Comparison of Neural Response to Language in Infants at Elevated Risk for ASD and in Infants with Nonsyndromic Craniosynostosis

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Introduction

Background: Autism spectrum disorder (ASD) is characterized by impaired social interaction and communication.[1] While language skills vary widely among individuals with ASD, language delay in infants is an important prognostic feature of ASD severity. The study of auditory event-related potentials (ERPs) in infants at higher risk for ASD (HR-ASD) has demonstrated atypical responses in several ERP components compared to typically-developing (TD) controls.[2] Mismatch negativity (MMN), an ERP component found between 80-300ms, has been used to index language acquisition by assessing the brain's responses to a standard versus a deviant stimuli--this is a phenomenon known as perceptual narrowing.[2,3] To better understand the specificity of atypical neural response to language in ASD, clinical comparisons are needed.

Nonsyndromic craniosynostosis (NSC), a congenital disorder characterized by the premature fusion of cranial vault sutures, is associated with impairments in learning and language that may resemble the deficits found in ASD. While sagittal synostosis (SSO), or fusion of the sagittal suture, has been shown to be associated with aberrations in the MMN component, this has not been demonstrated in metopic synostosis (MSO), or fusion of the metopic suture. Additionally, severity of MSO may affect the degree of ERP change, which was previously demonstrated in the P150 component.[4] Severity is determined by measuring the endocranial bifrontal angle based with the three-dimensional computed tomography (CT) reconstruction of the preoperative skull (Figure 1).[5]

Objective: Compare language processing using the MMN component in infants across two groups at risk for language impairment: HR-ASD and MSO subjects.

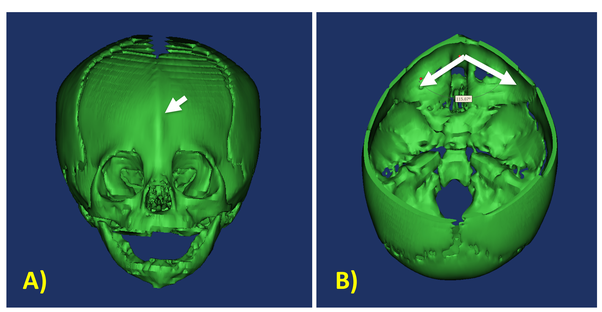

Figure 1. Three-dimensional reconstructions of metopic synostosis. A) Anterior view of a patient with metopic synostosis with prominent metopic ridge (arrow). B) Cut through skull demonstrating triangular forehead and measurement of the endocranial bifrontal angle.

Methods

Participants

- HR-ASD and TD subjects were recruited from the Yale Child Study Center, and MSO subjects were recruited from the Yale Craniofacial Center.
- Subjects were tested at two time points (T1 and T2). For MSO subjects, T1 was prior to surgical correction of deformity and T2 was after surgical correction.
- In total, there were 12 HR-ASD, 15 MSO (6 of which were severe, S-MSO), and 33 TD subjects.

Experimental Design:

- Auditory presentations of retroflex phoneme /Da/ and dental phoneme /da/ (non-native phoneme discrimination task) with 5 blocks and 20 trials per block.
- Each phoneme was presented 10 times per block in random order.
- Stimulus duration: 250ms; inter-stimulus interval: 610ms.

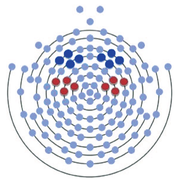

Figure 2. Electrode layout. Frontal (blue) and central (red) clusters were used for analysis.

Data Acquisition and Processing:

- EEG recorded at 250 Hz using 128 channel HydroCel Geodesic Sensor Net.
- EEG was segmented from 100ms before to 700ms after the stimulus, filtered from 0.1-30 Hz, and artifact corrected using NetStation 4.5.4.
- The difference wave was computed between dental and retroflex waveform responses, and the MMN was defined as the largest negative amplitude between 80-300ms.
- Clusters of central and frontal electrodes were selected based on previous literature (Figure 2).
- Severity of metopic synostosis was determined from 3D reconstruction of CT imaging in Materialise Mimics (Leuven, Belgium) based on the previously-defined endocranial bifrontal angle[5].

One-way analysis of variance (ANOVA) was performed for three groups: HR-ASD, MSO, and TD subjects, as well as a sub-analysis for severe metopic patients (S-MSO). Homogeneity of variance was tested using Levene's test with Tukey's HSD and Games-Howell tests were performed post hoc.

Results

T1	HR-ASD (n=12) (Mean ± SD, μV)	MSO (n=15) (Mean ± SD, μV)	Controls (n=33) (Mean ± SD, μV)	ANOVA p-val
Left Frontal	-3.30±2.77	-3.60±4.40	-6.24±5.45	0.090
Right Frontal	-5.80±3.99	-4.03±4.73	-4.65±4.96	0.623
Left Central	-2.95±3.12	-2.56±4.05	-4.06±4.89	0.498
Right Central	-5.18±3.27	-2.66±4.18	-3.61±4.87	0.344
T2	**HR-ASD (n=7)**	**MSO (n=6)**	**Controls (n=27)**	**ANOVA p-val**
Left Frontal	-2.63±4.96	-2.75±2.56	-4.99±5.24	0.393
Right Frontal	-2.47±5.24	-3.06±3.73	-3.47±3.59	0.830
Left Central	-6.14±5.46	-1.99±2.58	-4.36±5.15	0.330
Right Central	-4.96±4.18	-3.48±2.56	-3.65±3.38	0.642

Table 1. Mean MMN voltages (μV) by group. P-value is for one-way ANOVA between HR-ASD, MSO, and TD.

HR-ASD, MSO, and TD Subjects

- Both HR-ASD and MSO subjects had reduced MMN amplitude compared to controls preoperatively in the left frontal leads (p=0.090).
- There were no significant differences between groups postoperatively in any electrode cluster.

Sub-analysis for Severe MSO (S-MSO) Subjects

- On sub-analysis of severe metopic subjects with an endocranial bifrontal angle of less than 124 degrees, there was a significant difference in the MMN amplitude in the left frontal electrode cluster among the three groups (HR-ASD, S-MSO, TD subjects) preoperatively (p=0.028); post hoc testing demonstrated significant differences between controls and S-MSO patients (p=0.004) as well as approaching significance between controls and HR-ASD subjects (p=0.058).
- The non-severe MSO patients had a preoperative mean MMN of -5.16±4.88 μV, compared to a mean MMN of -1.25±2.27 μV in the S-MSO group (p=0.093); there were no differences postoperatively.

Results

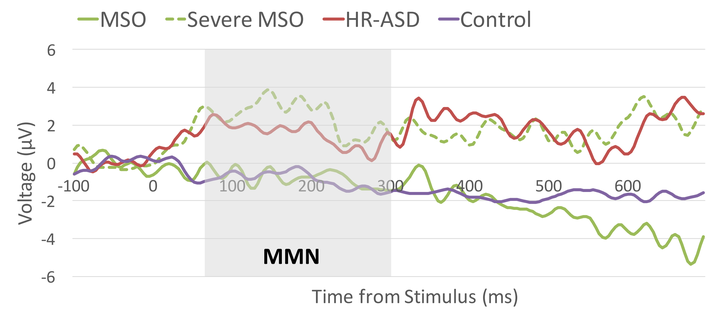

Figure 3. Difference waves for MSO, severe MSO, HR-ASD, and control subjects. The MMN component of the ERP is found between 80-300 ms after the stimulus.

Conclusions

- HR-ASD and MSO subjects had reduced MMN amplitude in the left frontal electrodes compared to controls, but this was not significant
- Individuals with severe forms of MSO had greater MMN attenuation compared to controls (p=0.004).
- There were no significant differences in MMN found between postoperative metopic synostosis, HR-ASD, or control subjects.
- Our previous work demonstrated shared abnormalities in the P150 in HR-ASD and SSO infants, suggesting abnormal processing as a shared basis for atypical language development in HR-ASD and SSO subjects.
- However, abnormal auditory MMN does not appear to be a shared feature of atypical language processing in HR-ASD and severe MSO subjects.
- Atypical language development in HR-ASD and NSC subjects reflects shared and distinct neural processes, highlighting the import of considering functional profiles when characterizing language deficits in clinical populations.

Acknowledgements

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