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ERPs to words correlate with behavioral measures in children with Autism Spectrum Disorder

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Children with Autism Spectrum Disorder (ASD) participated in a research study that involved both electrophysiological and behavioural measures. Event related potentials (ERPs) were recorded during auditory presentation of known and unknown words. Behavioural measures of language/cognitive function and severity of autism symptoms were also collected at the time of ERP testing and again 1 year later. In general, higher functioning children with ASD exhibited more localized brain effects for differences between known and unknown words. Lower functioning children with ASD had more diffuse patterns of response to the different word classes and also exhibited stronger right hemisphere lateralization. That is, they showed differences between known and unknown words at many electrode sites and larger differences in the right hemisphere. In addition, significant correlations were obtained between specific brain wave measurements for known words and various behavioural measures. Patterns of ERPs effectively predicted later behavioural scores.

1 Introduction

Language/communication deficits and social impairment are key components of autism spectrum disorder (ASD), and individuals vary widely in their degree of impairment [1]. Phonological, lexical, semantic, and syntactic deficits vary widely in children with autism, ranging from nearly normal abilities to profound impairments [2, 3].

Kuhl, Coffey-Corina, Padden & Dawson [4] provided evidence of links between social and linguistic processing of speech in preschool aged children with ASD. Children with ASD failed to show a significant ERP response to a syllable change. However, when divided into subgroups based on preference for nonspeech vs. "motherese," the subgroup that preferred nonspeech still failed to show a significant ERP response to syllable change while children with ASD who preferred motherese did not differ from TD controls. In addition, significant correlations were reported between a variety of social and linguistic measures.

There is also evidence of links between language ability and ERP responses to known (K) and unknown (UK) words in typically developing (TD) infants and toddlers. Mills, Coffey-Corina, and Neville [5,6] reported differences in ERP waveforms in response to known (K) and unknown (UK) words in 13 to 20 month old infants beginning 200 ms after word onset. The amplitude, latency and distribution of the ERP response differed with age and with participants' language production abilities. In the youngest infants, the differential ERP response was broadly and bilaterally distributed. With increasing age and language ability, latency and amplitude of the ERP components decreased and distribution became more focused.

In this study we examine ERP measures of word processing in TD toddlers and in toddlers with ASD, investigating the full group of toddlers with ASD as well as high functioning (HF) and low functioning (LF) subgroups defined by severity of autism symptoms in the social domain. In addition, we investigate the relationship between specific ERP measures and behavioural measures of linguistic and social function.

2 Methods

2.1 Participants

Participants were recruited from local parent advocacy groups, Washington State Department of Developmental Disabilities, clinics, hospitals and the University of Washington Infant and Child Subject Pool. Exclusionary criteria included the presence of a neurological disorder of known etiology (for toddlers with ASD only), significant sensory or motor impairment, major physical abnormalities, and history of serious head injury and/or neurological disease.

Toddlers with ASD

Toddlers with ASD were diagnosed using criteria described by Kuhl et al. [4]. Using these criteria, 24 toddlers with ASD were enrolled as participants in the study. These children were between 18- and 31-months-old (M = 24.32 months), 17 males and 7 females. An additional 24 children with ASD were excluded due to: insufficient numbers of ERP trials (n = 8), refusal to wear the Electro-cap (n = 12), and equipment problems during ERP recordings (n = 4).

Typically developing controls

Twenty typically developing (TD) toddlers were enrolled as control subjects in this study. These toddlers were between 20- and 31-months-old (M = 24.26 months), 13 males and 7 females. An additional 10 TD toddlers were excluded due to: insufficient numbers of ERP trials (n = 3), refusal to wear the Electro-cap (n = 5), and equipment problems during ERP recordings (n = 2).

2.2 Stimuli

The speech stimuli were 10 different words of each type: known (K), unknown (UK) and backwards words (B). Parental reports were used to create customized lists of known words for each individual subject (mean duration = 671 ms). Unknown words were matched for number of syllables and were similar in phonological form to known words (mean duration = 744 ms). Backwards words were created by reversing the wav files of the known words. Each word was presented 6 times for a total of 180 words presented.

2.3 Apparatus and procedure

EEG was collected continuously from 20 electrode sites using the standard international 10/20 system. Participants wore an elastic Electro-cap, and data was acquired using SAI amplifiers, band pass filtered at .1- 60 Hz. Participants listened passively while sitting on their parent's lap, watching an assistant playing quietly with toys while a silent child-oriented video played on a monitor behind the assistant. Stimuli were presented from two speakers placed on either side of the video monitor, approximately 4 feet in front of the participant. Words were presented at 65 - 67 dBA. The inter-stimulus interval was 2000 ms, onset to

onset. All data were processed off-line, using epochs of 100 ms pre-stimulus and 900 ms post-stimulus onset. Trials were hand edited to ensure artifact free data. Finally, data was filtered using a low pass filter with a cut off of 25 Hz. Grand averages of the ASD and TD groups were examined to determine the measurement windows. Measurements of waveforms were taken for peak amplitude and peak latency at 100-200 ms; and for mean amplitude at 200-500 and 500-700 ms for all 3 word types in both groups at lateral electrode sites (F3/4, F7/8, T3/4, C3/4, and P3/4). All participants processed backwards words in a similar way; no further discussion of this data will take place in this paper.

Diagnostic measures including the Autism Diagnostic Observation Schedule [7] and the Mullen Scales of Early Learning [8] were collected from toddlers with ASD prior to ERP testing and one year after testing. These measures were used to assess potential relationships among the variables examined in the study

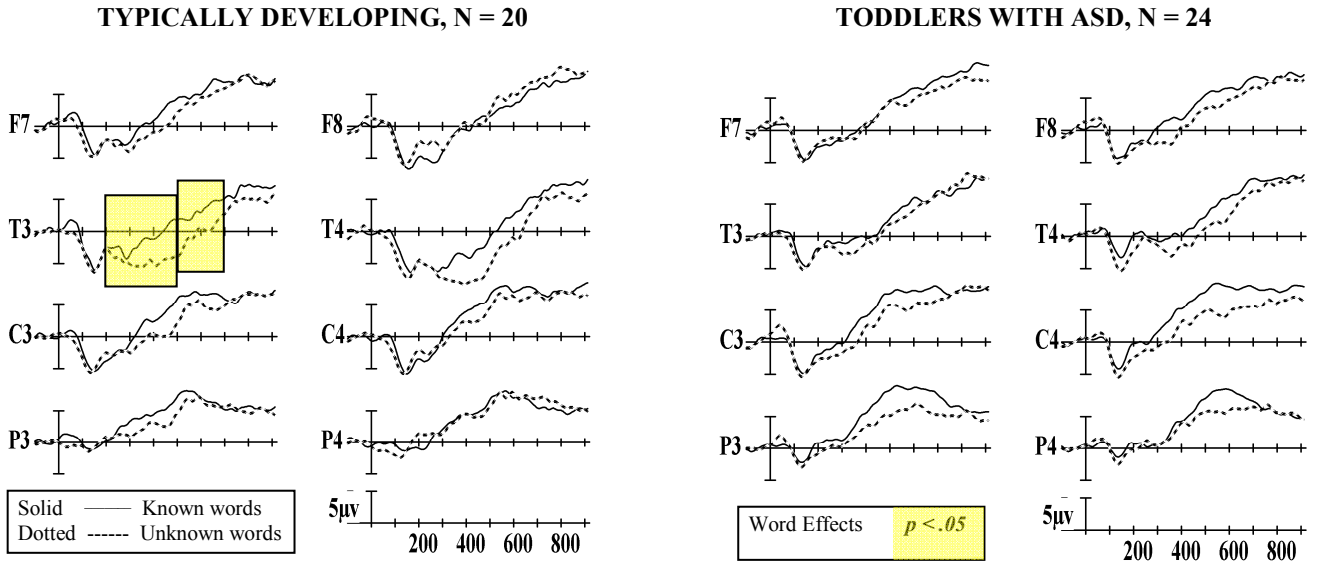

Fig. 1. ERP waveforms for TD toddlers (left) and toddlers with ASD (right). TD toddlers exhibit a localized response with significant differences between K and UK at left temporal electrode site (T3). Toddlers with ASD exhibit a diffuse response to K and UK – differences are significant across all electrode sites in the 500-700 ms measurement window.

3 Results

3.1 Group analysis

Measurements were taken for peak amplitude, peak latency, and mean amplitude for each subject in both groups. Repeated measures analyses of variance were completed on data obtained from ten lateral electrode sites for each group, examining the effects of word type, hemisphere, and electrode site as within-subject factors.

As expected, TD toddlers showed a significant difference between K and UK words localized to left temporal site (T3) in both 200-500 ms, F (1, 19) = 8.302, p = .010, and 500-700 ms measurement window, F (1, 19) = 8.306, p = .011 (Fig. 1, left). There were no significant effects at 100-200 ms for amplitude or latency. In contrast, toddlers with ASD showed a diffuse response to K and UK words. Known words were more negative than unknown words across all electrode sites, and at a later latency than TD's, 500-700 ms, F (1, 23) = 4.622, p = .042. There were no other significant effects for amplitude or latency.

3.2 Subgroup analysis

Toddlers with ASD were further subdivided into high functioning (HF) and low functioning (LF) groups based on a median split of ADOS social scores to further explore processing of K and UK words (ADOS median = 11.5, range = 6-14). Twelve toddlers with ASD were assigned to the HF subgroup. These participants were between 18- and 31-months-old (M = 23.96 months), 7 males and 5 female. Twelve toddlers with ASD were assigned to the LF subgroup. These participants were between 19- and 30-months-old (M = 24.69 months), 10 males and 2 females.

Waveforms for the HF toddlers with ASD appear similar to TD, exhibiting a localized response to K and UK words. Significant word type effects are observed only at the left parietal electrode site (P3) in the 200-500 ms time window, F (1, 11) = 7.912, p = .017 (Fig. 1, left). HF toddlers with ASD also exhibit significant hemisphere effects for peak latency for K words in the 100-200 ms measurement window at frontal (F7/8) and centro/temporal (C3/4) sites. Peak latency is significantly shorter at the left frontal site, F7 (F (1, 11) = 5.360, p = .041, and significantly longer at left centro/temporal, C3, F (1, 11) = 5.867, p = .034.

In contrast, ERP waveforms of LF toddlers with ASD exhibit a diffuse response to words. K words are significantly more negative than UK words at multiple electrode sites and in all measurement windows: at the right temporal site (T4) in the 100-200 ms, F (1, 11) = 8.914, p = .012, 200-500 ms, F (1, 11) = 15.386, p = .002, and 500-700 ms measurement windows, F (1, 11) = 9.448, p = .011; at the right frontal site (F8) in the 200-500 ms measurement window, F (1, 11) = 6.680, p = .025; and at the left centro/temporal site (C3) in the 500-700 ms

measurement window, F (1, 11) = 4.904, p = .049. The word type effect approaches significance at three additional electrode sites in the right hemisphere in the 500-700 ms measurement window (F8, C4, P4) and the difference in response to K and U words is significant in the 500-700 ms window when collapsed across all electrode sites, F (1, 11) = 7.252, p = .021.

The relationship among the three participant groups (HF toddlers with ASD, LF toddlers with ASD, and typically developing comparison toddlers) was examined with a repeated measures analysis of variance. Within-subject factors were word type; hemisphere, and electrode site, between-subject factor was group. There was a significant group by hemisphere interaction at 200-500 ms, F (2, 41) = 5.892, p = .006. This interaction is driven by the LF group which exhibits a more negative response in the right hemisphere for known words. Paired comparisons show a significant word type by hemisphere by group interaction for LF and TD groups, F (1, 30) = 5.662, p = .024, and for LF and HF groups, F (1, 22) = 11.220, p = .003. The word type by hemisphere by group interaction is not significant for TD and HF groups, F (1, 30) = 1.601, p = .215.

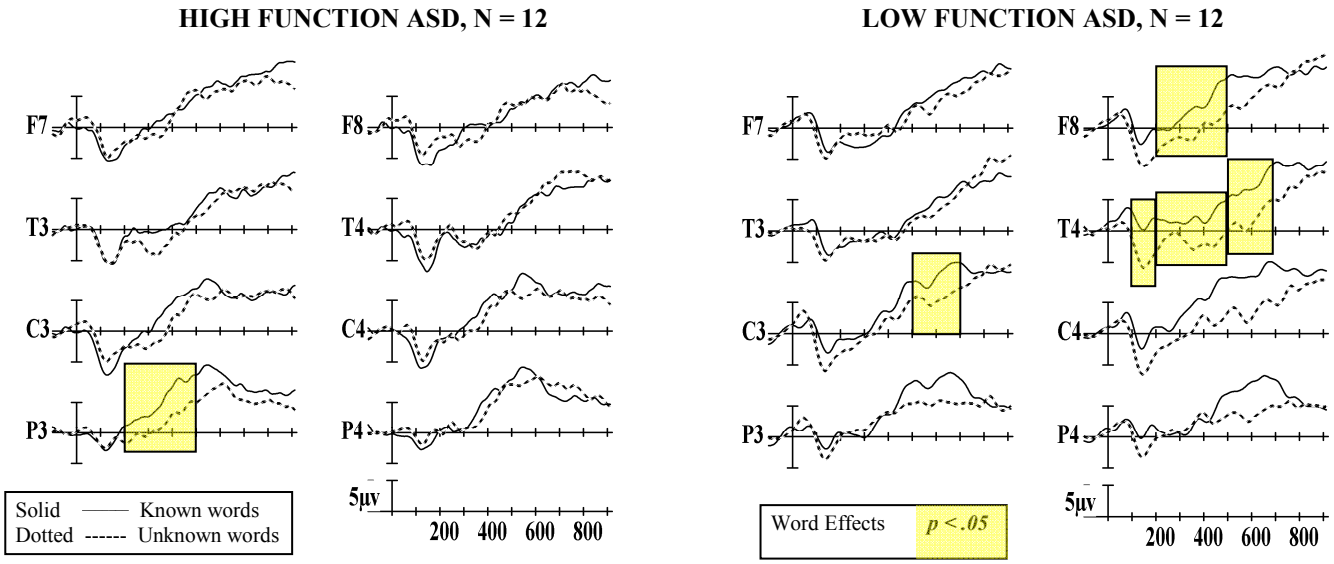

Fig. 2. ERP waveforms for HF toddlers with ASD (left) and LF toddlers with ASD (right). HF toddlers exhibit a localized response with significant differences between K and UK at the parietal electrode site in the left hemisphere (P3). LF toddlers exhibit a diffuse response to K and UK with significant differences in multiple time windows and electrode sites. In addition, the difference between K and UK is significant when collapsed across all electrode sites in the 500-700 ms measurement window.

3.3 Correlations: Known words

Toddlers with ASD exhibited significant positive correlations between peak latency of the early positive ERP component to K words at the left frontal electrode site (F7) and severity of autism symptoms, as reflected by the ADOS score for the social domain. Longer latency was associated with higher ADOS social scores (i.e., more severe symptoms) at the time the ERP data was collected (r = .431, p < .05, Fig. 3 left). There is also a predictive relationship between this latency measure and later ADOS social scores. Longer latency was associated with higher ADOS social scores collected one year following ERP data collection (r = .429, p < .05, Fig. 3 right).

Toddlers with ASD also exhibited a significant negative correlation between peak amplitude of the early positive ERP component to K words at the right temporal electrode site (T4) and ADOS social scores. Smaller amplitude of this positive ERP component was associated with higher ADOS social scores (i.e., more severe symptoms) at the time the ERP data was collected (r = -.563, p < .05).

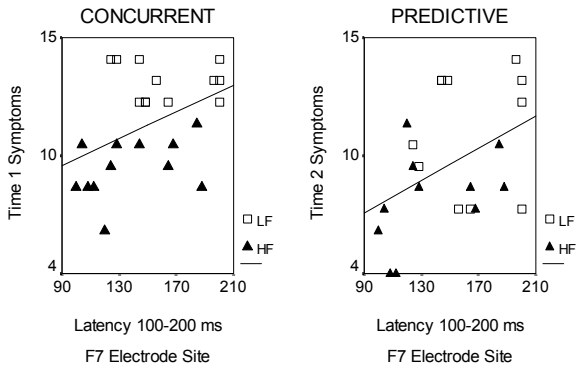

Fig.3 Significant concurrent (left) and predictive (right) correlations between peak latency for K words at the left frontal electrode site (F7) in the 100-200 ms measurement window and severity of autism symptoms. Longer latency is associated with more severe symptoms at the time ERP data was collected (r = .431, p < .05, left) and one year later (r = .429, p < .05, right).

In addition, toddlers with ASD exhibited negative correlations between mean amplitude of the first negative ERP component at the parietal electrode sites (P3/4) and Verbal IQ measured one year after ERP data collection. A stronger negative response was associated with higher Verbal IQ. The correlation was significant at left parietal, P3 (r = -.521, p = .013, Fig. 4 left) and approached significance at right parietal, P4 (r = -.421, p = .051, Fig. 4 right).

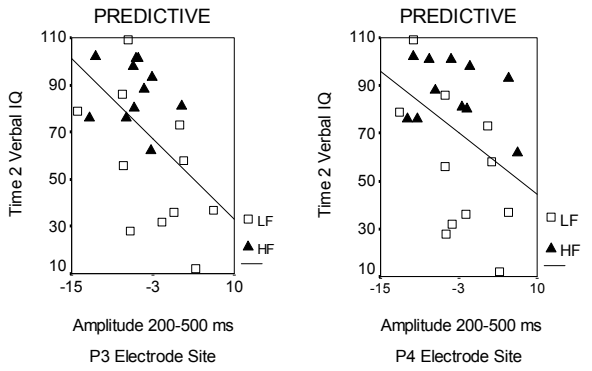

Fig.4 Predictive correlations between mean amplitude for K words at the parietal electrode sites (P3/4) in the 200-500 ms measurement window and verbal IQ. A more negative response predicted higher verbal IQ one year after ERP data was collected. The correlation was significant at left parietal, P3 (r = -.521, p = .013, left) and approached significance at right parietal, P4 (r = -.421, p = .051, right).

4 Discussion

ASD is characterized by wide variation in severity of symptoms and degree of language impairment. In this study we investigate the relationships between these variations and ERP measures of word processing. Our results reinforce the view that group results can underestimate individual children's skills.

In the present study, we observed group differences in ERP response to known (K) and unknown (UK) words: TD controls exhibited a focused response while toddlers with ASD exhibited a diffuse response with longer latency. However, dividing toddlers with ASD into high (HF) and low functioning (LF) groups based on severity of autism symptoms in the social domain reveals an interesting pattern of results. HF toddlers with ASD exhibit an ERP response to K and UK very similar to TD controls: both groups exhibit a focused response with significant differences at a single left hemisphere electrode site in the 200-500 ms measurement window. LF toddlers with ASD exhibit an ERP response to K and UK words that is significantly different from HF toddlers with ASD and TD controls: significant differences between K and UK words are broadly distributed across multiple measurement windows and many electrode sites, and almost completely confined to the right hemisphere. This pattern of group and subgroup results is similar to that reported by Kuhl et al. [4] in an ERP study of syllable processing that assigned preschool aged children with ASD to subgroups based on a different behavioral measure of social function, i.e., auditory preference for motherese vs. nonspeech. Analysis of the total group of children with ASD revealed no neural discrimination (based on the ERP's) of a syllable change; however, when divided into subgroups, the group that preferred nonspeech failed to show a significant ERP response to a syllable change while children with ASD who preferred motherese did not differ from TD controls.

The pronounced right hemisphere lateralization of ERP responses to K words revealed in the LF subgroup analysis has interesting parallels to neuroanatomical studies using magnetic resonance imaging. These MRI studies found morphometric differences in language regions, including Broca's area. Broca's area is larger in the left than right for typical subjects and has been implicated in phonological and semantic processing of language stimuli. Herbert et al. [9] reported reversed asymmetry in frontal language-related cortex (Broca's area) in school aged boys with ASD when compared to TD controls. In a follow up study, De Fosse et al. [10] examined school aged boys with specific language impairment (SLI), TD controls and a new sample of boys with ASD which were subdivided into those with language impairment (ALI) and those with normal performance on a standardized test of language ability (ALN). Children with SLI and children with ASD in the ALI subgroup exhibited the significant right-bias asymmetry in Broca's area reported in the earlier study in children with ASD [9], while the ALN subgroup exhibited left-bias asymmetry and did not differ significantly from TD controls – suggesting that the reversed asymmetry is related to language impairment in general. This abnormal development in Broca's area could account for some language deficiencies seen in people with ASD.

De Fosse et al. [10] noted that it was not possible to determine whether the development of language dominance in the right hemisphere causes language impairment or whether abnormal cortical asymmetry is the result of early left hemisphere language dysfunction. Our data suggest that whatever mechanism underlies this reversed asymmetry, the effects can be observed in toddlers with ASD described as LF based on the severity of autism symptoms in the social domain.

Harris and colleagues (2006) [11] reported more activation in Wernicke's area and reduced activation in Broca's area in an fMRI study of adults with ASD during word meaning tasks. This interesting finding is consistent with the topographical differences in the distribution of the focused ERP response we observed in HF toddlers with ASD and TD controls, and suggests a potential area for future study.

5 Conclusion

Children with Autism Spectrum Disorder (ASD) participated in a research study that involved both electrophysiological and behavioural measures. Event related potentials (ERPs) were recorded during auditory presentation of known and unknown words. Behavioural measures of language/cognitive function and severity of autism symptoms were collected at the time of ERP testing and again 1 year later. In general, higher functioning children with ASD exhibited more localized brain effects for differences between known and unknown words, similar to that of typically developing (TD) controls. Lower functioning children with ASD had more diffuse patterns of response to the different word classes and also

exhibited stronger right hemisphere lateralization. That is, they showed differences between known and unknown words at many electrode sites and larger differences in the right hemisphere. In addition, significant correlations were obtained between specific brain wave measurements for known words and various behavioural measures. Patterns of ERPs effectively predicted later behavioural scores. Further research using brain measures of speech processing to compare TD children and ASD children sub-grouped on the basis of their social skills, will contribute to our understanding of the nature of the relationship between the linguistic and social deficits characteristic of autism.

Acknowledgments

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