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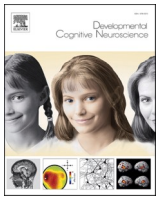

Exploring the relation between brain response to speech at 6-months and language outcomes at 24-months in infants at high and low risk for autism spectrum disorder: A preliminary functional near-infrared spectroscopy study

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ABSTRACT

Infants at high familial risk for autism spectrum disorder (ASD) are at increased risk for language impairments. Studies have demonstrated that atypical brain response to speech is related to language impairments in this population, but few have examined this relation longitudinally. We used functional near-infrared spectroscopy (fNIRS) to investigate the neural correlates of speech processing in 6-month-old infants at high (HRA) and low risk (LRA) for autism. We also assessed the relation between brain response to speech at 6-months and verbal developmental quotient (VDQ) scores at 24-months. LRA infants exhibited greater brain response to speech in bilateral anterior regions of interest (ROIs) compared to posterior ROIs, while HRA infants exhibited similar brain response across all ROIs. Compared to LRA infants, HRA+ infants who were later diagnosed with ASD had reduced brain response in bilateral anterior ROIs, while HRA- infants who were not later diagnosed with ASD had increased brain response in right posterior ROI. Greater brain response in left anterior ROI predicted VDQ scores for LRA infants only. Findings highlight the importance of studying HRA+ and HRA- infants separately, and implicate a different, more distributed neural system for speech processing in HRA infants that is not related to language functioning.

1. Introduction

Within the first few years of life, typically developing infants experience rapid growth in language abilities. In contrast, infants who are at high familial risk for autism spectrum disorder (ASD), defined as having an older sibling with ASD, show a reduced growth trajectory in language abilities relative to their typically developing (TD) peers (Hudry et al., 2014). The likelihood of these infants being diagnosed with ASD by the age of 36-months is almost 20% (Messinger et al., 2015). Regardless of whether or not they go on to develop ASD, infants at high risk for autism (HRA) are more likely to have language impairments than typically developing infants at low risk for autism (LRA; Iverson and Wozniak, 2007). Studying how the brains of HRA infants respond to speech will provide further insights into why some HRA infants go on to develop language impairments while others do not.

Previous work using functional magnetic resonance imaging (fMRI) and functional near-infrared spectroscopy (fNIRS) has shown that functional specialization occurs within the first few months of life in typically developing LRA infants. Between birth and 7-months of age, regions of the temporal and frontal lobes are fine-tuned to respond to forward speech compared to backward speech and silence (Dehaene--Lambertz et al., 2002; Pena et al., 2003). Less is known about the emergence of functional specialization for speech processing in HRA infants between birth and 7-months of age. Using fMRI and fNIRS, some studies have examined how 4- to 7-month-old HRA infants process non-speech vocalizations (i.e., crying, laughing, yawning); these studies

Abbreviations: LRA, low risk for autism; HRA, high risk for autism.

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found that HRA infants exhibit a lack of functional specialization for non-speech vocalizations in temporal and frontal regions of the brain (Blasi et al., 2015; Lloyd-Fox et al., 2013, 2018). These studies also reported that HRA infants exhibit reduced activation relative to LRA infants, and that this difference is most pronounced in HRA infants who later go on to develop ASD (Lloyd-Fox et al., 2018). While these findings demonstrate that HRA infants exhibit atypical brain response to non-speech vocalizations, these results cannot be used to draw conclusions about the neural correlates of speech processing. To our knowledge, only one study has examined how the brains of HRA infants process speech during this developmental period. This fNIRS study reported increased activation in regions of the temporal lobe when 3-month-old HRA infants listened repetitive and random syllable sequences (Edwards et al., 2017). fMRI studies conducted with older samples (12- to 48-months) have found that children with ASD also demonstrate functional specialization for speech processing, as indicated by greater activation in temporal regions of the brain when listening to forward speech compared to backward speech and silence (Eyler et al., 2012; Lombardo et al., 2015; Redcay and Courchesne, 2008). However, when compared to TD children, children with ASD exhibited reduced activation within regions of the frontal and temporal lobes and increased activation within regions of the parietal and occipital lobes (Eyler et al., 2012; Redcay and Courchesne, 2008). Findings from these fMRI and fNIRS studies suggest that HRA infants and children with ASD demonstrate atypical brain response to speech that is characterized by reduced activation within regions of the brain that are typically involved in speech processing and increased activation within regions of the brain that are not typically involved in speech processing. However, none of these fMRI or fNIRS studies on speech processing assessed whether brain response to speech differs in HRA infants who do go on to develop ASD (HRA+) compared to HRA infants who do not go on to develop ASD (HRA-). Thus, we do not know whether this atypical brain response to speech is present in all HRA infants, or only in those who are later diagnosed with ASD. Studies using other neuroimaging methods, such as electroencephalography (EEG), have shown that HRA+ and HRA- infants process speech differently at the neural level (Finch et al., 2018; Righi et al., 2014), highlighting the importance of studying these two groups of HRA infants separately.

Reduced and/or atypical localization of brain response to speech may lead to the development of language impairments in ASD. Indeed, several studies that used EEG to measure brain response to speech in HRA infants and children with ASD have reported significant relations between brain response and language abilities measured cross-sectionally (Sandbank et al., 2017) and longitudinally (Coffey-Corina et al., 2008; Kuhl et al., 2013; Seery et al., 2014). The EEG studies that examined this relation longitudinally showed that those who exhibited reduced amplitude in frontal, central, and parietal electrode sites when listening to words (Coffey-Corina et al., 2008; Kuhl et al., 2013) or repetitive vowel-consonants (Seery et al., 2014) had lower expressive and receptive language abilities, as measured by standardized assessments such as the Mullen Scales of Early Learning (Coffey-Corina et al., 2008; Seery et al., 2014) and the Preschool Language Scales (Kuhl et al., 2013). Findings from studies that used fMRI to measure brain response to speech in HRA infants and children with ASD are mixed, reporting positive (Redcay and Courchesne, 2008), negative (Lombardo et al., 2015), and non-significant (Eyler et al., 2012) within-group relations between brain response and concurrent language abilities. The only fMRI study to explore the longitudinal relation between brain response and language abilities within a group of children with ASD found that 12- to 24-month-olds who had greater brain response in "language-related" regions of the temporal and pre-frontal cortices when listening to stories had worse receptive and expressive language abilities one year later, as measured by the Mullen Scales of Early Learning (Lombardo et al., 2015). Additionally, in this study it was found that this relation was reversed within a group of TD children; greater brain response was related to *better* receptive and expressive language outcomes. Evidence of a significant relation between early brain function and longitudinal language abilities indicates a neural basis for language impairments in ASD. However, little is known about whether this brain-behavior relation emerges during the first 6-months of life, as all of these studies measured brain response when infants were 9-months of age or older. Assessing the relation between brain response at 6-months and longitudinal language outcomes will demonstrate whether a biological marker of future language impairment can be detected in HRA infants prior to 9-months of age. Identifying such a biological marker will improve our ability to predict language outcomes for this high-risk population.

Functional near-infrared spectroscopy (fNIRS) is a non-invasive neuroimaging tool that uses light to measure changes in oxyhemoglobin (oxyHb) and deoxyhemoglobin (deoxyHb) concentration, which reflects fluctuations in blood flow to different regions on the cortical surface of the brain. As a result of neurovascular coupling, this increase in blood flow to a specific region of the brain corresponds with an increase in neural activity (i.e., "brain response" or "activation"), as neural activation requires an influx of oxygen-rich blood (Villringer and Chance, 1997). fNIRS has many advantages over traditional neuroimaging methods that makes it suitable for use with young, atypical populations (Vanderwert and Nelson, 2014). Compared to fMRI, fNIRS is less susceptible to motion artifacts and allows us to measure infants' brain activity while they are awake and seated comfortably with a caregiver (Lloyd-Fox et al., 2010). fNIRS is particularly valuable when studying speech processing because, unlike fMRI, the equipment does not produce noises that may interfere with the infant's ability to hear the stimuli (Quaresima et al., 2012). While many researchers have opted to use EEG when working with HRA infants, the high spatial resolution of fNIRS allows us to identify which regions of the brain are exhibiting atypical activation. To date, no studies have used fNIRS to assess the relation between early brain function and longitudinal language abilities in HRA infants.

For the present study, we utilized fNIRS to investigate the neural correlates of speech processing in 6-month-old LRA and HRA infants. Our first aim was to determine whether brain response to speech differed between these groups. To gain further insights into whether 6-month-old infants can detect structural regularities in speech, infants listened to two types of speech – repetitive syllable sequences (ABB speech; ko-ba-ba) and random syllable sequences (ABC speech; ko-ba-fe). Because previous work has shown that 3-month-old LRA and HRA infants do not discriminate between repetitive and random syllable sequences (Edwards et al., 2017), we hypothesized that infants in our sample would show similar brain response to both types of speech. Based on previous literature (Eyler et al., 2012; Lombardo et al., 2015; Redcay and Courchesne, 2008), we also hypothesized that across both types of speech LRA infants would have greater brain response to speech compared to HRA infants, as indicated by greater oxyHb concentration values. In an exploratory analysis, we investigated whether oxyHb concentration values differed among HRA infants diagnosed with ASD by 24-/36-months (HRA+) and HRA infants not diagnosed with ASD by 24-/36-months (HRA-). Our second aim was to investigate the relation between brain response to speech at 6-months and language outcomes at 24-months, as measured by verbal developmental quotient scores on the Mullen Scales of Early Learning, within groups of LRA and HRA infants separately. Based on previous research (Lombardo et al., 2015), we hypothesized that greater brain response to speech at 6-months would be associated with better language outcomes at 24-months in LRA infants, but worse language outcomes at 24-months in HRA infants.

2. Material and methods

2.1. Participants

Participants were drawn from a larger sample of infants enrolled in a prospective, longitudinal research project that tracked the development

of infants at high risk for ASD across the first three years of life. Infants living in a metropolitan area were recruited into two groups – a high risk for autism group (HRA) and a low risk for autism group (LRA). Infants in the HRA group had an older sibling with a community diagnosis of ASD, which was confirmed using the Social Communication Questionnaire (SCQ; Rutter et al., 2003). Infants in the LRA group were typically developing with no behavioral or developmental disorders; LRA infants also had typically developing older sibling(s) and no family history of ASD in first- or second-degree relatives. All infants were later-born with at least one older sibling, came from primarily English-speaking households (heard English >80% of the time at home), were born full-term (>36 weeks) with a birth weight above 2500 g, and had no known neurological or genetic disorders. All families gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved and monitored by the Institutional Review Board (IRB) at Boston Children's Hospital.

fNIRS data was initially collected from 35 LRA infants and 23 HRA infants at the 6-month visit. To be included in the final sample, infants needed to have usable fNIRS data from one or more of the channels within each brain region of interest (ROI). The fNIRS data was considered to be unusable if the raw intensity signal exceeded a certain threshold (see Section 2.5 on fNIRS data processing). Additionally, infants were only included if they had at least eight usable trials for each type of syllable sequence (minimum of 16 trials total). In the LRA group, 4 participants were excluded because they had a family history of ASD, 1 was excluded for being too old at the time of testing (<8-months-old), 1 was excluded because fNIRS data was unusable, 2 were excluded because they did not have enough trials, and 9 were excluded because of attrition (no 24- or 36-month visits). In the HRA group, 1 was excluded due to experimenter error, 1 was excluded for being too old at the time of testing (<8-months-old), 2 were excluded because fNIRS data was unusable, 4 were excluded because they did not have enough trials, and 1 was excluded because of attrition (no 24- or 36-month visits). The percentage of infants excluded from the final sample here (44.8%) is similar to what has been reported in previous studies (Lloyd-Fox et al., 2010).

The final sample used for analyses included 18 infants in the LRA group and 14 infants in the HRA group. Groups did not significantly differ on any demographic variables (Table 1). At their final lab visit, which occurred at either 24-months ($N = 6$) or 36-months ($N = 26$), all infants were evaluated for ASD using the Autism Diagnostic Observation Schedule (ADOS-2; Lord et al., 2000). Video recordings of infants who met criteria on the ADOS-2, or who came within three points of the cutoff score, were reviewed by a licensed clinical psychologist who provided a best estimate clinical judgment. Based on this best estimate clinical judgment, infants were divided into three groups based on their risk status (high or low risk) and eventual ASD diagnosis (ASD or no ASD). Out of the 14 HRA infants included in the final sample, 5 received a diagnosis of ASD (HRA+) and 9 did not (HRA-). None of the 18 LRA infants included in the final sample received a diagnosis of ASD (LRA).

2.2. Procedure

Infants and their parents came into the lab for multiple visits between 3- and 36-months of age, during which they completed a battery of assessments. At their 3-, 6-, 9-, and 12-month visits, infants completed the fNIRS task described below. At their 6-, 12-, 18-, 24-, and 36-month visits, infants completed the Mullen Scales of Early Learning. For the present study, we analyzed fNIRS data from the 6-month visit because functional specialization of language-related brain regions begins between 3- and 7-months of age (Dehaene-Lambertz et al., 2002, 2010; Grossman et al., 2010). We analyzed Mullen data from the 24-month visit because this is the age during which previous work has observed the greatest difference in Mullen scores between LRA and HRA infants (Estes et al., 2015; Landa and Garrett-Mayer, 2006).

Table 1
Sample Demographics by Group.

	Infants at Low Risk for Autism (LRA)	Infants at High Risk for Autism (HRA)	*p*-value
N	18	14	
Number of Trials			.278
Mean	27.3	26.2	
Range	19.0 – 28.0	16.0 – 28.0	
Age (days)			.516
Mean	210.9	215.2	
Range	187.0 – 241.0	174.0 – 242.0	
Mullen VDQ Scores			.592
Mean	114.2	110.5	
Range	79.0 – 146.0	74.0 – 154.0	
Household Income			.143
Mean	3.6	3.9	
Range	1.0 – 4.0	3.0 – 4.0	
Maternal Education			.541
Mean	3.2	2.9	
Range	1.0 – 4.0	1.0 – 4.0	
Sex (%)			1.00
Female	50.0	50.0	
Male	50.0	50.0	
Race (%)			.419
White	83.3	92.9	
Some other race or more than one race	16.7	7.1	
Ethnicity (%)			.854
Hispanic/Latino	5.6	7.1	
Not Hispanic/Latino	94.4	92.9	

Note: Responses for household income were collapsed to a four-point scale: (1) $25,000–35,000, (2) $45,000–55,000, (3) $65,000–75,000, (4) >$75,000. Responses for maternal education were collapsed to a four-point scale: (1) Community college, some college, or professional degree, (2) Four-year college degree, (3) Some graduate school, (4) Masters or doctorate. $N = 3$ participants ($N = 1$ LRA, $N = 2$ HRA) were missing household income and maternal education data. Groups were compared using independent samples t-tests and chi-square tests.

2.3. fNIRS task and stimuli

During the fNIRS task, infants were seated on their parents' lap in a dimly lit, soundproof room. Auditory stimuli were played through a hidden speaker that was placed in front of the infants. To minimize infants' movement during the task and maximize the number of trials heard, infants were presented with a silent video of moving shapes; toys and/or bubbles were used if the infant became uninterested in the video. The fNIRS task lasted approximately 20 min.

Stimuli presented during the fNIRS task were identical to those used in previous studies (Edwards et al., 2017; Gervain et al., 2008; Keehn et al., 2013; Wagner et al., 2011). Two types of speech were presented – repetitive syllable sequences (ABB speech) and random syllable sequences (ABC speech). ABB speech was defined as the presentation of 3 sequential syllables in which the last 2 syllables were identical (e.g., ko-ba-ba). ABC speech was defined as the presentation of 3 sequential syllables in which all 3 syllables were different (e.g., ko-ba-fe). Both types of speech were computer-generated at a monotonous pitch (200 Hz) using a female voice, and were matched on syllabic repertoire, frequency of syllables, phonological characteristics, and prosody (Gervain et al., 2008).

Stimuli were presented in a block trial design (Fig. 1). Each trial included 10 different presentations of the same type of syllable sequence; each presentation lasted 270 ms and was separated by randomly varying intervals of silence that ranged from 500 ms to 1500 ms. The entire trial lasted approximately 16 s. Trials were manually triggered by the experimenter and were separated by a period of silence that ranged from 15.5 to 119.9 s ($M = 19.2$ s; 96.4% of intertrial periods of silence were less than 30 s in length). Trial order was pseudo-randomized and counterbalanced based on risk status and sex.

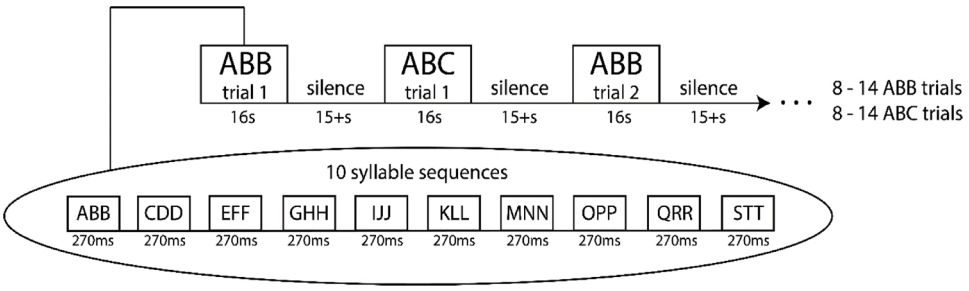

Fig. 1. Visual representation of stimuli presented during fNIRS task. Each trial was composed of 10 different presentations of the same type of syllable sequence (ABB or ABC). Trials lasted approximately 16 s and were separated by at least 15 s of silence. Each infant heard between 8 and 14 trials of each type of syllable sequence. Abbreviations: s = seconds, ms = milliseconds.

2.4. fNIRS system

For fNIRS data collection, we used the Hitachi ETG-4000 system with two wavelengths (695 nm and 830 nm). Data were collected at a sampling rate of 10 Hz. The fNIRS probe consisted of 10 sources and 8 detectors placed bilaterally over the scalp in a 3 × 3 array. Sources and detectors were separated by a distance of 3 cm and secured onto a soft, flexible headband. 24 channels covered both hemispheres of the brain (Fig. 2). The headband was placed on infants' heads using the modified combinatorial nomenclature 10−10 system; channel 3 was centered on T7 and channel 20 was centered on T8. To be consistent with previously published work that used the same fNIRS probe and stimuli (Edwards et al., 2017; Keehn et al., 2013), channels were grouped into four regions of interest (ROIs) – left anterior, right anterior, left posterior, and right posterior. Channels 5, 6, 7, 8, 15, 18, 19, and 22 were excluded from these ROIs to ensure adequate separation between ROIs. ROIs were defined more generally as "anterior" and "posterior" relative to infants' ears to account for the asymmetrical chevron layout of the probe on each hemisphere and any variations in placement of the probe across infants. Using AtlasViewer (Aasted et al., 2015), we registered the probe to the average head size of infants in the present sample (circumference =44.4 cm, Iz to Cz =25.9 cm, LPA to RPA =28.3 cm). This registration showed that the anterior ROIs covered regions of the temporal and frontal lobes (T, FT, FC, and C positions) and the posterior ROIs bilaterally covered regions of the parietal and occipital lobes (P, CP, and PO positions; Fig. 2). Signals from channels within each ROI were compiled using simple averaging.

2.5. fNIRS data processing

fNIRS data were processed using Homer2 (Huppert et al., 2009). First, channels were excluded from analyses if the raw intensity signal exceeded 4.95 or went below 0.1 for more than 5 s (Edwards et al., 2017). The percentage of channels excluded from analyses ranged from 0%\ to 62.5% in the LRA group (M = 22.2%)%) and 0 to 41.7% in the HRA group (M = 13.7 %). Second, we converted the raw intensity signal to optical density and performed wavelet motion correction (iqr = .5). Remaining motion artifacts that were not corrected were then identified as any change in the signal greater than a threshold of 20 standard deviations within a 500 ms window using "hmrMotionArtifactbyChannel" (Behrendt et al., 2018; Cooper et al., 2012; Di Lorenzo et al., 2019). Then, we performed band pass filtering ($.01 < f < .8$) to remove biological noise (heart rate, respiration, blood pressure), and converted optical density to concentration of oxyHb using the modified Beer-Lambert law (ppf = 5.0). Finally, we estimated the hemodynamic response function (HRF) using ordinal least square method of general linear modeling (GLM) with a time range of −2 to 20 s and drift order correction of 3. Motion artifacts that were previously identified using "hmrMotionArtifactbyChannel" were excluded when estimating the HRF using GLM. For each subject, oxyHb values by time were extracted from the Homer2 group results and converted from molar (mol) to micromolar (μM) using in house MATLAB scripts. All infants in the final sample had usable data from one or more channels within each ROI, and had at least eight usable trials for each type of syllable sequence. Average oxyHb concentration values from 6 to 20 s post-stimulus onset was used for analyses. This time window was selected by visually inspecting the range of hemodynamic responses across all infants within this sample. Similar time windows have been used in previous infant

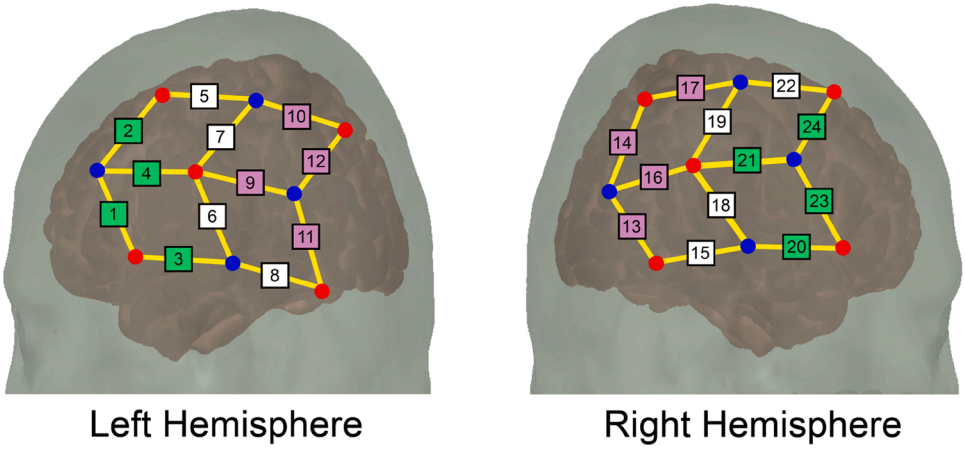

Fig. 2. fNIRS probe registered to head and brain template in AtlasViewer. Sources (red) and detectors (blue) are represented as circles. Channels are represented as squares. Each region of interest (ROI) was composed of 4 measurement channels. Channels in the left and right anterior ROIs are green, and channels in the left and right posterior ROIs are purple. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).

fNIRS studies (Edwards et al., 2017; Emberson et al., 2017; Grossmann et al., 2010).

2.6. Mullen Scales of Early Learning

The Mullen Scales of Early Learning is a developmental measure commonly-used to assess children from birth to 68-months of age (Mullen, 1995). Infants completed all 5 scales of the Mullen (gross motor, fine motor, visual reception, receptive language, expressive language). The receptive language scale assesses children's comprehension of spoken language (i.e., how does child respond to questions, directions, and commands). The expressive language scale assesses children's ability to use speech to communicate and express ideas (i.e., babbling, use of consonant and syllable sounds, size of vocabulary). Verbal developmental quotient (VDQ) scores were calculated by first averaging age equivalent scores from the expressive language and receptive language scales; this average was then divided by chronological age in months and multiplied by 100 (Bishop et al., 2011).

2.7. Data analysis

To address our first aim, we conducted a 2 × 4 × 2 mixed factorial ANOVA – Syllable Sequence (ABB, ABC) × ROI (Left Anterior, Right Anterior, Left Posterior, Right Posterior) × Group (LRA, HRA). For this ANOVA, both HRA+ and HRA- infants were included in the HRA group. To determine whether there were differences in oxyHb concentration values among infants in the HRA+, HRA-, and LRA groups, we also ran an exploratory 2 × 4 × 3 ANOVA – Syllable Sequence (ABB, ABC) × ROI (Left Anterior, Right Anterior, Left Posterior, Right Posterior) × Group (LRA, HRA-, HRA+). For both ANOVAs, significant interaction effects were explored using simple effects post-hoc testing and Bonferroni correction for multiple comparisons. We also conducted an additional analysis modeled after Gervain et al. (2008), in which we used independent samples t-tests to compare oxyHb concentration values in each channel across groups of LRA and HRA infants. To address our second aim, we conducted zero-order Pearson's correlations using oxyHb concentration values in each ROI measured during the 6-month visit and Mullen VDQ scores measured during the 24-month visit. We conducted these correlations within the LRA group and the HRA group separately. Exploratory correlations were conducted with VDQ scores measured during the 6- 12-, 18-, and 36-month visits (see Supplementary Materials). All statistical analyses were carried out in SPSS (Version 24.0.0.1) and were conducted using oxyHb concentration values, as previous literature has shown that oxyHb has a better signal to noise ratio than deoxyHb (Lloyd-Fox et al., 2010). For transparency of reporting, analyses were repeated using deoxyHb concentration values; these analyses yielded similar results and are reported in our Supplementary Materials.

3. Results

3.1. ANOVA with two groups (LRA, HRA)

Results of the 2 × 4 × 2 (syllable sequence x ROI x group) mixed factorial ANOVA are summarized in Table 2. The ROI by group interaction effect was significant ($F(3, 90) = 6.66$, $p < .001$; Fig. 3). All other main effects and interaction effects were non-significant.

Simple effects post-hoc testing with Bonferroni correction showed that for both types of speech, the LRA group had greater oxyHb concentration in the left anterior ROI compared to the left posterior ROI ($p = .04$) and right posterior ROI ($p = .006$), and greater oxyHb concentration in the right anterior ROI compared to the left posterior ROI ($p = .04$) and right posterior ROI ($p = .002$). In the LRA group, there were no significant differences in oxyHb concentration between the left anterior and right anterior ROIs ($p = 1.00$), nor between the left posterior and right posterior ROIs ($p = 1.00$). In the HRA group, there were no significant differences in oxyHb across all ROIs ($ps = 1.00$).

Table 2
Results of mixed factorial ANOVA (LRA and HRA groups).

Source	SS	df	Mean Square	F	p-value	Partial η^2
Main Effects						
Syllable Sequence	.00	1	.00	.06	.81	.00
ROI	.19	3	.06	1.90	.14	.06
Group	.00	1	.00	.00	.99	.00
Interaction Effects						
Syllable Sequence×ROI	.03	3	.01	.92	.43	.03
Syllable Sequence×Group	.01	1	.01	.22	.64	.01
ROI×Group	.65	3	.22	6.66***	<.001	.18
Syllable Sequence×ROI×Group	.04	3	.01	1.05	.37	.03

Note: HRA group includes HRA+ and HRA- infants.
*** $p < .001$.

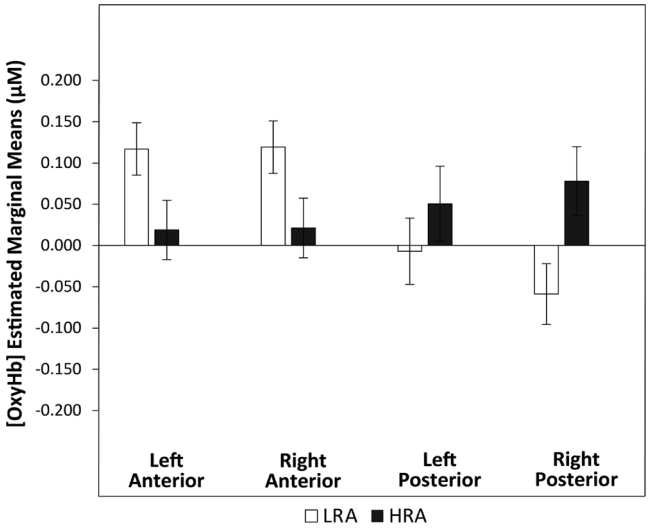

Fig. 3. ROI × Group Interaction with two groups (LRA, HRA). OxyHb concentration estimated marginal means reflect brain response to both types of speech (ABB and ABC). The LRA group is represented by white bars and the HRA group is represented by black bars. The HRA group includes HRA+ and HRA- infants. Error bars reflect standard error. Abbreviations: HRA = high risk for autism, LRA = low risk for autism, μM = micromolar, oxyHb = oxyhemoglobin.

Post-hoc testing also showed that the HRA group had significantly lower oxyHb concentration than the LRA group in the left anterior ROI ($p = .050$) and the right anterior ROI ($p = .050$). In the left posterior ROI, there were no significant differences in oxyHb concentration between groups ($p = .35$). In right posterior ROI, the HRA group had significantly greater oxyHb concentration than the LRA group ($p = .02$).

3.2. Exploratory ANOVA with three groups (LRA, HRA-, HRA+)

Results of the 2 × 4 × 3 (syllable sequence x ROI x group) mixed factorial ANOVA are summarized in Table 3. The main effect of group was significant ($F(2, 29) = 3.61$, $p = .04$), and, as in the prior analysis, the ROI by group interaction effect was significant ($F(6, 87) = 3.68$, $p = .003$; Fig. 4). All other main effects and interaction effects were non-significant.

Exploring this ROI by group interaction effect further using post-hoc testing with Bonferroni correction for multiple comparisons, the LRA group had greater oxyHb concentration in the left anterior ROI compared to the left posterior ROI ($p = .04$) and right posterior ROI ($p = .007$), and greater oxyHb concentration in the right anterior ROI

Table 3
Results of exploratory mixed factorial ANOVA (LRA, HRA-, and HRA+ groups).

Source	SS	df	Mean Square	F	p-value	Partial η^2
Main Effects						
Syllable Sequence	.00	1	.00	.13	.72	.00
ROI	.01	3	.00	.08	.97	.00
Group	.49	2	.25	3.61 *	.04	.20
Interaction Effects						
Syllable Sequence×ROI	.05	3	.02	1.41	.25	.05
Syllable Sequence×Group	.01	2	.00	.11	.90	.01
ROI×Group	.72	6	.12	3.68 **	.003	.20
Syllable Sequence×ROI×Group	.11	6	.02	1.60	.16	.10

* $p < .05$.
** $p < .01$.

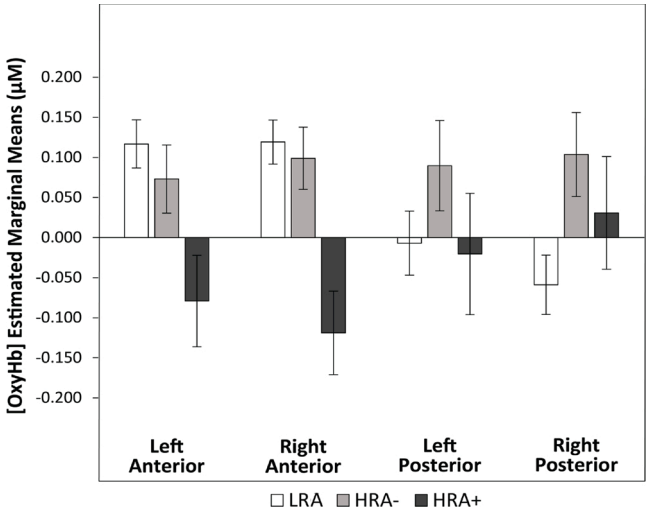

Fig. 4. ROI × Group Interaction with three groups (LRA, HRA-, HRA+). OxyHb concentration estimated marginal means reflect brain response to both types of speech (ABB and ABC). The LRA group is represented by white bars, the HRA- group is represented by light grey bars, and the HRA+ group is represented by dark grey bars. Error bars reflect standard error. Abbreviations: HRA+ = high risk for autism with autism diagnosis by 24-/36-months, HRA- = high risk for autism with no autism diagnosis by 24-/36-months, LRA = low risk for autism, µM = micromolar, oxyHb = oxyhemoglobin.

compared to the left posterior ROI ($p = .04$) and right posterior ROI ($p = .001$). In the LRA group, there were no significant differences in oxyHb concentration between the left anterior and right anterior ROIs ($p = 1.00$), nor between the left posterior and right posterior ROIs ($p = 1.00$). In the HRA- and HRA+ groups, there were no significant differences in oxyHb concentration across all ROIs ($ps > .43$).

Post-hoc testing also showed that in the left anterior ROI, the HRA+ group had significantly lower oxyHb concentration than the LRA group ($p = .02$), but there were no significant differences in oxyHb concentration between the HRA+ group and HRA- group ($p = .12$) nor between the HRA- group and the LRA group ($p = 1.00$). In the right anterior ROI, the HRA+ group had significantly lower oxyHb concentration than the LRA group ($p = .001$) and the HRA- group ($p = .007$); the difference between the HRA- group and the LRA group was non-significant ($p = 1.00$). In the left posterior ROI, there were no significant differences in oxyHb concentration among the three groups ($ps > .52$). In the right posterior ROI, the HRA- group had greater oxyHb concentration than the LRA group ($p = .05$); there were no significant differences in oxyHb concentration between the HRA- group and HRA+ group ($p = 1.00$), nor between the LRA group and HRA+ group ($p = .81$).

3.3. Group differences in oxyHb concentration by channel

In channel 1 ($t(28) = 2.06, p = .05$), channel 7 ($t(24) = 2.26, p = .03$), channel 20 ($t(21) = 2.10, p = .05$), and channel 23 ($t(28) = 2.13, p = .04$), LRA infants had significantly greater oxyHb concentration values than HRA infants (Fig. 5). In channel 15 ($t(21) = -2.09, p = .05$) and channel 16 ($t(26) = -2.09, p = .05$), HRA infants had significantly greater oxyHb concentration values than LRA infants. Significant differences did not survive correction for multiple comparisons. All other independent samples *t*-tests were nonsignificant.

3.4. Pearson's correlation analyses

Because we did not detect differences in oxyHb concentration values for ABB speech versus ABC speech, Pearson's correlation analyses were conducted using average oxyHb concentration values across all trials, regardless of syllable sequence type. Within the LRA group, oxyHb concentration values in the left anterior ROI at 6-months were significantly correlated with VDQ scores at 24-months ($r(16) = .57, p = .01$; Fig. 6). Within the HRA group, oxyHb concentration values in the left anterior ROI at 6-months were not significantly correlated with VDQ scores at 24-months ($r(12) = .25, p = .40$; Fig. 6). All other correlations with VDQ within the LRA and HRA groups were non-significant (Table 4). When examining HRA- and HRA+ infants separately, all brain-behavior correlations were nonsignificant within the HRA- group ($ps > .85$) and HRA+ group ($ps > .19$).

In post-hoc exploratory analyses, we examined the relation between oxyHb concentration values at 6-months and VDQ scores at 6-, 12-, 18-, and 36-months in the HRA and LRA groups. All correlations were non-significant (see Supplementary Materials), except for the relation between oxyHb concentration values in the left posterior ROI at 6-months and verbal DQ scores at 36-months in the HRA group ($r(10) = -.59, p = .04$).

4. Discussion

In the present study, we investigated the neural correlates of speech processing in 6-month-old infants at high risk (HRA) and low risk (LRA) for autism. For our first aim, we found that HRA and LRA infants respond similarly to repetitive and random syllable sequences. When looking at brain response to both types of speech, we found brain response was greater in the bilateral anterior ROIs compared to the posterior ROIs within the LRA group, but similar across all ROIs within the HRA group. Compared to LRA infants, HRA infants showed reduced brain response in the bilateral anterior ROIs. However, our exploratory analysis showed that this reduced brain response within the HRA group was driven by the HRA+ infants who were later diagnosed with ASD. We also found that compared to LRA infants, HRA infants showed greater brain response in the right posterior ROI. Our exploratory analysis showed that this increased brain response in the HRA group was driven by the HRA- infants who were not later diagnosed with ASD. Because we did not detect differences in how the brains of LRA and HRA infants responded to repetitive versus random syllable sequences, we addressed our second aim by using average brain response to speech across all trials. We found that LRA infants who exhibited greater activation in the left anterior ROI at 6-months had higher VDQ scores at 24-months. However, this relation was non-significant in the HRA group. Findings suggest that the neural correlates of speech processing differ across groups of LRA, HRA-, and HRA+ infants.

In the group of LRA infants, brain response to speech was greater in the bilateral anterior ROIs compared to the posterior ROIs. Our findings are consistent with previous work that has shown that speech activates regions of the temporal and frontal lobes in 6-month-old infants (Blasi et al., 2015; Imada et al., 2006). It is likely that we did not observe

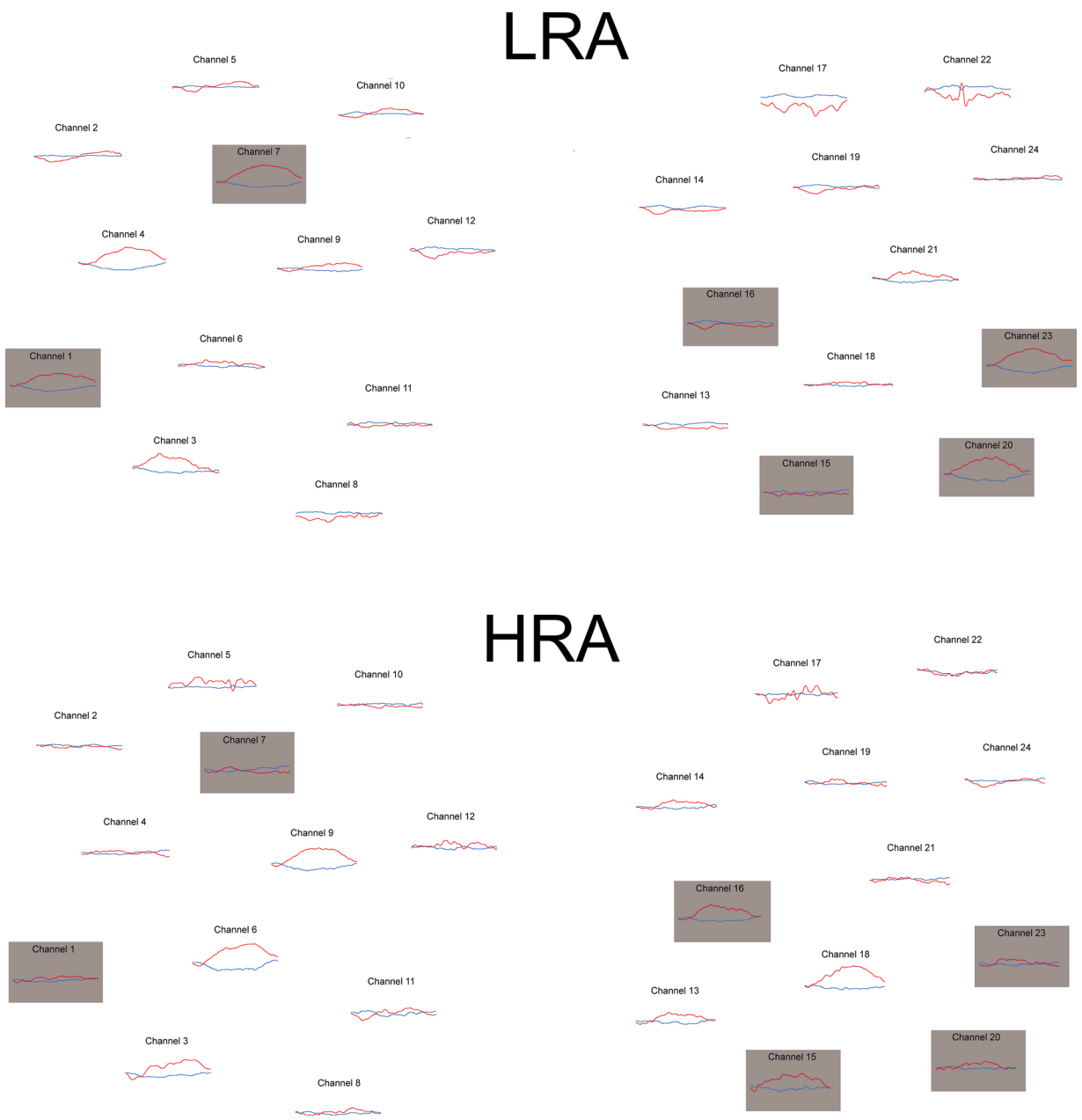

Fig. 5. Average hemodynamic response to both types of speech (ABB and ABC) within each channel. OxyHb (red) and deoxyHb (blue) concentration values are plotted on the y-axis from -.30 μM to .35 μM. Time is plotted on the x-axis from 0 s to 30 s. Channels that showed a significant difference in average oxyHb concentration during the analysis window (6 to 20 s post-stimulus onset) between groups of HRA and LRA infants are highlighted in grey (*ps* < .05, uncorrected). Abbreviations: HRA = high risk for autism, LRA = low risk for autism. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article).

significant differences in brain response between the left and right anterior ROIs because of our sample's very young age. Indeed, others have found that speech activates both hemispheres of the brain in 6-month-old infants (Blasi et al., 2015). However, as development progresses, brain response to speech becomes more left-lateralized (see Holland et al., 2007 and Rosselli et al., 2014 for review). These findings suggest that in typically developing LRA infants, functional specialization for speech processing, but not lateralization, is observable by 6-months of age. In contrast, HRA infants had similar brain response to speech across the anterior and posterior ROIs. Our exploratory analysis showed that both HRA+ and HRA- infants exhibited this lack of functional specialization. Because activation becomes more localized to specific brain regions with age, this finding may indicate that the brains of HRA infants are less functionally "mature" than the brains of LRA infants at this point in development (Johnson, 2001). This lack of functional specialization may contribute to language impairments and other social difficulties in HRA infants (Coffey-Corina et al., 2008; Keehn et al., 2015; Kuhl et al., 2013; Lloyd-Fox et al., 2013), regardless of whether or not they go on to develop ASD.

When comparing oxyHb concentration values across groups, brain response in the bilateral anterior ROIs was lower in the HRA group than in the LRA group. Our exploratory analysis indicated that this reduced brain response in the HRA group was driven by the HRA+ infants who were later diagnosed with ASD, as brain response in the anterior ROIs did not significantly differ between the LRA and HRA- groups, but did significantly differ between LRA and HRA+ groups. Although the group sizes in this exploratory analysis were small, other studies have reported similar findings in older children with ASD. For example, studies found

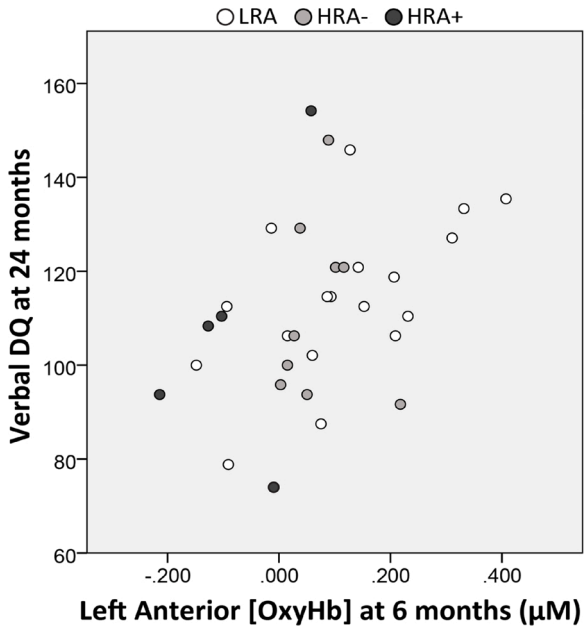

Fig. 6. Scatterplot of brain-behavior relation, which was only significant within the LRA group. OxyHb concentration values reflect brain response to both types of speech (ABB and ABC) in the left anterior region of interest, measured at the 6-month visit. Verbal DQ scores on the Mullen Scales of Early Learning were measured at the 24-month visit. The LRA group is represented by white points, the HRA- group is represented by light grey points, and the HRA+ group is represented by dark grey points. Abbreviations: HRA+ = high risk for autism with autism diagnosis by 24-/36-months, HRA- = high risk for autism with no autism diagnosis by 24-/36-months, LRA = low risk for autism, μM = micromolar, oxyHb = oxyhemoglobin, DQ = developmental quotient.

Table 4
Zero-order Pearson's correlations between oxyHb concentration values at 6-months and VDQ scores at 24-months within the LRA group and HRA group.

LRA Group				
	[oxyHb] Left Anterior	[oxyHb] Right Anterior	[oxyHb] Left Posterior	[oxyHb] Right Posterior
VDQ Scores	.57*	.29	.00	.04
HRA Group				
	[oxyHb] Left Anterior	[oxyHb] Right Anterior	[oxyHb] Left Posterior	[oxyHb] Right Posterior
VDQ Scores	.25	.09	−.06	−.25

Note: HRA group includes HRA+ and HRA- infants.
* $p < .05$.

reduced brain response in regions responsible for speech processing, such as the superior temporal gyrus and middle frontal gyrus (Eyler et al., 2012; Redcay and Courchesne, 2008), both brain regions which likely overlap with those measured in our anterior ROIs. Thus, it is likely that this reduced brain response to speech in these anterior regions of the frontal and temporal lobes is only present in high-risk infants who go on to develop ASD.

We also found that brain response in the right posterior ROI was greater in the HRA group compared to the LRA group. Our exploratory analysis indicated that this increased brain response in the HRA group was driven by the HRA- infants who were not later diagnosed with ASD. It is possible that HRA+ infants also demonstrate this increased activity in the right posterior ROI, but that we did not have the statistical power to detect this in our sample. Alternatively, HRA+ infants may exhibit this increased response in right-lateralized posterior regions, but that this is not yet detectable at 6-months of age. This possibility is supported by previous studies that found that older children with ASD have increased brain response to speech in right-lateralized posterior regions responsible for domain-general sensory processing, including the inferior parietal lobule, occipital gyrus, and postcentral gyrus (Eyler et al., 2012; Redcay and Courchesne, 2008), all brain regions which likely overlap with those measured in our posterior ROIs. In this case, increased activation in right-lateralized posterior regions of the brain may be biological marker of ASD risk regardless of diagnostic outcome. Alternatively, this increased response in the right posterior ROI of HRA- infants could indicate some type of compensatory or protective response that emerges early in development. The group sizes in this exploratory analysis were small and thus results should be interpreted with caution. Nevertheless, preliminary findings emphasize the importance of studying HRA+ and HRA- infants separately, as the neural correlates of speech processing may differ for high risk infants who do and do not go on to develop ASD.

Taken together, these group-level differences in how the brains of HRA infants process speech may lead to language impairments. Alternatively, these differences may implicate a different, more distributed neural system for language processing in HRA infants that does not directly impact language functioning. To better understand the clinical implications of these group-level differences in brain function, we investigated the relation between early brain response to speech and longitudinal language abilities. Within the LRA group, infants who exhibited greater brain response in the left anterior ROI at 6-months had greater VDQ scores at 24-months. The observed effect size of this correlation was large and similar to what has been found in other studies that explored this brain-behavior relation longitudinally (Junge et al., 2012; Kooijman et al., 2013; Kushnerenko et al., 2013). While previous work on typically developing LRA infants has shown that brain response to speech, as measured by EEG, is predictive of language abilities later in development (Junge et al., 2012; Kooijman et al., 2013; Kushnerenko et al., 2013), the present study is the first to demonstrate this brain-behavior relation using fNIRS. With further investigation, this increased brain response, as indicated by higher oxyHb concentration values within the left anterior ROI, could be used clinically to predict language outcomes in infants who are not at high familial risk for ASD.

In the HRA group, language abilities at 24-months were not significantly related to brain response at 6-months in any of the ROIs measured. Based on numerous studies that have demonstrated a significant brain-behavior relation in HRA infants (Coffey-Corina et al., 2008; Kuhl et al., 2013; Lombardo et al., 2015; Redcay and Courchesne, 2008; Seery et al., 2014; but see Eyler et al., 2012), it is possible that this relation was non-significant in our small sample because our analyses were underpowered. Alternatively, the significance of this brain-behavior relation may vary depending on the age in which language outcomes are assessed. As reported in our Supplementary Materials, post-hoc exploratory analyses showed that brain response in the left posterior ROI at 6-months was significantly and negatively correlated with verbal DQ scores at 36-months in the HRA group. The direction and effect size of this relation is similar to what was reported in Lombardo and colleagues (2015), who also measured language abilities at 36-months. Thus, it is possible that increased brain response within left posterior regions of the brain may be a biomarker for language impairments that do not emerge until 36-months of age in HRA infants. Future research on HRA infants and children with ASD should explore whether early brain response to speech predicts language outcomes at later points in development when language abilities are more stable (e.g., 5 years of age or older; Tager-Flusberg and Kasari, 2013). It is also possible that the significance of this brain-behavior relation in HRA infants and children with ASD may differ based on the neuroimaging method used; EEG studies reported a significant longitudinal relation between brain response and language outcomes (Coffey-Corina et al., 2008; Kuhl et al., 2013; Seery et al., 2014) while fMRI studies and the present fNIRS study reported both significant (Redcay and Courchesne, 2008; Lombardo et al., 2015), and non-significant (Eyler et al., 2012) results. In this case, EEG may be a more reliable neuroimaging method

to use when identifying biomarkers for language impairments in ASD.

4.1. Limitations

A number of limitations of the current study should be acknowledged. Although our total sample size was similar to what has been published in previous fNIRS studies (Braukmann et al., 2018; Fox et al., 2013; Lloyd-Fox et al., 2018; Wagner et al., 2011), we had a relatively small number of infants in our HRA group, which may explain some of our non-significant findings. Our sample size of $N = 32$ provides adequate power (.80) to detect large effect sizes ($\eta^2 = .42$) for a 2 × 4 x2 mixed factorial ANOVA and large within-group effect sizes ($r = .61$ for LRA and $r = .68$ for HRA) for correlation analyses. Because our study was underpowered, findings should be interpreted with caution. The small sample size also limited our choice of statistical methods. For example, we were unable to use early brain response to predict changes in VDQ scores overtime using latent growth modeling (Hertzog et al., 2008). We also were unable to include sex as an additional factor in our ANOVAs, even though previous work has shown that HRA infants exhibit sex differences in brain function (Edwards et al., 2017). Furthermore, we acknowledge that our sample is likely not representative of the larger HRA population. The majority of infants in our sample had VDQ scores that were above average, and no infants had VDQ scores indicative of clinically significant language delay (<70; Mullen, 1995). Follow-up studies should explore this brain-behavior relation in a larger, more heterogeneous sample of HRA+ and HRA- infants. Finally, we were unable to determine the precise location of brain response for each infant because we did not collect structural MRI data. We also acknowledge that the asymmetrical arrangement of channels on our fNIRS probe may have measured brain response in slightly different locations on each hemisphere. Future studies interested in using fNIRS to identify more specific neural correlates of speech processing should consider using new data processing techniques that allow for the precise localization of brain response measured by fNIRS that do not require collection of structural MRI data (see Wijeakumar et al., 2015 and Singh et al., 2005).

5. Conclusions

In summary, the neural correlates of speech processing in 6-month-old infants differ for those at high and low risk for autism. When listening to speech, LRA infants exhibited strongest activation in anterior regions of the brain, while HRA infants exhibited similar activation across all regions of the brain. Compared to LRA infants, HRA+ infants who were later diagnosed with ASD had reduced brain response in the bilateral anterior ROIs, while HRA- infants who were not later diagnosed with ASD had increased brain response in the right posterior ROI. However, this atypical brain response was not predictive of 24-month language abilities in HRA infants. This suggests that some HRA infants may have a “different but not less” neural system involved in speech processing that does not negatively impact language functioning. Future work is needed to determine whether these preliminary findings replicate in a larger, more heterogeneous sample of HRA+ and HRA- infants.

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Declaration of Competing Interest

The authors report no declarations of interest.

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Appendix A. Supplementary Materials

Supplementary materials related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.dcn.2020.100897.

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