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Neural responses to linguistic stimuli in children with and without autism spectrum disorder

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Abstract

Atypical neural responses to language have been found in toddlers with autism spectrum disorder (ASD) and in their unaffected siblings. However, given that language difficulties are often seen in these children, it is difficult to interpret whether these neural differences are a result of the diagnosis of ASD or impairments in their language abilities. In this study, we recorded event-related potentials (ERPs) from four groups of 36-month-olds: low-risk control (LRC), high risk for ASD defined as having an older sibling with ASD (HRA) but who do not have ASD or milder autism-like symptoms (HRA-Typ), HRA children who do not have ASD but exhibit milder autism-like symptoms (HRA-Atyp) and HRA children diagnosed with ASD (ASD). Children listened to words expected to be acquired early (e.g. ball) and words expected to be acquired late (e.g. calf). ERPs were analysed over time windows sensitive to word processing as well as frontal and temporo-parietal sites over the left and right hemispheres. When controlling for language abilities, there were group differences within the temporo-parietal sites. Specifically, the HRA-Atyp group showed a different timed response to late words compared to the ASD and LRC groups. In addition, we found a relation between neural responses in the left frontal sites and ASD severity. Our results suggest that both language abilities and ASD diagnoses are important to consider when interpreting neural differences in lexical processing.

Introduction

With the recent update to the DSM-5, the diagnostic criteria of autism spectrum disorder (ASD) no longer include language impairments as a core symptom (American Psychiatric Association, 2013). Nevertheless, there is still substantial heterogeneity in the language abilities of individuals with ASD, with some achieving normal language skills, while others remain nonverbal (Tager-Flusberg, 2015). In the early development of children with ASD, lexical knowledge and processing are often impaired as they have been found to have smaller receptive vocabularies, more superficial definitions of words, and poorer understanding of relatedness between words compared to their typically developing peers (Boucher, 2011; McGregor *et al.*, 2011; Henderson *et al.*, 2014; Haebig *et al.*, 2015). Moreover, even young toddlers and children with ASD with normal language abilities show atypicalities in their ability to learn and generalize new words (Tek *et al.*, 2008; Norbury *et al.*, 2010; McGregor & Bean, 2012).

Language delays and disorders are not unique to the ASD diagnosis, as they are also found in individuals at familial risk for ASD, specifically first-degree relatives of individuals with ASD (Gamliel *et al.*, 2009; Georgiades *et al.*, 2013; Messinger *et al.*, 2013; Ozonoff *et al.*, 2014). Similar to children with ASD, siblings of children with ASD exhibit lexical processing impairments including difficulties in identifying less familiar words as well as impairments in using various social cues and linguistic constraints to learn new words (Bedford *et al.*, 2013; Gliga *et al.*, 2012; Malesa *et al.*, 2012; Ference & Curtin, 2013; Chita-Tegmark *et al.*, 2015). However, although this group as a whole might show impairments in language processing, there is variability among these siblings. Approximately 30% of infant siblings exhibit milder autism-like traits (broader autism phenotype, BAP) including atypical development within the language domain (Ozonoff *et al.*, 2014; Charman *et al.*, 2016).

Given the behavioural atypicalities, better understanding of the underlying neural mechanisms of language processing may allow for a more encompassing view of the difficulties within these individuals. In fact, numerous studies have found atypicalities in both structure and function for neural regions associated with language in toddlers, children and adults with ASD (see Herringshaw *et al.*,

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2016; Lindell & Hudry, 2013 for reviews). Moreover, neural atypicalities in response to speech sounds have also been found in infants with an older sibling with ASD (Seery *et al.*, 2013; Righi *et al.*, 2014; Finch *et al.*, 2017). However, little work has investigated the neural correlates of lexical processing in the early development of these populations.

Kuhl *et al.* (2013) examined the neural correlates of lexical processing in toddlers with ASD by recording event-related potentials (ERPs) to known and unknown words in 24-month-olds with and without ASD. Typically developing toddlers showed a differential response depending on word familiarity with a more negative response 200-500 ms after hearing a known word as compared to an unknown word within the left temporal region. On the other hand, toddlers with ASD exhibited an atypical ERP response to words and their response varied depending on the severity of the social impairment. Similar to the typically developing toddlers, toddlers with ASD with less severe social symptoms showed differential responses to known and unknown words, but within a slightly different topographical area, specifically the left parietal region. Toddlers with ASD with severe social impairments exhibited a differential response between known and unknown words in the right frontal region. Not only did the topographical location of differential responses to known and unknown words differ depending on ASD symptom severity, but these neural responses at 24 months predicted their language and cognitive abilities at later time points.

This study might suggest toddlers with ASD, especially those with more severe ASD, process known and unknown words differently from their typically developing peers. However, Kuhl *et al.* (2013) matched the groups of children with ASD and typically developing controls on chronological age and not language abilities. As children with ASD tend to show difficulties in their lexical processing, it might be that differences in lexical processing abilities were driving the distinct topographical neural response in Kuhl *et al.* (2013) sample of toddlers with ASD.

Several studies using similar paradigms in typically developing toddlers have found that neural differences to known and unknown words vary depending on experience and language abilities (Mills *et al.*, 1993, 1997, 2005; Conboy & Mills, 2006). Twenty-month-old toddlers show focal ERP responses to known words compared to unknown or nonsense words, unlike younger fourteen-month-old toddlers (Mills *et al.*, 1993, 1997, 2004). Moreover, these differences in ERPs were more pronounced, over and above age, depending on the degree of familiarity of the words as well as the language abilities of the children (Mills *et al.*, 1997, 2005; Conboy & Mills, 2006). Given their findings, it is possible that the language abilities of the ASD group might partially be driving the differences seen in the study by Kuhl *et al.* (2013).

This study expands on past findings by investigating the neural responses to words in older toddlers with and without ASD as well as toddlers who are considered at familial risk for ASD. We also further divided the children at familial risk into those with BAP features from those without BAP features. We investigated group differences of ERPs to words expected to be acquired early (by 18 months of age) and words expected to be acquired late. Importantly, given the language difficulties often seen in children with ASD or children at familial risk for ASD, we controlled for language abilities in our analyses. If there were no group differences in ERPs in response to words, then any previous group differences found might have been completely driven by language abilities. If differences did still arise while controlling for language abilities, then it might suggest atypical neural processing of words specific to a particular group.

Methods

Participants

Participants were infants enrolled in collaborative longitudinal study conducted at Boston University and Boston Children's Hospital/Harvard Medical School. The study was approved by the Institutional Review Boards at both institutions, and all study procedures were performed in accordance with the Declaration of Helsinki. Infants were screened for exclusionary criteria (gestational age less than 36 weeks, time spent in neonatal intensive care, maternal steroid use during pregnancy, maternal diabetes, family history of genetic disorders, or English spoken less than 75% of the time in the household) and enrolled in one of two groups: 1) low-risk control (LRC; those with no family history of ASD) or 2) high risk for ASD (HRA; infants with at least one older sibling with ASD). All older siblings of the HRA group had a community diagnosis of ASD, and their diagnoses were confirmed independently in the project with the Social Communication Questionnaire (Rutter *et al.*, 2003) and/or Autism Diagnostic Observation Schedule (ADOS; Lord *et al.*, 2000). Once enrolled, infants completed visits from 3 months to 36 months of age. Informed consent to participate in the study was obtained by the parent or legal guardian of all participating children at the family's first visit. Toddlers who completed the 36-month visit were considered for inclusion in this study.

A total of 134 toddlers completed the 36-month visit with 85 contributing usable ERP data (20 were too fussy to complete the task, 13 had insufficient number of trials, nine had noisy data and seven had technical difficulties). Of these 85 toddlers, 42 were considered LRC, 29 were HRA who did not go on to receive a diagnosis of ASD (HRA-) and 14 received a diagnosis of ASD (ASD). The non-ASD HRA toddlers were further categorized on the basis of whether they exhibited signs of atypical development in toddlerhood that would be considered evidence for BAP. BAP was defined by elevated ASD symptoms, impaired language ability or impaired cognitive ability at any point in toddlerhood; this is consistent with classifications used by other researchers studying HRA infants (e.g. Ozonoff *et al.*, 2014). Toddlers were considered to have elevated autism symptoms (but not ASD) if they received a severity score of 3 or higher on the ADOS at 18, 24 or 36 months but did not meet criteria for the ASD group. Language and cognitive delay at 18, 24 and 36 months were determined from the Mullen Scales of Early Learning (MSEL; Mullen, 1995), a developmental assessment with fine motor, visual reception, expressive language, and receptive language subscales. Toddlers were considered to have a delay if they had a standardized T-score lower than 30 on a single MSEL subscale at 18, 24 or 36 months or T-scores lower than 35 on more than one subscale at a single age. At 36 months, of the 29 HRA toddlers, 13 met at least one of these criteria and were subsequently classified into an HRA-Atyp group. The remaining 16 were classified as typically developing (HRA-Typ). In addition, 31 LRC toddlers met the typically developing criteria (LRC-Typ) and were included as a comparison group. Behavioural characteristics of participants are given in Table 1.

ASD diagnoses for the participants were based on the ADOS (Lord *et al.*, 2000) administered at 24 or 36 months in addition to expert clinical judgement at 36 months. The ADOS is a semi-structured, standardized assessment consisting of play and social activities that elicit behaviours related to diagnosis of ASD. From the ADOS, a severity score ranging from 1 to 10 is obtained with a score of 4 or higher indicative of ASD. The ADOS was administered by experienced research staff and co-scored by an ADOS-reliable researcher via video recording. Cases of concern (those

TABLE 1. Characteristics of participants included in analyses.

	Group				Significance					
	LRC-Typ	HRA-Typ	HRA-Atyp	ASD	LRC vs. HRA-Typ*	LRC vs. HRA-Atyp*	LRC vs. ASD*	HRA-Typ vs. HRA-Atyp*	HRA-Typ vs. ASD*	HRA-Atyp vs. ASD*
Total *N*	31	16	13	14						
Female: male	24:7	9:7	5:8	2:5						
ADOS severity scores (SD)										
18 month- N	26	15	12	13						
Mean	1.12 (0.3)	1.07 (0.3)	3.58 (2.1)	3.15 (2.3)	1.00	0.0002	0.004	0.0007	0.006	1.00
24 month- N	28	16	12	14						
Mean	1.29 (0.46)	1.25 (0.5)	2.83 (1.6)	4.50 (2.0)	1.00	0.025	0.00001	0.409	0.001	0.364
36 month- N	31	16	13	14						
Mean	1.06 (0.25)	1.50 (0.5)	1.38 (0.6)	5.07 (2.5)	1.00	1.00	0.00001	1.00	0.00001	0.00001
MSEL T-Scores (SD)										
18 month- N	28	15	13	12						
Fine motor	53.00 (7.1)	52.53 (5.9)	52.38 (8.6)	50.67 (6.5)	0.997	0.994	0.774	1.00	0.903	0.929
Visual reception	53.57 (7.4)	51.27 (8.8)	51.00 (8.4)	46.69 (10.3)	0.830	0.802	0.083	1.00	0.488	0.568
Receptive language	56.75 (14.3)	49.80 (10.7)	49.23 (17.0)	36.83 (17.7)	0.463	0.435	0.001	1.00	0.118	0.167
Expressive language	50.00 (6.7)	51.73 (7.3)	48.15 (13.9)	43.08 (15.3)	0.953	0.951	0.221	0.797	0.145	0.612
24 month- N	30	16	11	14						
Fine motor	56.73 (12.2)	54.69 (6.5)	50.27 (7.5)	46.79 (7.8)	0.903	0.240	0.012	0.651	0.125	0.808
Visual reception	58.67 (9.3)	55.63 (7.9)	57.55 (11.6)	51.00 (11.2)	0.748	0.988	0.083	0.959	0.572	0.354
Receptive language	59.87 (6.8)	57.47 (5.3)	52.55 (11.5)	47.50 (17.7)	0.885	0.200	0.003	0.634	0.057	0.627
Expressive language	59.70 (9.5)	55.13 (7.5)	51.09 (11.9)	48.36 (14.8)	0.518	0.114	0.009	0.773	0.320	0.921
36 month- N	31	16	13	14						
Fine motor	57.16 (12.4)	56.69 (11.6)	43.77 (8.2)	43.93 (11.4)	0.999	0.004	0.003	0.018	0.017	1.00
Visual reception	65.65 (8.8)	61.31 (10.6)	54.62 (10.4)	54.36 (13.3)	0.537	0.011	0.007	0.324	0.274	1.00
Receptive language	58.45 (7.4)	57.75 (7.6)	51.62 (8.5)	47.14 (10.8)	0.993	0.073	0.0004	0.211	0.005	0.511
Expressive language	63.10 (6.8)	58.06 (7.7)	54.54 (10.8)	49.64 (8.3)	0.188	0.011	0.00001	0.648	0.029	0.400

*One-way ANOVAS for MSEL *t*-test scores with Tukey's test for post hoc analyses; Kruskal–Wallis tests for comparison of ADOS severity scores with Dunn's test for post hoc analyses.

meeting criteria on the ADOS or coming within 3 points of cut-off) were reviewed by a licensed clinical psychologist by evaluating video recordings of behavioural assessments and their scores to determine final clinical judgement: typically developing, ASD or non-spectrum concerns (e.g. ADHD, anxiety, language delay). Toddlers were included in the ASD group if they had a severity score of 4 or higher on the ADOS at either 24 or 36 months *and* received a final clinical judgement of ASD at 36 months.

Stimuli

Toddlers listened to a stream of two different groups of concrete nouns: words expected to be acquired early (hereafter 'early words') and words expected to be acquired late (hereafter 'late words'; see Table 2 for a full list of words used). Early words were understood, on average, by 84% of 18-month-olds according to MacArthur-Bates Communicative Development Inventories (MCDI; Fenson *et al.*, 2007) normative data (Dale & Fenson, 1996). In addition, within our sample, the majority of parents (30 LRC-Typ, 16 HRA-Typ, 12 HRA-Atyp, 9 ASD) confirmed that the child comprehended each of the early words (scale ranging from 0 to 4; 4 being very confident that the child understands the word). Based on parent report, these groups did not differ in their scaled responses of understanding the early words ($F_{3,63} = 0.193$, $P = 0.900$). Of the late words, none were even included on the MCDI at 18 months (Dale & Fenson, 1996). Early and late words were matched on syllabic length and phonemic structure. Words were spoken by a female with a maximum duration of 600 milliseconds. Each noun was presented a maximum of three times for up to 120 trials total, and the order of presentation of the words was randomized across participants.

Procedure

Toddlers sat in a sound- and electrically shielded, dimly lit room while passively listening to a stream of words playing from bilateral loudspeakers (70–80 dB). An experimenter was in the room to ensure that the child remained quiet and tolerated the net (providing opportunities for breaks, blowing bubbles, or snack). The procedure took approximately ten minutes.

ERP recording and data processing

Continuous electroencephalogram (EEG) was recorded using a 128-channel Geodesic Sensor Net (Electrical Geodesics Inc., Eugene, OR) based on the child's head circumference and referenced online to a single vertex electrode (Cz). The electrical signal was amplified with a Net Amps 300 amplifier using a 0.1–100 band pass, digitized at 250 Hz and stored on a computer drive. The data were processed offline using NetStation 4.5.1 analysis software (Electrical Geodesics Inc., Eugene, OR). The continuous EEG signal was segmented into 1300-ms post-stimulus epochs with a baseline period of 100 ms before stimulus presentation, digitally filtered using a 30-Hz low-pass elliptical filter, and baseline-corrected against the mean voltage during the 100-ms pre-stimulus baseline period.

Segments were visually examined by an experimenter blind to the study group, and individual channels were marked bad if contaminated by artefacts such as body movement, eye movement, eye blinks or off-scale activity (±200 μV). A segment would be excluded from further analysis if it had more than 15% of the channels marked as bad. If the number of segments for one condition (i.e. early or late words) differed significantly from the other

TABLE 2. Stimuli

Early words	Late words
Ball	Bone
Balloon	Cage
Banana	Calf
Bath	Cash
Bear	Deck
Bird	Fan
Boat	File
Book	Fog
Bunny	Gorilla
Cheese	Hero
Cookie	Hip
Cup	Peacock
Duck	Pen*
Fish	Pitch
Hat	Ruler
Juice	Shell
Keys	Tone
Kitty	Vase
Nose	Waiter
Sock	Yam

*Pen did not meet our classification criteria of a late word. As a result, we excluded all pen trials from further analyses.

condition, then segments were randomly excluded until the number of segments per condition differed by five or fewer within individual participants. Participants with fewer than 10 good segments in either of the conditions were excluded from remaining analysis. For all remaining participants, bad channels of accepted segments were replaced by means of a spherical spline interpolation. Average waveforms for each condition for each participant were generated and re-referenced to the average reference. For the final sample, this resulted in an average of 28.38 (SD = 11.04) early word trials and 27.69 (SD=10.99) late word trials. There were no differences in the number of trials across groups for either the early or late words (all $P > 0.128$; see Table 3).

Analysis of the ERP data addressed the mean amplitude of two time bins, representative of two components sensitive to word processing: N200 (200–350 ms post-stimulus) and N350 (350–500 ms post-stimulus). These time windows were chosen based on past research using similar paradigms (Mills *et al.*, 1997, 2004, 2005; Kuhl *et al.*, 2013). Unlike previous work, which reports negativity across the scalp during these time windows, visual inspection of our waveforms revealed an inverse polarity pattern with positivity in the anterior regions and negativity in the posterior regions within these same time bins. This is likely due to differences in the systems and ERP processing steps as past studies have used low-density electrode nets and mastoid-based references. Our study uses a high-density system and an average reference, which has been argued to be ideal when processing a signal from a high-density system (Picton *et al.*, 2000; Luck, 2005). Given that reference choice has been shown to affect the topography of the signal (e.g. Joyce & Rossion, 2005; Yao *et al.*, 2005), it is not surprising that our waveforms' topographical distribution differs from previous work.

Two regions of interest (ROIs) from each hemisphere were constructed: frontal and temporo-parietal (see Fig. 1 for details). The electrodes we used for each region with corresponding 10–20 system sites are as follows. The left frontal region included electrodes 24 (F3), 13 (FC1), 28 (FC5); the right frontal region included electrodes 124 (F4), 112 (FC2), 117 (FC6); the left temporo-parietal region included electrodes 60 (P1), 52 (P3), 51 (P5); the right temporo-parietal region included electrodes 85 (P2), 92 (P4), 97 (P6). These ROIs were chosen based on similar research using the same electrodes (Kuhl *et al.*, 2013) or similar areas used in a custom electrode array (Mills *et al.*, 2004). As is common practice with high-density systems, ROIs were computed by averaging the signal across the three channels in each ROI.

Statistical approach

Because of the polarity differences found within our sample, we first examined the components separately within the ROIs (frontal, temporo-parietal) and groups (LRC-Typ, HRA-Typ, HRA-Atyp and ASD) to investigate general patterns of ERPs within each of the groups. We computed repeated measures ANOVAS with condition (early, late), time bin (200–350 ms, 350–500 ms), and hemisphere (left, right) as within-subjects factors and the average amplitude of the frontal and temporo-parietal sites as the dependent variables.

To examine group differences between the LRC-Typ, HRA-Typ, HRA-Atyp and ASD children, we performed two repeated measures, mixed-model ANOVAS with condition (early, late) time bin (200–350 ms, 350–500 ms), and hemisphere (left, right) as within-subjects factors and group (LRC-Typ, HRA-Typ, HRA-Atyp and ASD) as a between-subjects factor with average amplitude of the frontal and temporo-parietal sites as the dependent variables. Additionally, given that our groups differed in language abilities as measured by the MSEL (Mullen, 1995; see Table 1), we used the verbal developmental quotient of the MSEL, a measure of both expressive and receptive language abilities, as a covariate in these analyses. By controlling for language abilities, we are able to determine that group differences in lexical processing, if they arise, are due to the group identity and not the varying language abilities seen across these groups. Significant main and interaction effects were further explored using simple effects tests with Bonferroni's correction for multiple comparisons. Effect sizes are reported as partial eta-square (η^2).

To better understand the relations among ERPs and language abilities and ASD severity, we computed Spearman's rho correlations between ERPs (keeping conditions, time bins and hemispheres separate), MSEL verbal developmental quotient and ADOS severity scores across all participants as well as within the four groups (LRC-Typ, HRA-Typ, HRA-Atyp, ASD). Bonferroni's correction for multiple comparisons was applied.

Results

ERPs to words at 36 months: patterns within the groups

ERP waveforms are presented in Figs 2 and 3, and descriptive data appear in Table 4.

LRC-Typ: For frontal electrodes, the ANOVA revealed a significant main effect of time ($F_{1,30} = 23.66$, $P = 0.00003$, $\eta^2 = 0.441$) such that the N200 was more positive than the N350. There were no significant effects involving condition as well as no other significant main or interaction effects within the frontal sites.

For temporo-parietal electrodes, there was a significant main effect of condition ($F_{1,30}$) = 6.52, $P = 0.016$, $\eta^2 = 0.179$) such that early words were more negative than late words. There were no other significant main or interaction effects.

HRA-Typ: For frontal sites, the ANOVA revealed a significant main effect of time ($F_{1,15} = 32.67$, $P = 0.00004$, $\eta^2 = 0.685$) with the N200 being more positive than the N350. There were no significant effects involving condition as well as no other significant main or interaction effects within the frontal sites.

TABLE 3. Characteristics of the 36-month ERP visit

	Group				Significance Group Comparison*
	LRC-Typ	HRA-Typ	HRA-Atyp	ASD	
Age months (SD)	36.39 (0.8)	36.06 (0.6)	36.15 (0.4)	36.08 (0.5)	0.158
36-month ERP trials					
Early words (SD)	29.58 (12.0)	33.31 (10.2)	24.31 (7.7)	23.86 (10.2)	0.237
Early words range	10–54	12–51	14–36	11–46	
Later words (SD)	29.19 (11.7)	32.38 (10.22)	24.08 (9.0)	22.36 (9.7)	0.128
Late words range	12–52	11–47	13–38	11–43	

*One-way ANOVAS for age and ERP trials.

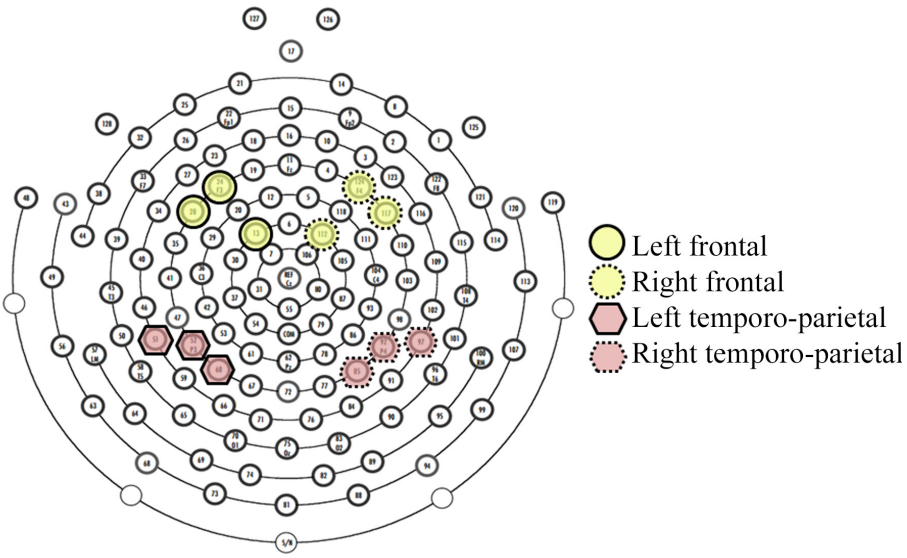

FIG. 1. Electrode groupings used for the 128-channel HydroCel Sensor Net.

For temporo-parietal sites, there was a significant main effect of time ($F_{1,15}$ = 4.61, P = 0.048, η^2 = 0.235) with the N200 being more negative than the N350. There was a significant main effect of hemisphere ($F_{1,15}$ = 7.11, P = 0.018, η^2 = 0.321) with a more negative response in the right hemisphere. There was also a significant time by hemisphere interaction ($F_{1,15}$ = 5.37, P = 0.035, η^2 = 0.263). This interaction was driven by a more negative N200 than the N350 in the right hemisphere (P = 0.014, η^2 = 0.339) and no difference between the time bins within the left hemisphere (P = 0.304). There were no significant effects involving condition and no other significant main or interaction effects for the temporo-parietal sites.

Similar to the LRC-Typ group, the HRA-Typ group displayed differences across time bins for the frontal sites. However, LRC-Typ children showed differential responses to early compared to late words, specifically within the temporo-parietal sites, while HRA-Typ children did not show a differential response. Additionally, the LRC-Typ showed no varying hemispheric responses, and the HRA-Typ children did within the temporo-parietal sites.

HRA-Atyp: For frontal sites, the ANOVA revealed a significant main effect of time ($F_{1,12}$ = 50.37, P = 0.00001, η^2 = 0.808) with N200 being more positive than the N350. There was also a significant condition by hemisphere interaction ($F_{1,12}$ = 5.13, P = 0.043, η^2 = 0.299) such that late words exhibited a more positive response than early words in the right hemisphere (P = 0.043, η^2 = 0.298) with no difference in the left hemisphere (P = 0.621).

For temporo-parietal sites, there was a significant main effect of condition ($F_{1,12}$ = 4.81, P = 0.049, η^2 = 0.286) with a more negative response to late words compared to early words. There was a significant main effect of time ($F_{1,12}$ = 6.23, P = 0.028, η^2 = 0.342) with the N200 being more negative than the N350. There was also a significant time by hemisphere interaction ($F_{1,12}$ = 4.82, P = 0.49, η^2 = 0.287). This interaction was driven by a more negative N200 than the N350 in the right hemisphere (P = 0.009, η^2 = 0.443) and no difference between the time bins within the left hemisphere (P = 0.328).

Similar to the patterns seen in the LRC-Typ and HRA-Typ groups, the HRA-Atyp group displayed differences across time bins in frontal and temporo-parietal sites. Moreover, both the HRA groups, HRA-Typ and HRA-Atyp, showed a similar hemispheric timed pattern in the temporo-parietal sites. However, the HRA-Atyp group did differ in their responses to early and late words as they showed the opposite pattern compared to the LRC-Typ group.

ASD: For frontal sites, the ANOVA revealed a significant main effect of time ($F_{1,13}$ = 10.57, P = 0.006, η^2 = 0.448) with N200 being more positive than the N350. There was an approaching significant condition by time interaction ($F_{1,13}$ = 4.58, P = 0.052, η^2 = 0.261) such that early words exhibited a more positive N200 than N350 (P = 0.004, η^2 = 0.487), with no such pattern emerging for late words (P = 0.561). There was also an approaching significant condition by time by hemisphere interaction ($F_{1,13}$ = 4.56, P = 0.052, η^2 = 0.260). This interaction was driven by a more positive N200 than the N350 in the right hemisphere for early words (P = 0.002, η^2 = 0.519), but no significant difference within the right hemisphere for late words (P = 0.599).

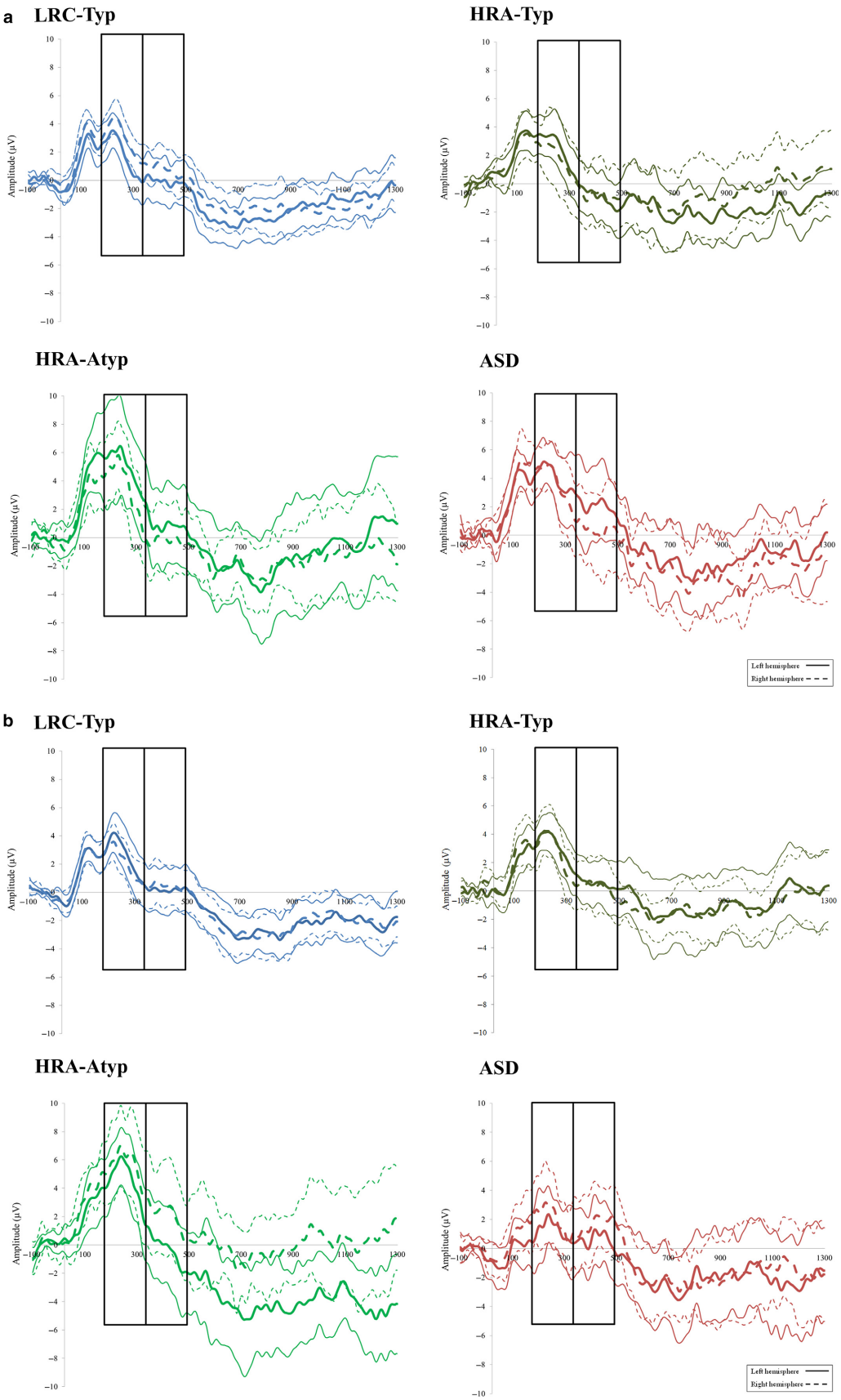

FIG. 2. (a) Grand-averaged waveforms of early words over left and right frontal sites with 95% confidence intervals. (b) Grand-averaged waveforms of late words over left and right frontal sites with 95% confidence intervals.

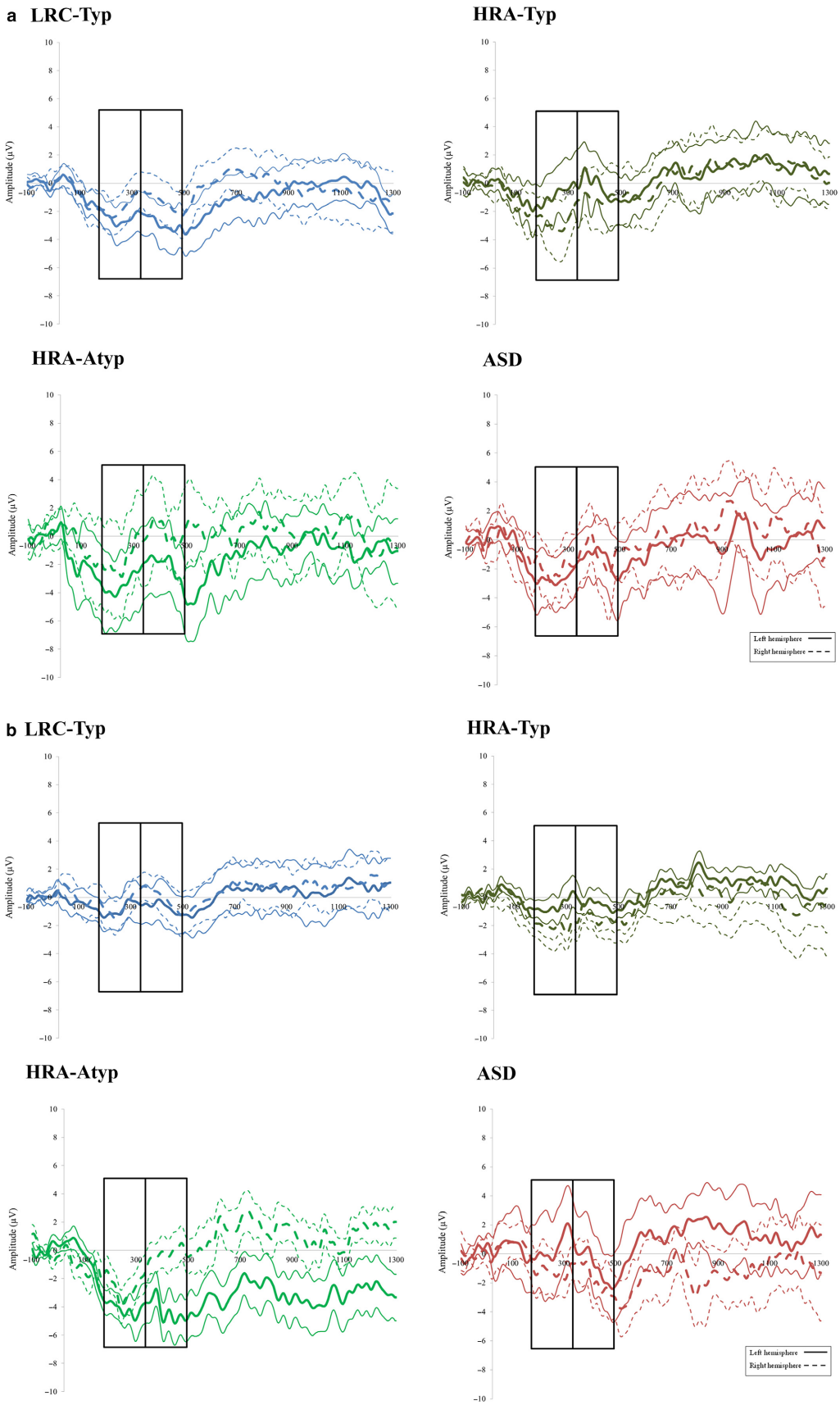

FIG. 3. (a) Grand-averaged waveforms of early words over left and right temporo-parietal sites with 95% confidence intervals. (b) Grand-averaged waveforms of late words over left and right temporo-parietal sites with 95% confidence intervals.

TABLE 4. Average amplitude (μV) of ERPs to early and late acquiring words in LRC-Typ, HRA-Typ, HRA-Atyp and ASD children

	Early words							
	LRC-Typ		HRA-Typ		HRA-Atyp		ASD	
	Left hem	Right hem	Left hem	Right hem	Left hem	Right hem	Left hem	Right hem
Frontal								
200–350 ms	1.82 (3.5)	3.02 (2.9)	2.11 (3.0)	1.57 (4.7)	5.15 (5.6)	3.65 (4.5)	4.15 (3.4)	3.87 (3.2)
350–500 ms	−0.06 (4.2)	0.79 (3.7)	−1.07 (3.3)	−0.85 (4.5)	0.86 (5.1)	−0.08 (4.1)	2.17 (5.1)	0.61 (4.9)
Temporo-parietal								
200–350 ms	−2.51 (3.3)	−1.66 (3.3)	−0.75 (3.6)	−2.65 (3.4)	−3.24 (4.3)	−1.89 (5.3)	−2.60 (3.3)	−2.05 (3.1)
350–500 ms	−2.82 (4.1)	−1.19 (3.7)	−0.24 (3.8)	−0.97 (3.8)	−2.06 (4.2)	0.46 (4.8)	−1.17 (3.8)	−1.05 (3.9)
	Late words							
	LRC-Typ		HRA-Typ		HRA-Atyp		ASD	
	Left hem	Right hem	Left hem	Right hem	Left hem	Right hem	Left hem	Right hem
Frontal								
200–350 ms	2.60 (3.7)	2.04 (3.8)	2.93 (2.7)	2.66 (3.3)	4.59 (3.5)	5.73 (4.8)	1.34 (3.5)	2.35 (4.0)
350–500 ms	0.20 (4.1)	0.45 (4.1)	0.44 (3.1)	0.16 (3.4)	0.16 (4.6)	2.43 (5.7)	1.00 (3.9)	1.93 (4.1)
Temporo-parietal								
200–350 ms	−0.84 (3.0)	−0.54 (3.4)	−0.62 (3.5)	−2.72 (2.5)	−4.27 (3.2)	−2.82 (3.3)	0.66 (4.7)	−1.02 (2.4)
350–500 ms	−0.59 (4.0)	0.21 (3.6)	−0.30 (3.0)	−2.01 (2.0)	−4.09 (4.6)	−0.48 (4.0)	−0.05 (3.9)	−1.55 (2.1)

For temporo-parietal sites**,** there was a significant condition by time interaction ($F_{1,13}$ = 11.03, P = 0.006, η^2 = 0.459). This interaction was driven by a more negative N200 than N350 within the early words (P = 0.015, η^2 = 0.378) and no such pattern emerging within the late words (P = 0.255). There was also a significant condition by hemisphere interaction ($F_{1,13}$ = 6.03, P = 0.029, η^2 = 0.317). However, closer inspection of this interaction revealed no significant differences in follow-up analyses (all P > 0.091). There were no other significant main or interaction effects.

Similar to the LRC, HRA-Typ and HRA-Atyp groups, the ASD group exhibited differences across time bins for the frontal sites. Additionally, the ASD, LRC-Typ and HRA-Atyp children showed differential responses to early and late words unlike the HRA-Typ children. However, the ASD children had different patterns within the time bins depending on the word familiarity, while LRC-Typ and HRA-Atyp children did not.

ERPs to words at 36 months: group differences

Because there were different numbers of boys and girls in each of our groups, we investigated potential sex differences within ERPs to early and late words while controlling for language abilities. We found no sex differences in either the frontal (all . P > 0.09) or the temporo-parietal (all P > 0.18) sites.

Controlling for language abilities, within the frontal sites, we found a significant time by group interaction ($F_{3,69}$ = 3.62, P = 0.017, η^2 = 0.136). There was a trending group difference within the N200 (P = 0.054), but closer inspection revealed no group differences (all P > 0.080); groups did not differ from each other for the N350 (P = 0.469). There were no significant effects involving condition as well as no other significant main or interaction effects within the frontal sites.

Controlling for language abilities, within the temporo-parietal sites, we found a significant hemisphere by group interaction ($F_{3,69}$ = 3.52, P = 0.020, η^2 = 0.133). This interaction was driven by group differences in the left hemisphere (P = 0.041), but closer inspection within the left hemisphere revealed no differences between each of the groups (all P > 0.070). We also found a significant condition by time by group interaction ($F_{3,69}$ = 2.96, P = 0.038, η^2 = 0.114). This was driven by the HRA-Atyp children showing a more negative response in the N200 for the late words compared to the LRC-Typ children (P = 0.046) and the ASD children (P = 0.004). There were no other significant main or interaction effects.

Relations between ERPs, language abilities and ASD severity

We found no significant relations between any of the ERPs and the MSEL verbal developmental quotient. However, we did find a relation between the N200 frontal left hemisphere response to late words and ADOS severity (r_s = −0.402, P = 0.0004), such that the less positive the N200 response to late words in the frontal left hemisphere, the more severe the ASD symptoms. Following up on this association, we found that the HRA-Atyp group was driving the correlation between the N200 response to late words in the frontal left hemisphere and severity of ASD symptoms (r_s = −0.773, P = 0.003), and this association was not significant for any of the other groups (all P > 0.063). We found no other significant relations between ERPs and ASD severity.

Discussion

Our current study investigated the ERP responses to early and late words in groups of LRC-Typ, HRA-Typ, HRA-Atyp and ASD 36-month-olds. We found that the LRC-Typ, HRA-Atyp and ASD children showed differential neural responses to early compared to late words, but this general pattern did not hold for the HRA-Typ group. All groups showed a tendency to show differential time responses. When looking at group differences while controlling for language, there were group differences within temporo-parietal sites such that the HRA-Atyp group showed atypical responses to late words. Finally, we found a relation between neural response to late words

in the frontal sites and ASD severity. Below, we discuss the implications of these findings by considering possible interpretations while emphasizing the limitations and need for follow-up studies.

Similar to past research (Conboy & Mills, 2006; Kuhl *et al.*, 2013), our LRC-Typ group showed differential responses to words of varying familiarity with a more negative response to early compared to late words. In contrast, the HRA-Typ children were not sensitive to word familiarity as they showed no differential responses. While the HRA-Typ group is defined as having no delays in cognitive development, past work has found a slower developmental trajectory, specifically in expressive and receptive language abilities, for HRA-Typ groups compared to LRC-Typ groups (Ozonoff *et al.*, 2014). The slower, albeit typical, development of language within the first few years of life of these toddlers might lead to a different type of neural processing of early and late words. At 36 months, HRA-Typ children might simply lack a differential response to early and late words like their LRC-Typ peers, or they might show a distinct differential pattern in other topographical areas or later time bins. Future infant sibling work should continue to make the distinction between LRC-Typ and HRA-Typ groups to investigate the differences in their early neurodevelopmental patterns.

The HRA-Atyp and the ASD groups showed different patterns in response to the varying word familiarity. Specifically, both the HRA-Atyp children and children with ASD exhibited differential responses to early and late words in the frontal sites, unlike the LRC-Typ and HRA-Typ groups. The HRA-Atyp group had a more positive response in the right hemisphere for late words, while the ASD group had a more positive N200 in the right hemisphere for early words. These group differences in scalp topography might suggest atypical specialization of cortical areas specific for language. Additionally, this rightward asymmetry in response to early words for children with ASD as well as the late words for the HRA-Atyp children might reflect slower and more effortful processing. Typically developing children with better language abilities tend to show greater leftward hemispheric specialization in response to known words, and researchers have argued that the absence of this leftward pattern might be linked to more effortful processing (Conboy & Mills, 2006).

HRA-Atyp and ASD groups also showed differential responses to early and late words in the temporo-parietal sites. The HRA-Atyp group showed the opposite pattern compared to the LRC-Typ group with a more negative response to late words compared to early words. Children with ASD exhibited a more negative response across all temporo-parietal sites for the early words, like the LRC-Typ group, but this was specific for the N200. These differences in responses depending on word familiarity might reflect each group's language abilities, especially the HRA-Atyp group. As we categorized the HRA-Atyp group to include any child with a cognitive delay as measured by the MSEL, this includes possible delays in the language domain. Indeed, when looking at the HRA-Atyp children who were included in this group based on cognitive delay, all children were delayed in the language domain of the MSEL. The differences in language abilities between the HRA-Atyp and the LRC groups might be driving the opposite pattern of responses we find at the temporo-parietal sites. In addition, there could be differences in their receptive vocabulary, specifically the extent to which these groups of children know the late words. Future research should consider the children's receptive vocabulary to better understand whether these differences only reflect differences in their vocabulary size.

Similarly, differences in general patterns of responses to early and late words might also reflect a subtle, processing deficit related to vocabulary acquisition. Using an eye-tracking task that measured accuracy and speed of looking towards target images for both early and late words, Chita-Tegmark *et al.* (2015) found that 18- and 24-month HRA toddlers performed like the LRC toddlers. In contrast, at 36 months, HRA toddlers, while still performing at similar speeds as their LRC peers, were lower in accuracy in identifying the target image. Chita-Tegmark *et al.* (2015) argued that the difference in accuracy is not due to a difference in vocabulary knowledge, but rather a difficulty in the ability to form strong lexical representations of words. Although we do not have information on the group's vocabulary knowledge, we do know that by 36 months, the HRA-Atyp and ASD groups were showing no language impairments as measured by the MSEL despite having poorer language abilities than the LRC-Typ and HRA-Typ groups. Thus, the different neural signature in the processing of words in the HRA-ATyp children and the children with ASD might represent a lexical processing difference such as a weaker lexical representation of words.

The inconsistent findings of hemispheric specialization within our sample, specifically the LRC-Typ group, is surprising given that language shows strong leftward lateralization in the majority of typically developing individuals, emerging as early as a few days after birth (Molfese *et al.*, 1975; Toga & Thompson, 2003; Gervain *et al.*, 2008). However, this might be due to several factors. One possibility is the difference in systems and reference choice compared to past studies, since reference configuration has been shown to affect the topography of the signal (e.g. Joyce & Rossion, 2005; Yao *et al.*, 2005). Another possibility is that the children within our sample are showing bilateral activation in response to words. Language does not solely rely on the left hemisphere as the right hemisphere is strongly involved in many components of language including prosody and pragmatics (see Lindell, 2006 for a review). Although the current study does not make use of full sentences, as often seen in experiments testing prosody and pragmatics, the stimuli were words spoken in a naturally engaging voice which might include various prosodic cues, resulting in bilateral activation. Indeed, bilateral activation has also been found in paradigms studying other aspects of language such as phonemes, which is thought to be due to the natural prosodic cues (Liebenthal *et al.*, 2005, 2010; Meyer *et al.*, 2005).

To better understand whether the groups differed in their ERP responses to words, we compared them directly while controlling for language abilities. We found no group differences within the frontal sites. In contrast, within the temporo-parietal sites, we found that the HRA-Atyp group exhibited a more negative response to late words during the N200 time bin compared to the LRC-Typ and ASD groups. This difference within our HRA-Atyp group may, again, reflect their weaker lexical representation of words. Chita-Tegmark *et al.* (2015) found behavioural differences that emerged solely at 36 months for the HRA group within the late words condition. Within the early words condition as well as prior to 36 months, LRC and HRA children performed similar in both accuracy and speed. By 36 months, the HRA-Atyp children might have difficulties in processing and forming an accurate lexical representation of words, specifically late words, and this difficulty might be reflected in their atypical neural responses.

The fact that the HRA-Atyp group differed from the ASD group is surprising. Perhaps this is due to the variability often seen in the language abilities of children with ASD. Language impairment is no longer a core symptom of ASD, and indeed, some of the children in our ASD sample displayed no language delays as measured by the MSEL while others showed a delay at 18 and 24 months, similar to the HRA-Atyp children. This finding might also be the result of the toddlers with ASD within our sample receiving early behavioural intervention. Early intervention has been shown to significantly

improve cognitive abilities, specifically expressive and receptive language skills (Dawson *et al.*, 2009). Thus, participation in early intensive interventions may have led to improvements in the underlying lexical representation of words in our ASD children, resulting in a differential pattern to early and late words that was similar to the LRC-Typ group but the opposite of the HRA-Atyp group. Additionally, it should be noted that our language abilities assessment was a combined measure of expressive and receptive abilities and not a receptive vocabulary measure, which might be a better indicator of underlying lexical processing skills of these groups. Future work should investigate the children's developing vocabulary abilities, specifically the depth of their lexical representations as well as their vocabulary level, to better understand how word meaning might interact with their topographical and timing of neural responses in a lexical processing task.

Finally, we investigated potential relations between ERPs and language abilities and ASD severity. Here, we found a significant correlation between an ERP response and ASD severity, such that the less positive the N200 response to late words in the frontal left hemisphere, the more severe the ASD symptoms. Interestingly, this association was driven by the HRA-Atyp group and not the ASD group. While fMRI studies using language tasks show decreased activation in the left hemisphere in individuals with ASD, it is unclear how this might extend to individuals at familial risk for ASD (Kleinhans *et al.*, 2008; Knaus *et al.*, 2008, 2010). Specific to our sample, the HRA-Atyp group with a more atypical N200 to late words in the frontal sites was more likely to display milder autism symptoms, while the HRA-Atyp group as a whole exhibited an atypical N200 to late words in the temporo-parietal sites. Future work should continue to look at scalp topography differences in the frontal and temporo-parietal sites and how they relate to both language abilities and ASD severity in toddlers with ASD as well as toddlers at familial risk for ASD.

In interpreting these results, several limitations should be considered. First, we do not know the extent to which the child understands the late words. Future work should consider a better measure of children's vocabulary, including some type of lexical processing measure, as group differences might emerge on lexical items that are not strongly represented within children's repertoires. Second, although this sample size is reflective of typical infant sibling studies, there were a limited number of children within the HRA groups as well as the children with a diagnosis of ASD. Work should continue to expand on the sample size. Despite these limitations, our results indicate that atypical neural processing of words might be a result of an inaccurate lexical representation of words and is not specific to the children with ASD. Future studies should continue to consider the developmental trajectory of language abilities in addition to diagnoses to better understand the similarities and differences in lexical processing in young children with and without ASD.

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Competing interests

The authors declare that they have no competing interests.

Author contributions

CAN and HTF conceived and designed the Infant Sibling Project. KHF analysed ERP and statistical data. KHF, HTF and CAN contributed to the writing of the manuscript.

Data accessibility

The data sets generated during and/or analysed during the current study are available from the corresponding author upon reasonable request.

Abbreviations

ADOS, Autism Diagnostic Observation Schedule; ASD, Autism spectrum disorder; BAP, Broader autism phenotype; EEG, Electroencephalogram; ERP, Event-related potential; HRA-Atyp, HRA with milder autism-like symptoms; HRA, High risk for autism; HRA, HRA without ASD diagnosis; HRA-Typ, HRA without milder autism-like symptoms; LRC, Low-risk control; MCDI, MacArthur-Bates Communicative Development Inventories; MSEL, Mullen Scales of Early Learning; ROI, Region of interest.

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