Language Associated Neural Responses of Infants at High Risk for ASD and Nonsyndromic Craniosynostosis

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Introduction

- Infants with nonsyndromic craniosynostosis (NSC), an early cranial suture fusion syndrome, have similar language acquisition profiles to infants at high risk for autism spectrum disorder (HR-ASD).[1]
- Following surgery for NSC, these patients may or may not recover language development similar to the normal population.
- Auditory event-related potentials (ERPs) measure passive neurological responses to speech sounds, offering a promising method to study infant speech development.
- The mismatch negativity (MMN) quantifies perceptual narrowing and can predict future language development.[2]
- The MMN component is attenuated in HR-ASD infants compared to typically-developing (TD) controls.
- Auditory ERPs of HR-ASD and those of metopic synostosis (MSO)[3] and sagittal synostosis (SSO)[4,5] infants have been identified.
- However, ERPs have not been applied to compare coronal synostosis (CSO) or across groups of NSC.

We present cohort comparisons among SSO, CSO, MSO prior to and following surgery for NSC, and HR-ASD at two similar developmental time points.

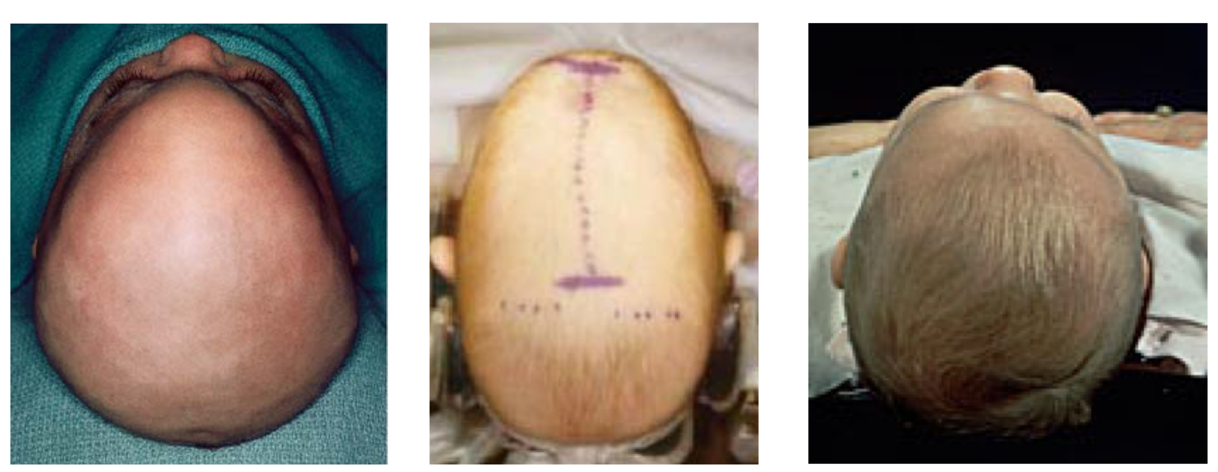

Figure 1. Morphometric differences in head shape between metopic (left), sagittal (middle), and unicoronal (right) craniosynostosis.

Methods

Infant BSID and ERP Testing

- HR-ASD, NSC, and TD infants were recruited from the Yale Autism Program and Yale Craniofacial Clinic.
- Participants were presented with a non-native phoneme discrimination paradigm involving the Hindi retroflex phoneme /da/ and the dental phoneme /da/ in random order.
- Auditory stimuli were set at 80 dB, and EEG was recorded at 250 Hz with a 128-channel HydroCel Geodesic Sensor Net.
- Analysis focused on four electrode clusters (Figure 2).
- The MMN component was calculated as the largest negative amplitude in the difference wave between 80-300ms after stimulus presentation.
- Statistical comparisons were performed with ANOVAs and studentized T-tests.

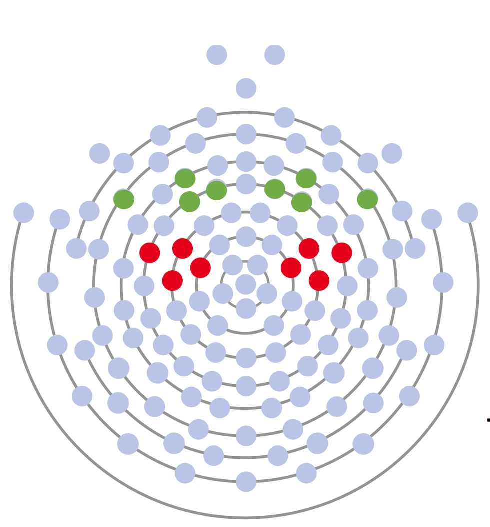

Figure 2. Diagram of left and right frontal (green) and central (red) electrodes.

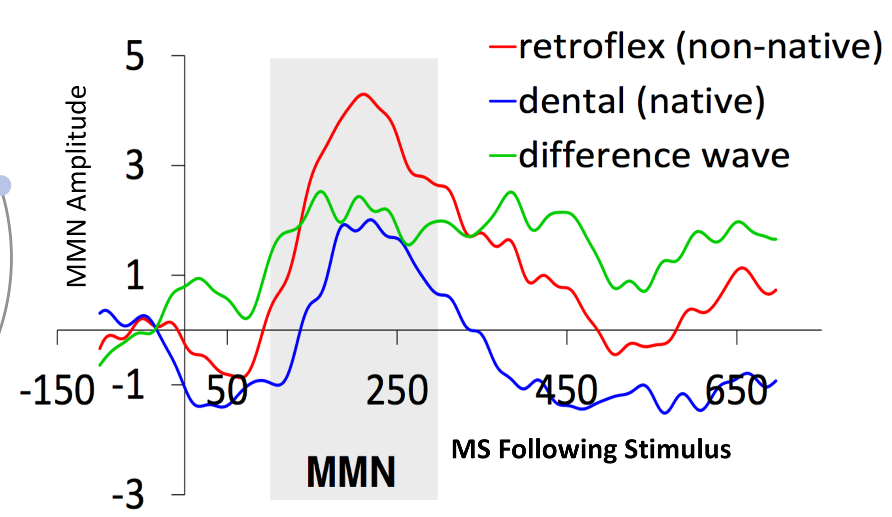

Figure 3. Example of an MMN difference wave calculated from subtracting the dental from the retroflex phoneme.

Results

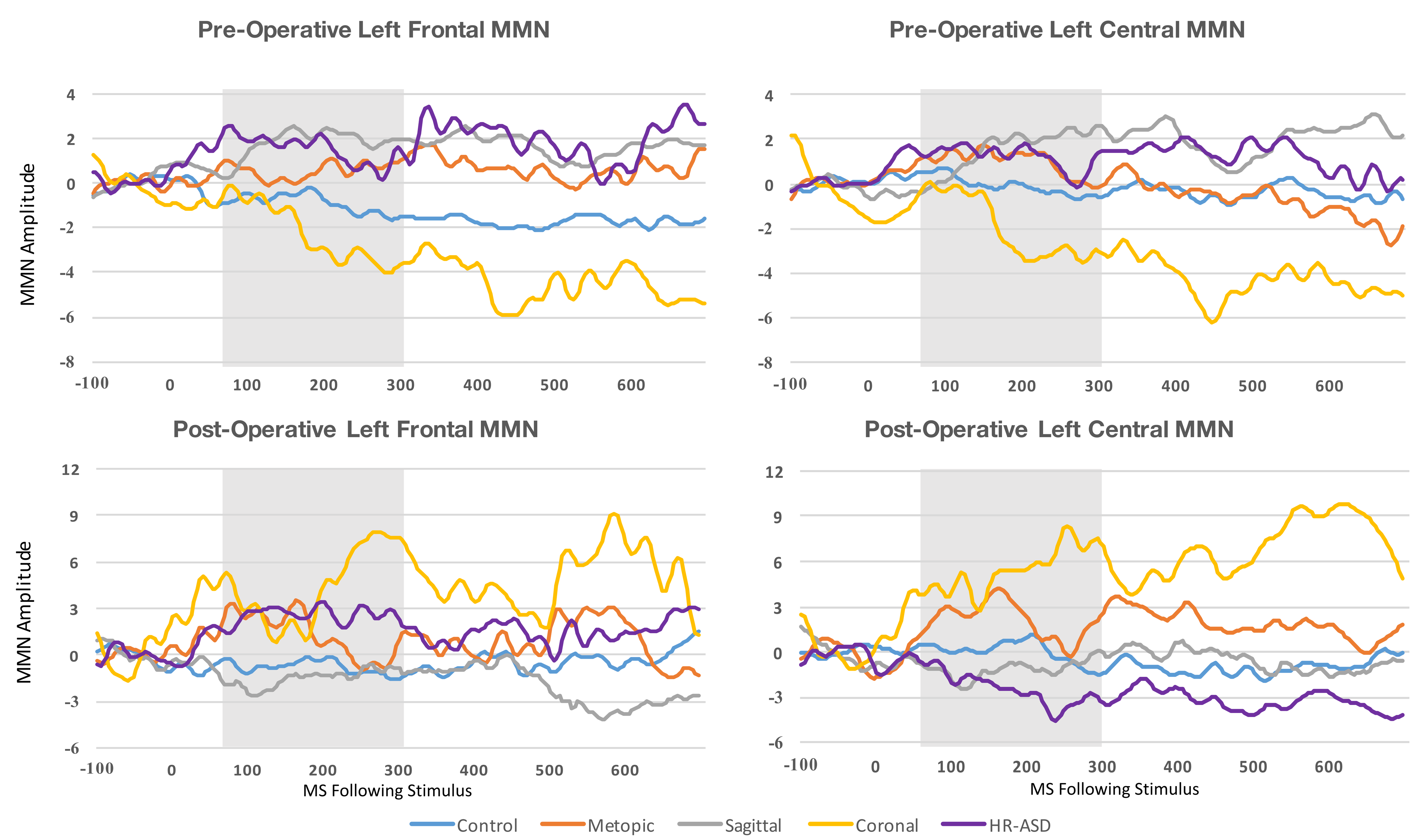

Figure 4. Pre- (top) and post- (bottom) operative MMN difference waves for craniosynostosis, HR-ASD, and control patients.

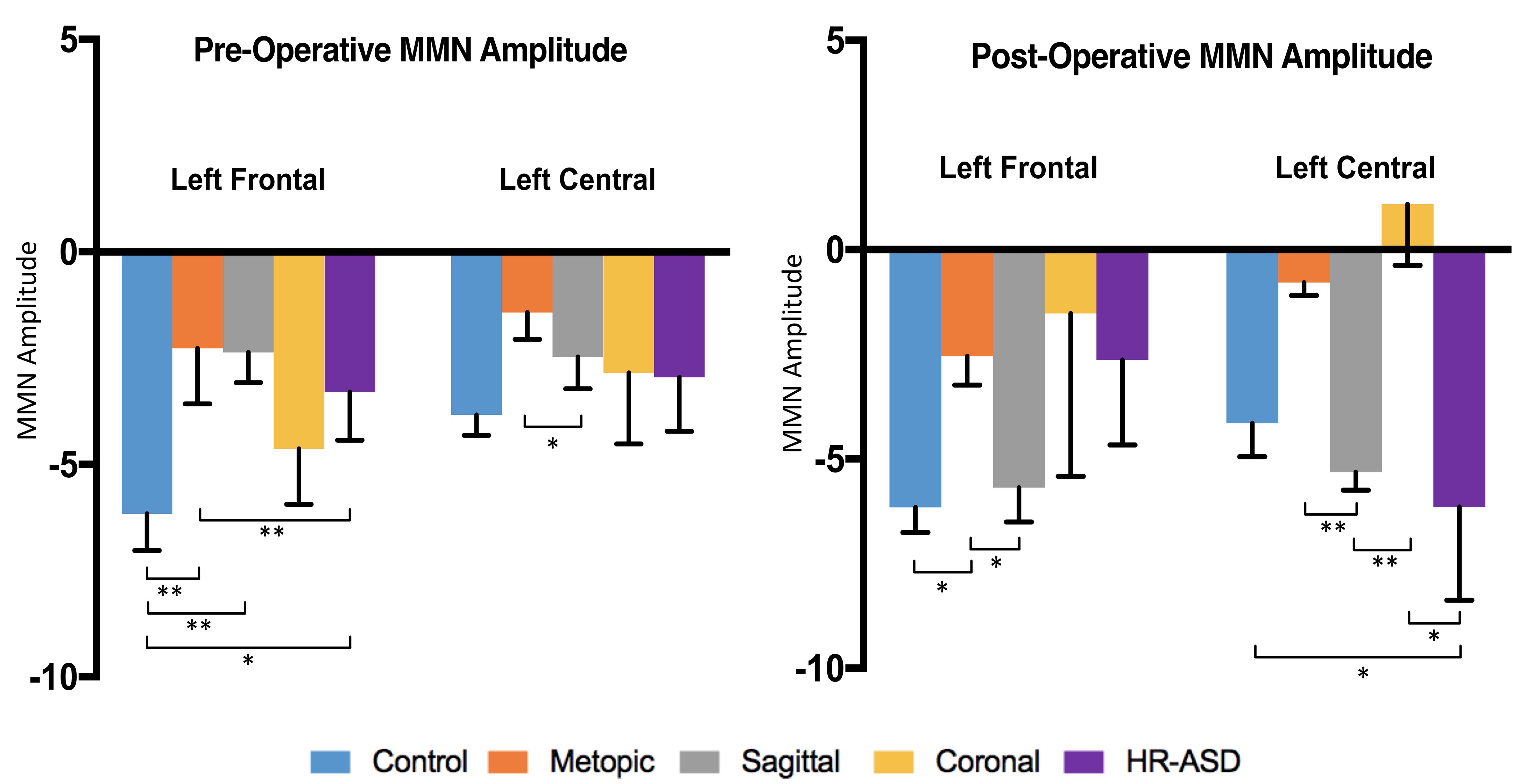

Figure 5. Pre (left) and post (right) operative comparison of MMN amplitudes between subtypes of craniosynostosis, HR-ASD, and control patients.

Results

- 12 HR-ASD, 5 CSO, 14 SSO, 14 MSO, and 34 age-matched TD infants were included in analyses. Pre-operative average age was 6.46 months for HR-ASD, 7.13 for SSO, 7.61 for SSO, 7.67 for CSO, and 6.66 for TD. The average time between pre and post operative was 218 days.
- While both right and left electrodes were compared, we were primarily interested in left hemisphere areas associated with language.
- MMN amplitudes measured in left frontal clusters were statistically different among cohorts (p=0.043).
- HR-ASD, SSO, and MSO infants produced attenuated left frontal responses compared to TDs (p=0.025, p=0.001, p=0.003, respectively).
- Among NSC cohorts, SSO and MSO infants had attenuated MMN responses in the left frontal clusters compared to CSO (p=0.022, p=0.041, respectively).
- MMN amplitudes in the left central clusters were also significantly different among cohorts (p=0.006).
- SSO and MSO infants demonstrated attenuation in the left central clusters compared to TDs (p=0.015).
- In comparison to HR-ASD, SSO produced attenuated right frontal and central clusters (p=0.031, p=0.008), while MSO demonstrated attenuated right central clusters (p=0.005). There were no differences between CSO infants and TD or HR-ASD infants.

Conclusions

- Results replicate earlier findings that HR-ASD infants respond with lower MMN amplitudes than TD infants.
- In comparison with SSO and MSO infants, HR-ASD infants manifest attenuation neural responses over the left hemisphere, the hemisphere associated with language production.
- Between time points, HR-ASD infants had left frontal MMNs that became more like those of TD and left central MMN that became attenuated compared to TD.
- Between timepoints, MSO infants had no difference in left frontal or central MMNs.
- Between time points, SSO infants had left frontal and central MMNs that became more similar to those of TDs.
- CSO infants did not experience differences pre/post-operatively compared to TDs.
- This study begins to develop the early language profile of HR-ASD infants within the clinical context of different suture fusion craniosynostosis.
- Future efforts will attempt to include more unicoronal patients in analysis.
- Results warrant future studies comparing language acquisition in HR-ASD and NSC.

Citations

1. Naran, S. *et al.* Nonsyndromic Craniosynostosis and Associated Abnormal Speech and Language Development. *Plastic and Reconstructive Surgery* **140**, 62e-69e (2017).
2. Näätänen, R., Paavilainen, P., Rinne, T. & Alho, K. The mismatch negativity (MMN) in basic research of central auditory processing: a review. *Clinical Neurophysiology* **118**, 2544-2590 (2007).
3. Yang, J. F. *et al.* The Severity of Deformity in Metopic Craniosynostosis Is Correlated with the Degree of Neurologic Dysfunction. *Plastic and reconstructive surgery* **139**, 442-447 (2017).
4. Becker, D. B. *et al.* Speech, cognitive, and behavioral outcomes in nonsyndromic craniosynostosis. *Plastic and reconstructive surgery* **116**, 400-407 (2005).
5. Hashim, P. W. *et al.* Direct brain recordings reveal impaired neural function in infants with single-suture craniosynostosis: a future modality for guiding management? *Journal of Craniofacial Surgery* **26**, 60-63 (2015).

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