing speech, and previous studies on children with language problems show deficits in phonetic perception skills, indicating a possible link between the two.[23] Our previous study used the P150 ERP component, which is thought to reflect acoustic processing in recognizing sound characteristics such as pitch and intensity.[27] The current study builds on this work by examining the next step of sound processing, phonemic discrimination. In addition to analyzing a different ERP component, this study includes one specific form of craniosynostosis (sagittal), while our previous study included metopic, sagittal, and unicoronal synostoses. Examining only one form of craniosynostosis eliminates potential variation that could exist between the different synostoses. Study of preoperative and postoperative ERPs grouped by specific type of craniosynostosis has potential for more refined evaluation of speech/language outcomes in assessments of merits of different treatment options.

Historical studies on neurocognitive status of infants in craniosynostosis using the BSID initially suggested no differences in cognitive or motor performance.[10] These findings were later contradicted by studies of school-age intelligence and academic performance.[5,28] The opposing results may have occurred due to modest correlation of infant neurodevelopmental assessments with future intellectual and academic functioning, especially with earlier age at testing.[12–15] This is supported by our current study, as we also detected no significant differences in the cognitive and language scores on the BSID between the TD and NSC groups before surgery, despite the fact we observed differences in speech processing in our ERP findings, and that previous studies show poor school-age neurocognitive outcomes in nonsyndromic craniosynostosis compared with population norms and controls.[5,7]

Lack of reliable infant neuropsychologic testing measures brings up challenges because, in effect, we lack a tool to measure neurocognitive function reliably associated with future school-age function before the time of treatment. Auditory ERPs could address this issue by providing a predictive tool to measure infant neurocognitive function, if future studies find strong sensitivity and specificity for future language abilities in craniosynostosis. This assessment of function could be used to measure impact of surgery, as done in this study, and extend this analysis to measure impact of different treatment modalities closer to the time of treatment in infancy without having to wait 5 or more years for school-age neurocognitive testing. Auditory ERPs could also be used to identify individuals more at risk for neurocognitive deficits with more potential benefit from surgery. Further studies that correlate auditory ERPs such as the MMN and P150 with school-age neuropsychologic testing in craniosynostosis can evaluate the predictive value of auditory ERPs in this population.

A limitation of this study was the lack of a nonoperated control group of patients with sagittal synostosis, because all patients with sagittal synostosis are generally recommended for surgery to prevent complications of elevated intracranial pressure, potentially worsened neurocognitive outcome, and abnormal headshape. Ideally, the study design would incorporate measurement of auditory ERPs in NSC infants at the initial and final time points without undergoing an operative procedure. That was not an option in the current study because all families chose to have their infants undergo surgery. In addition, preoperatively, the craniosynostosis group was significantly younger than the control group (age 133 vs 171 days). However, Kushnerenko et al previously recorded the MMN at birth, 3 months, 6 months, 9 months, and 12 months, and observed no statistical difference in MMN amplitude at the different ages.[26] Based on these MMN findings, we did not expect the difference in initial age observed in this study to significantly impact the MMN response. A Pearson correlation analysis showed no significant correlation of age with MMN amplitude ($P > 0.05$).

CONCLUSION

Infants with NSC demonstrated attenuated auditory MMN response to speech sounds compared with TD infants before surgery, indicating abnormal phonemic processing in infants with NSC. After surgery, auditory MMN amplitude was no longer different between groups, suggesting some normalization of speech processing after skull remodeling surgery. This normalization of speech processing suggests that whole vault cranioplasty may improve neurocognitive outcomes in sagittal craniosynostosis. Auditory ERPs are a potential predictive tool to assess infant language development noninvasively and preoperatively, which can be correlated to future language abilities.

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