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Atypical Hemispheric Specialization for Faces in Infants at Risk for Autism Spectrum Disorder

Brandon Keehn, Vanessa Vogel-Farley, Helen Tager-Flusberg, and Charles A. Nelson

Among the many experimental findings that tend to distinguish those with and without autism spectrum disorder (ASD) are face processing deficits, reduced hemispheric specialization, and atypical neurostructural and functional connectivity. To investigate the earliest manifestations of these features, we examined lateralization of event-related gamma-band coherence to faces during the first year of life in infants at high risk for autism (HRA; defined as having an older sibling with ASD) who were compared with low-risk comparison (LRC) infants, defined as having no family history of ASD. Participants included 49 HRA and 46 LRC infants who contributed a total of 127 data sets at 6 and 12 months. Electroencephalography was recorded while infants viewed images of familiar/unfamiliar faces. Event-related gamma-band (30–50 Hz) phase coherence between anterior–posterior electrode pairs for left and right hemispheres was computed. Developmental trajectories for lateralization of intra-hemispheric coherence were significantly different in HRA and LRC infants: by 12 months, HRA infants showed significantly greater leftward lateralization compared with LRC infants who showed rightward lateralization. Preliminary results indicate that infants who later met criteria for ASD were those that showed the greatest leftward lateralization. HRA infants demonstrate an aberrant pattern of leftward lateralization of intra-hemispheric coherence by the end of the first year of life, suggesting that the network specialized for face processing may develop atypically. Further, infants with the greatest leftward asymmetry at 12 months were those that later met criteria for ASD, providing support to the growing body of evidence that atypical hemispheric specialization may be an early neurobiological marker for ASD. *Autism Res* 2015, ••: ••–••. © 2015 International Society for Autism Research, Wiley Periodicals, Inc.

Keywords: autism; EEG coherence; face processing; hemispheric specialization; endophenotype; gamma; infancy

Introduction

Behavioral and neurofunctional assays of face processing in autism spectrum disorder (ASD) have revealed atypical processing and recognition of faces across the lifespan [Dawson, Webb, & McPartland, 2005a; Sasson, 2006]. Prospective longitudinal studies of infants at high risk for autism (HRA) because they have an older sibling diagnosed with autism [Ozonoff et al., 2011] may provide a window into the earliest manifestations of ASD [Rogers, 2009]. Electrophysiological studies of HRA infants have demonstrated atypical patterns of face and gaze processing within the first year of life [Elsabbagh et al., 2009, 2012; Key & Stone, 2012; McCleery, Akshoomoff, Dobkins, & Carver, 2009]. Multiple studies have additionally shown a familial risk for face processing deficits in ASD [Adolphs, Spezio, Parlier, & Piven, 2008; Dalton, Nacewicz, Alexander, & Davidson, 2007; Dawson et al., 2005a, 2005b; Wallace, Sebastian, Pellicano, Parr, &

Bailey, 2010; Webb et al., 2010], suggesting atypical face processing may represent an endophenotype [Gottesman & Gould, 2003].

In addition to face processing impairments, individuals with ASD also evidence atypical hemispheric specialization. Prior studies have revealed differences in gray [Herbert et al., 2005] and white matter [Fletcher et al., 2010] and electroencephalography (EEG) spectral power [Stroganova et al., 2007] asymmetries as well as the absence of functional lateralization for domains such as language [Cardinale, Shih, Fishman, Ford, & Muller, 2013; Eyler, Pierce, & Courchesne, 2012; Kleinhans, Muller, Cohen, & Courchesne, 2008a]. More recently, gene expression anomalies associated with cortical patterning pathways that regulate left–right asymmetry have also been found [Chow et al., 2012]. With respect to face processing, atypical lateralization of the electrophysiological indices of face processing have been shown in high-risk infants [McCleery et al., 2009], children [Webb,

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Dawson, Bernier, & Panagiotides, 2006], adolescents and adults [McPartland, Dawson, Webb, Panagiotides, & Carver, 2004] with ASD, and parents of children with ASD [Dawson et al., 2005a, 2005b]. Moreover, the left visual field (LVF) bias for faces, which may be associated with specialization of right hemisphere for face processing abilities, is reduced in at-risk infants [Dundas, Gastgeb, & Strauss, 2012b] and adults with ASD [Ashwin, Wheelwright, & Baron-Cohen, 2005; Dundas, Best, Minshew, & Strauss, 2012a]. Therefore, similar to face processing abnormalities, reduced or atypical hemispheric specialization may also represent an endophenotype in ASD.

In conjunction with atypical neurofunctional and structural asymmetries, previous research has also demonstrated that ASD is characterized by abnormal neural connectivity [Belmonte et al., 2004; Muller, 2007; Wass, 2011]. Aberrant development of anatomical connectivity during the first years of life in high-risk infants that develop ASD [Wolff et al., 2012] and functional connectivity in infants at risk [Keehn, Wagner, Tager-Flusberg, & Nelson, 2013] and in toddlers with ASD [Dinstein et al., 2011] have been found. The ASD connectivity literature includes patterns of both over- and underconnectivity across development, which is likely dependent on differences in methodology and analytic approaches, and may also reflect reduced network differentiation and specialization [Muller et al., 2011]. Functional connectivity magnetic resonance imaging (fcMRI) studies investigating face processing have revealed reduced connectivity between nodes of the face processing network in adults with ASD [Kleinmans et al., 2008a, 2008b; Koshino et al., 2008]. Infants at risk for ASD exhibit early differences in their attention to facial features [Jones & Klin, 2013]. Atypical attention to faces during sensitive periods of development could lead to deviations in the emergence and organization of the network specialized for face processing in ASD [Karmiloff-Smith, 2007].

The current study investigates event-related intra-hemispheric gamma-band phase coherence. Variations in gamma power are thought to represent synchronized activity of smaller (local) neural assemblies [Lachaux et al., 2007; Nir et al., 2007]. Therefore, gamma-band coherence among discrete regions may represent coupling of distributed generators necessary for large-scale integration of functionally specialized cortical regions [Varela, Lachaux, Rodriguez, & Martinerie, 2001]. In accord with this idea, spontaneous low-frequency blood oxygen level-dependent fluctuations, associated with intrinsic functional connectivity, and gamma-band power show similar region-specific correlation structures [He, Snyder, Zempel, Smyth, & Raichle, 2008]. The acquisition of new skills and changes in behavior during development may reflect and lead to inter-regional interactions and the emergence of specialized networks, rather

than the maturation of any single cortical region [Johnson, 2001]. Thus, understanding the coordinated communication between discrete regions may provide unique and important information about early functional brain development.

Prior research investigating gamma-band activity in HRA infants has revealed an atypical developmental trajectory of resting gamma power in frontal brain regions [Tierney, Gabard-Durnam, Vogel-Farley, Tager-Flusberg, & Nelson, 2012] and reduced differentiation of gamma activity to direct and averted gaze [Elsabbagh et al., 2009]. Coherence studies in ASD have primarily examined lower frequency bands (i.e. delta, theta, alpha, and beta) and have shown both increased and decreased coherence across unique frequencies [Coben, Clarke, Hudspeth, & Barry, 2008; Murias, Webb, Greenson, & Dawson, 2007]. Given prior evidence of early face processing anomalies, reduced hemispheric specialization, and neural underconnectivity in ASD and in those that share a genetic liability for ASD, the primary goal of the current study was to investigate the development of hemispheric specialization for face processing across the first year of life. Specifically, the current study sought to examine lateralization of event-related gamma-band phase coherence to faces in high- and low-risk infants at 6 and 12 months. A secondary goal was to determine whether early differences in hemispheric specialization differed in infants that later met criteria for ASD.

Methods and Materials

Participants

A total of 156 infants ($n = 77$ HRA; $n = 79$ low-risk comparison [LRC]) completed visits at 6 and 12 months of age. After exclusion of participants who were unable to tolerate the net and/or who did not contribute a minimum number of usable trials (see Table 1), the final sample included a total of 95 infants ($n = 49$ HRA; $n = 46$ LRC) that contributed 127 data sets (see Table S2 for number of participants contributing data for one or both

Table 1. Attrition Rates for Entire Sample of Participants

	HRA		LRC	
	6 months	12 months	6 months	12 months
Included	27 (47%)	39 (63%)	31 (48%)	30 (47%)
Excluded: refused net; fussed-out	4 (7%)	3 (5%)	3 (5%)	7 (11%)
Excluded: <10 Trials administered	11 (19%)	9 (15%)	10 (16%)	11 (17%)
Excluded: <10 Trials post-preprocessing	15 (26%)	11 (18%)	20 (31%)	16 (25%)

Percentage based on group and age.

Table 2. Participant Information

	HRA		LRC	
	6 months (<i>n</i> = 27)	12 months (<i>n</i> = 39)	6 months (<i>n</i> = 31)	12 months (<i>n</i> = 30)
Age [days]	193 (11) 177–214	373 (11) 353–413	195 (12) 170–223	371 (9) 359–390
Sex [males; females]	12;15	20;19	15;16	18;12
MSEL Early Learning Composite ^a	99 (10) 81–122	102 (15) 76–138	96 (10) 77–115	110 (12) 90–134
Total Trials	28 (7) 13–43	30 (9) 14–51	29 (5) 20–39	29 (7) 12–43
Accepted trials	17 (6) 10–31	20 (8) 10–38	16 (6) 10–31	17 (6) 11–29
Head circumference (mm)	44.1 (1.3) 41–46	46.8 (1.3) 44–50	43.8 (1.8) 40–49	46.9 (1.5) 45–51

^aScore for LRC group significantly higher than the HRA group at 12 months, $P < 0.05$ Mean (SD) range.

time points). All infants had a minimum gestational age of 36 weeks, no history of prenatal or postnatal medical or neurological problems, and no known genetic disorders (e.g. fragile X, tuberous sclerosis). Infants at high risk for ASD were defined by having an older full sibling with a diagnosis of autistic disorder, Asperger's disorder, or pervasive developmental disorder—not otherwise specified (HRA and LRC infants with older half-siblings were excluded). Community diagnosis of the older sibling with ASD was confirmed using the Social Communication Questionnaire [SCQ; Rutter, Bailey, & Lord, 2003], the Social Responsiveness Scale [SRS; Constantino & Gruber, 2005], and/or the Autism Diagnostic Observation Schedule [ADOS; Lord, Rutter, DiLavore, & Risi, 2001]. Low-risk infants had a typically developing older sibling (confirmed using SCQ, ADOS, and/or SRS), and no first- or second-degree family members with autism or other neurodevelopmental disorders. At 6- and 12-month visits, infants were administered the Mullen Scales of Early Learning [MSEL; Mullen, 1995] in order to obtain a measure of developmental functioning. Independent samples *t*-tests and Fisher's exact tests confirmed that at 6- and 12-month visits, the HRA and LRC groups did not differ significantly on age, sex, head circumference, or MSEL Early Learning Composite score (ELCS) (all *P* values $>.1$), with the exception of ELCS at 12 months, $t(67) = -2.3$, $P < .05$, on which the LRC group had a significantly higher score compared with the HRA group (see Table 2). Final ASD diagnostic outcome was determined on the basis of ADOS administration and clinical best estimate rating made by an expert clinician for the infant's most recent study visit. Of the 49 HRA infants, 11 were diagnosed with ASD based on 18-month ($n = 2$), 24-month ($n = 1$), or 36-month ($n = 8$) visits, 30 were classified as non-ASD, and 8 have not completed follow-up visits. Of the 46 LRC infants, 37 have completed follow-up visits, including diagnostic assessment, and have been classified as typically developing. Informed consent was obtained from all caregivers in accordance with the Boston Children's Hospital and Boston University Institutional Review Boards.

Stimuli

Stimuli consisted of color images of the infant's mother's face and an unfamiliar female face. All images were taken with a neutral expression with a gray background and with a gray cloth draped over the shoulders and neck. Images were cropped from mother's collarbone to the top of the head and laterally, approximately 1 inch on each side of the head to remove background and were then resized to a fixed width. Stimuli subtended approximately 14° by 17–24° visual angle. Unfamiliar (stranger) faces were chosen based on matching mother faces on as many features as possible (e.g. ethnicity and skin tone, glasses, hair up/down, hair/eye color). A different unfamiliar face was presented at 6- and 12-month visits.

Procedure

Data were acquired in a dimly lit electrically and acoustically shielded room. Infants were seated on their caregivers' lap (in all but two cases [HRA = 1; LRC = 1], infants included in final analyses were seated on their mother's lap), at a viewing distance of approximately 65 cm from the computer monitor. Caregivers were instructed not to provide feedback or respond to infant during the testing session; however, their view of the monitor was not occluded during the testing session. Each trial, which was initiated by an examiner who monitored the infant's gaze, consisted of a face (mother/stranger) presented for 500 ms followed by at least a 1000 ms inter-stimulus interval. Trials in which the infant's attention shifted away from the face prior to onset were tagged during data collection by the experimenter and subsequently rejected prior to preprocessing and analysis. Mother and stranger faces were randomly presented until a total of 100 trials were presented (regardless of the number of trials tagged for infant inattention) or until the infant could no longer sustain attention to faces.

Acquisition and processing. EEG was recorded using 64- or 128-channel high-density Geodesic sensor nets (Electrical Geodesics, Inc., Eugene, OR, USA) with either NetAmps 200 or NetAmps 300 high-input amplifier (see Appendix S1 for more details). Data were collected from 62 of 64 and 124 of 128 possible channel locations. In order to decrease fussiness and attrition, Electrooculography (EOG) electrodes were not used. Data were sampled at 250 Hz and referenced to the vertex electrode (Cz). NetStation 4.5 was used to pre-process the data. A 60 Hz notch filter was applied to the raw data, which was subsequently segmented into 1200 ms epochs (200 ms pre-stimulus, 1000 ms post-stimulus onset). Artifact detection was carried out using both computer-based automatic and manual hand-editing procedures. Channels were marked bad if the maximum voltage exceeded $\pm 200 \mu\text{V}$. Epochs were rejected if they contained blinks or eye movements, significant drift, or muscle artifact. In the absence of EOG electrodes, the spatial location of the electrodes on the scalp (frontal for blinks, lateral frontal for saccades) and the polarity of the signal (large positive deflection for blinks, reversed polarity on left/right for saccades) were used to identify each type of artifact. Epochs were also rejected if they contained greater than 9 or 18 bad channels for 64- and 128-channel nets, respectively. Bad channels for accepted trials were replaced using spherical spline interpolation, and, lastly, data were re-referenced to the average reference. For the present analysis, only mother trials were used (for mother-stranger comparison, see Appendix S1); we focused solely on the mother condition because prior electrophysiological studies examining face processing during the first year of life have shown that an event-related potential (ERP) component associated with the allocation of attentional resources (the negative central [Nc] component) is larger for mother compared with stranger faces [de Haan, Johnson, & Halit, 2003; de Haan & Nelson, 1997]. Furthermore, infants spend more time attending to mother as compared with stranger faces [Wagner, Luyster, Yim, Tager-Flusberg, & Nelson, 2013]. Infants with fewer than ten acceptable trials for the mother condition were excluded. Groups did not differ for total number of trials administered or total number of accepted trials at 6- or 12-months visit (all P values $>.1$; see Table 2). However, coherence values are sensitive to the number of trials, particularly when the number of included trials is small [Cohen, 2014]. Measures of coherence are restricted from zero to one, and experimental conditions or groups with fewer trials will generally have higher coherence values (e.g. in an extreme case, an individual with only one trial would produce a coherence value of 1). Because coherence values are inversely related to the number of trials included in the analysis (see Appendix S1 for further dis-

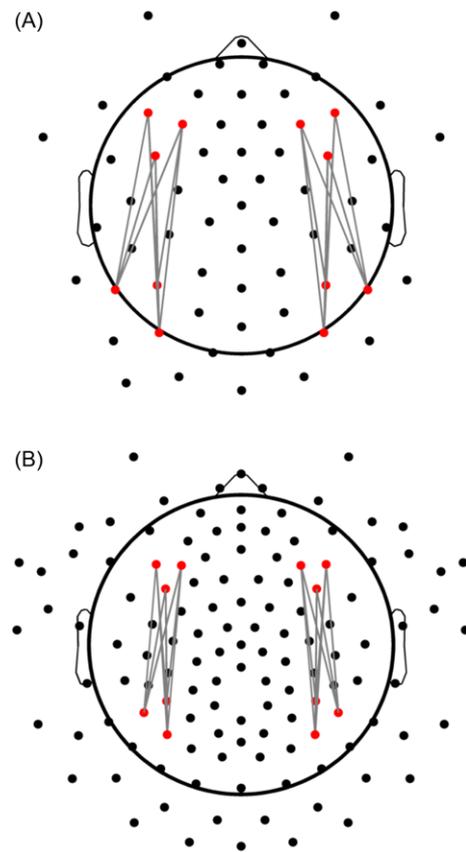


Figure 1. Four regions of interest (ROI) marked in red. Intra-hemispheric coherence was calculated for each intra-hemispheric anterior-posterior electrode pair (gray lines) for 64- (A) and 128-channel nets (B).

ussion), ten trials were randomly selected for participants with more than ten accepted trials (thus, the data duration for each child equaled 12 sec).

Coherence analysis. EEG data were analyzed using EEGLAB [Delorme & Makeig, 2004]. For each hemisphere, anterior and posterior regions of interest (ROI) were selected. Each ROI included three electrodes (see Fig. 1), which were selected based on previous studies examining frontal gamma response to faces with direct gaze [Grossmann, Johnson, Farroni, & Csibra, 2007] and prior event-related potential studies examining face processing in infants [Webb et al., 2006]. ROI included left frontal (64 channel: 13, 15, 16; 128 channel: 24, 27, 28) and posterior (64 channel: 27, 28, 32; 128 channel: 51, 52, 59), and right frontal (64 channel: 57, 61, 62; 128 channel: 117, 123, 124) and posterior (64 channel: 45, 46, 49; 128 channel: 91, 92, 97). Across nets, these channel locations have similar correspondence to 10-10 channel locations for frontal (F3/F4, F7/F8, FC5/FC6) and posterior (P5/P6, P7/P8, PO7/PO8) channel locations. Phase coherence within the gamma-band (30–50 Hz) between

each anterior–posterior intra-hemispheric electrode pair (nine pairs per hemisphere; see Fig. 1) was calculated and then averaged producing a value between 0 (no coherence; random phase difference across trials) and 1 (complete coherence; constant phase difference across trials). Event-related changes in phase coherence were calculated using modified complex Morlet wavelet with the EEGLAB function *newcrossf*. Coherence for gamma-band frequencies was calculated in 1 Hz intervals from 30 to 50 Hz. Gamma-band coherence was then averaged across 100 ms time bins starting at 50 ms post-stimulus. A lateralization index was then calculated for each time bin ($[(RH-LH)/(RH+LH)]$), such that positive values were indicative of greater right intra-hemispheric coherence. We chose to focus on a single time window 150–350 ms after stimulus onset relevant to face-specific processing as demonstrated by previous infant ERP studies [i.e. the N290 component; de Haan et al., 2003]. The purpose of this was twofold: (a) coupling between discrete regions necessary for large-scale integration is a transient process, and (b) selection of a single, hypothesis-driven, time window reduces the number of statistical comparisons and the inflation of type I error. All statistical analyses were performed using SPSS, version 21.0 (IBM Corp., Armonk, NY).

Results

Longitudinal Analysis

To assess longitudinal changes in coherence and lateralization, we utilized a linear mixed model that accounts for missing data points and unbalanced designs. For the analysis of coherence, the model included group (HRA, LRC), hemisphere (left, right), and age (6, 12 months), and all two-way and three-way interactions as fixed factors and intercept as a random effect. There was no main effect of group, $F(1,246) = 0.14$, $P = 0.71$; hemisphere, $F(1,246) = 1.52$, $P = 0.22$; or age, $F(1,246) = 3.65$, $P = 0.06$, nor were any of the two-way interactions (all $P > 0.7$); however, there was a significant group \times hemisphere \times age interaction, $F(1,246) = 6.58$, $P < 0.05$ (see Fig. 2A). For the analysis of lateralization index, the model included group (HRA, LRC), and age (6, 12 months), and group \times age interaction as fixed factors and intercept as a random effect. There was no main effect of group, $F(1,123) = 0.98$, $P = 0.32$, or age, $F(1,123) = 0.05$, $P = 0.82$; however, there was a significant group \times age interaction, $F(1,123) = 12.19$, $P < 0.01$, indicating that developmental trajectories of the two groups differed. As seen in Figure 2B, the LRC group has a positive slope indicative of increasing rightward lateralization of intra-hemispheric coherence, whereas the HRA group has a negative slope reflecting greater leftward asymmetry over time. To address possible confounds of net and amp combination, MSEL ELCS, and head circumference were

entered separately into the model as covariates. Inclusion of these covariates did not change the outcome of the original model and are not reported.

Cross-Sectional Analysis

Next, differences in coherence and lateralization were examined in a cross-sectional manner at 6 and 12 months. Mean left and right hemisphere coherence values for the time window of interest were entered into a 2 (group: HRA, LRC) \times 2 (hemisphere: left, right) mixed model repeated measures analysis of variance (ANOVA) separately for 6 and 12 months. As can be seen in Figure 2A, at 6 months, there was no group difference in coherence, $F(1, 56) = 0.01$, $P > 0.05$, nor was there a significant main effect of hemisphere, $F(1, 56) = 1.35$, $P > 0.05$, or interaction between group and hemisphere, $F(1, 56) = 2.53$, $P > 0.05$. Similarly, at 12 months, there was no significant main effect of group, $F(1, 67) = 0.24$, $P > 0.05$, or hemisphere, $F(1, 67) = 1.28$, $P > 0.05$; however, there was a significant group by hemisphere interaction, $F(1, 67) = 10.83$, $P < 0.01$. Because MSEL scores were significantly greater in LRC compared with HRA infants at 12 months, 12-month MSEL ELCS was entered as a covariate; results were identical with the exception of the main effect of hemisphere, which was now significant, $F(1, 66) = 4.77$, $P < 0.05$. Identical results were also obtained when 12-month head circumference was entered as a covariate. Follow-up independent samples *t*-tests revealed significantly greater left hemisphere coherence for the HRA group compared with the LRC group, $t(67) = 2.35$, $P < 0.05$, and marginally greater right hemisphere coherence for the LRC group compared with the HRA group, $t(67) = -1.96$, $P = 0.054$.

The lateralization index was entered into univariate ANOVAs with group (HRA, LRC) as the between-subjects factor. At 6 months, the lateralization index was not significantly different for HRA and LRC groups, $F(1, 56) = 2.89$, $P > 0.05$; however, at 12 months, the HRA group showed significantly greater left lateralized intra-hemispheric coherence compared with the LRC group, $F(1,67) = 10.93$, $P < 0.01$ (see Fig. 2B). The difference between HRA and LRC remained when either 12-month MSEL ELCS or head circumference was entered as a covariate.

Twelve-Month Coherence and ASD Outcome: Preliminary Findings

To determine whether between-group differences in lateralization emerging at 12 months were driven by infants who later met criteria for ASD, we conducted a follow-up analysis on a subsample of infants for whom an ASD diagnosis had been confirmed. Of the 39 HRA infants who contributed data at 12 months, ten have been

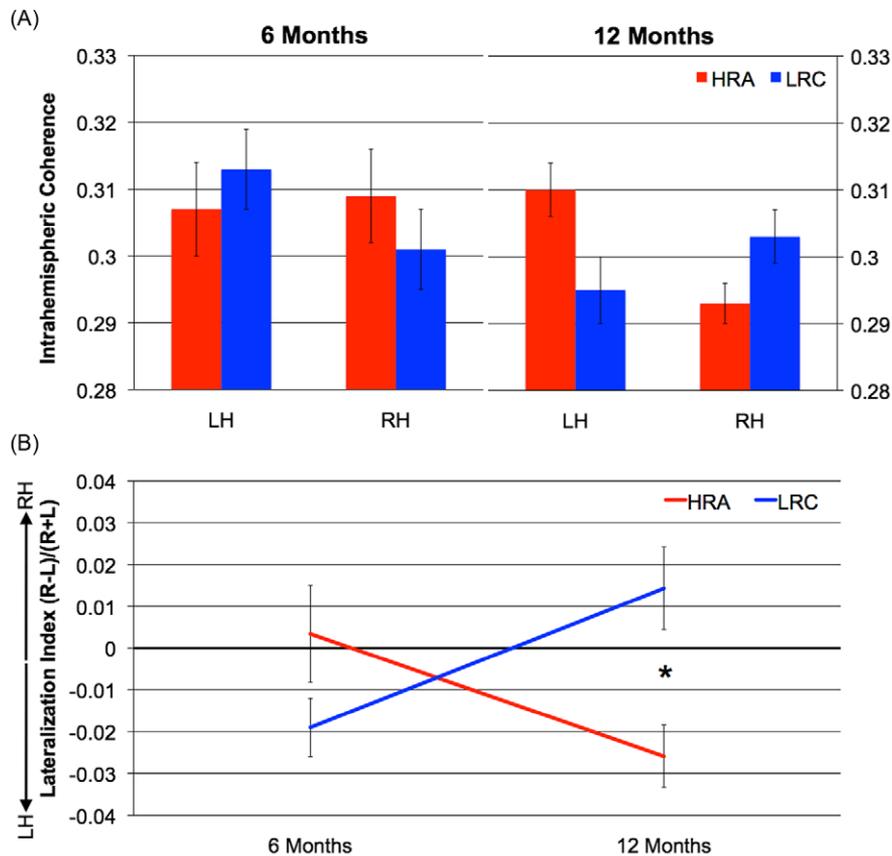


Figure 2. (A) Intra-hemispheric anterior-posterior gamma band (30–50 Hz) coherence for left and right hemispheres at 6 (left panel) and 12 months (right panel) for high- and low-risk infants. Error bars represent one standard error of the mean. (B) Lateralization index for intra-hemispheric coherence across 6 and 12 month olds. Positive values are indicative of rightward lateralization; negative values indicative of leftward lateralization. Error bars represent one standard error of the mean. Infants at high-risk for ASD, HRA; low-risk comparison infants, LRC; left hemisphere, LH; right hemisphere, RH. * $P < 0.01$

Table 3. Outcome Subgroups for EEG Data Acquired at 12 Months

	HRA+ ($n = 10$)	HRA- ($n = 24$)	LRC- ($n = 26$)
Age [days]	376 (15) 363–413	372 (10) 353–389	370 (9) 359–390
Sex [males; females]	5;5	12;12	10;16
Mullen Scales of Early Learning ELCs ^a	95 (15) 76–119	107 (14) 84–138	110 (11) 94–132
Total trials	33 (9) 18–49	29 (9) 14–51	29 (6) 20–43
Accepted trials	23 (10) 11–38	19 (8) 10–37	17 (6) 11–29
Head circumference (mm)	46.9 (1.3) 45–50	46.8 (1.2) 45–49	46.9 (1.6) 45–51

^aMullen ELCs for LRC- \rightarrow HRA+, $P < 0.05$, and HRA- \rightarrow HRA+, $P < 0.05$. Mean (SD) range.

classified as ASD (HRA+) and 24 have been classified as non-ASD (HRA-) (see Table 3). Twenty-six of the 30 LRC infants included in the 12-month sample have been assessed at 36 months; none of these infants met criteria for ASD. As with the complete sample, the outcome groups differed in 12-month MSEL ELCs scores, $F(2, 57) = 5.42$, $P < 0.01$. Follow-up t -tests revealed that the HRA+ group had a significantly lower scores than the

LRC-, $t(34) = -3.52$, $P < 0.05$, and the HRA- group, $t(32) = -2.35$, $P < 0.05$; MSEL ELCs was not significantly different in the HRA- as compared with the LRC- group, $t(48) = -0.85$, $P > 0.3$.

As seen in Figure 3, the HRA+ group showed the greatest leftward lateralization with the HRA- group falling between HRA+ and LRC- groups. Lateralization index was entered into a univariate ANOVA with outcome group

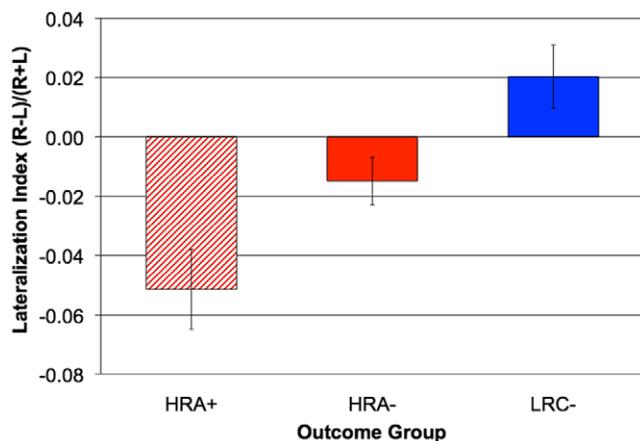


Figure 3. Lateralization index as measured at 12 months of age for each outcome group. Positive values indicative of rightward lateralization; negative values indicative of leftward lateralization. Error bars represent one standard error of the mean. Infants at high-risk for ASD (HRA-; $n = 24$), low-risk comparison infants (LRC-; $n = 26$) who did not meet criteria for ASD, and infants who met criteria for ASD (HRA+ = 10).

(HRA+, HRA-, LRC-) as between-subjects factor. There was a significant main effect of group, $F(2, 57) = 9.19$, $P < 0.01$. The difference between the HRA+, HRA-, and LRC- groups remained when 12-month MSEL ELCS was entered as a covariate. Follow-up t -tests showed that the HRA+ group had significantly greater leftward lateralization than both the HRA-, $t(32) = -2.4$, $P < 0.05$, and the LRC- group, $t(34) = -3.75$, $P < 0.01$. In addition, the lateralization index differed significantly between HRA- and LRC- groups, $t(48) = -2.61$, $P < 0.05$, with greater leftward lateralization in the HRA- compared with the LRC- group.

Correlational analyses revealed that the lateralization index at 12 months was inversely related to ADOS total scores measured at both 24, $r(59) = -0.38$, $P < 0.01$, and 36 months, $r(49) = -0.47$, $P < 0.01$, demonstrating that increased leftward lateralization at 12 months of age was associated with later increased ASD symptom severity across low- and high-risk infants at 24 and 36 months (see Fig. 4). To ensure that the relation between the lateralization index and ADOS total scores was independent of developmental level, additional correlational analyses were conducted. Partial correlations controlling for the effects of developmental level (as measured by the 12-month MSEL ELCS) remained significant.

Discussion

The goal of the current study was to employ event-related coherence analysis to investigate intra-hemispheric connectivity across the first year of life in infants at low- and

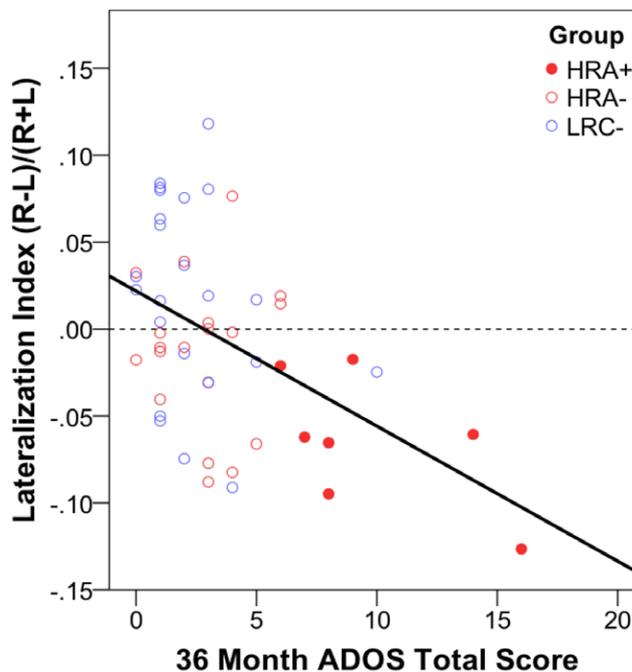


Figure 4. Negative correlation between the lateralization index and final outcome ADOS total scores among all participants. Positive values are indicative of rightward lateralization; negative values indicative of leftward lateralization.

high-risk for developing ASD. Two important findings emerged from our current investigation. First, our results suggest that HRA infants do not show the neurotypical pattern of right hemispheric specialization for face processing during the first year of life; HRA infants showed the opposite trend, such that by 12 months, there was significant leftward lateralization. Second, we found that high-risk infants who later met criteria for ASD showed the greatest pattern of leftward lateralization. Each of these findings will be discussed in turn.

Prior studies have demonstrated that nodes within the social brain network are at least partially active by 2 to 3 months of age [Johnson et al., 2005; Tzourio-Mazoyer et al., 2002]. Specialization of these discrete cortical regions is shaped by region-to-region interactions within a network of brain areas [Johnson, 2011]. Our results suggest that coordinated communication between anterior and posterior regions during face processing becomes increasingly right lateralized during the first year of life in typically developing infants. This face processing network continues to develop, such that by adulthood, there are robust face-selective increases in gamma-band coherence between fusiform gyrus and a distributed network of regions in the right hemisphere [Klopp, Marinkovic, Chauvel, Nenov, & Halgren, 2000].

Although there were no between-group differences in overall levels of intra-hemispheric coherence, our high-risk infants evidenced a pattern of increasingly leftward

lateralization, suggesting that they may rely to a greater extent on coordinated communication between anterior-posterior brain areas of the left hemisphere during face processing. These results are consistent with those of McCleery et al. [2009] who showed that 10-month-old high-risk infants do not show the neurotypical pattern of hemispheric asymmetries of face-sensitive event-related potentials and with Dundas et al. [2012b] who demonstrated that 11-month-old high-risk infants fail to show an LVF bias that is associated with right hemisphere face processing advantage. Importantly, the results of the current study indicate that this atypical pattern is not present earlier in development, but rather emerges only during the second half of the first year of life. Eye-tracking studies of infants at risk for ASD have provided inconsistent evidence of atypical face processing. Equivalent patterns of attention between HRA and LRC infants has been shown at 6 [Young, Merin, Rogers, & Ozonoff, 2009], 9 [Key & Stone, 2012], and 12 months [Dundas et al., 2012b]. However, a more recent report has demonstrated that differences between HRA and LRC emerge gradually across the first two years of life in HRA infants later diagnosed with ASD [Jones & Klin, 2013], though the groups were not significantly different from one another until 12 months. Likewise, subtle differences in attention to faces have been shown in 2-year-old children with ASD, with a greater divergence in attention to inner features of the face emerging by 4 years of age [Chawarska & Shic, 2009]. In a similar fashion, our results suggest that aberrant lateralization of intra-hemispheric coherence is not present at 6 months, but rather develops by the end of the first year of life. In sum, our results add to the growing body of evidence of atypical development of hemispheric specialization for face processing in ASD.

What might leftward asymmetry to faces in HRA infant represent? In typically developing individuals, the development of perceptual expertise for a given stimulus category has been hypothesized to result in a greater reliance on configural processing [Gauthier & Tarr, 2002]. Configural (or holistic) processing, generally speaking, refers to use of information about the spatial relationship between unique local features (e.g. eyes above nose, nose above mouth); alternatively, featural (or local or part based) processing is defined as using distinct local components (e.g. eyes, nose, or mouth). Whereas LRC infants show a neurotypical pattern of rightward lateralization across the first year of life, likely associated with greater face processing expertise and reliance on configural processing, HRA infants show an increasing leftward asymmetry over time. Electrophysiological evidence from both infants and adults suggests that the left hemisphere may be more sensitive to featural information, whereas the right hemisphere is more sensitive to configural information [Scott, 2006]. Infants as young as 4 months old show a right hemisphere advantage for configural information

and left hemisphere advantage for featural information [Deruelle & de Schonen, 1998]. Thus, the leftward shift in HRA infant may represent, in part, a face processing strategy that may rely more on featural than configural processing. It should be noted however that although prior research investigating hemispheric specialization for face processing in ASD has shown the *absence* right hemisphere lateralization, the *presence* of significant left lateralization in ASD has not been reported [although see Dundas et al., 2012b, Figure 4, for a similar pattern of results in high-risk infants]. Further research is necessary to confirm whether the emergence of cortical networks associated with face processing in those at risk for ASD shows an early leftward shift at 12 months and whether later trajectories include a return towards a more bilateral cortical organization.

Nevertheless, the question remains as to why individuals with and at risk for ASD may fail to develop hemispheric specialization for faces. Prior research has shown abnormalities in the genetic pathways that may regulate cortical lateralization in ASD [Chow et al., 2012]. Therefore, early perturbations in genetically regulated cortical patterning may influence the development of later functional asymmetries. Alternatively or in conjunction with genetic disturbances, failure to develop specialization may be due to early differences in attention to faces. Whether reduced attention to faces in individuals with ASD is due to a lack of social motivation [Dawson et al., 2002; Schultz, 2005] or as result of hyperarousal [Hutt & Ounsted, 1966], decreased attention to faces [including attention to eyes; Jones & Klin, 2013] early in life may also impact the development of the specialized neurofunctional network responsible for face processing.

More broadly, atypical hemispheric specialization in ASD has also been shown in the domain of speech and language processing. Prior studies has shown reduced leftward lateralization of ERPs associated with speech perception in high-risk infants [Seery, Vogel-Farley, Tager-Flusberg, & Nelson, 2013] and know and unknown words in toddlers with ASD [Kuhl et al., 2013], as well as atypically right-lateralized brain activation for speech perception using functional magnetic resonance imaging [Eyler et al., 2012; Redcay & Courchesne, 2008]. Future prospective longitudinal studies combining genetic, behavioral, eye tracking, and neuroimaging measures will help to define the role of atypical hemispheric specialization in the development of ASD sociocommunicative impairments, including face-processing deficits.

Atypical Hemispheric Specialization and ASD Outcome

Previous electrophysiological studies have demonstrated that event-related potentials [Elsabbagh et al., 2009; Key & Stone, 2012; McCleery et al., 2009] and gamma-band power [Elsabbagh et al., 2009] elicited during face and

gaze processing may distinguish high- and low-risk infants during the first year of life. Moreover, compared with our previous ERP studies [Luyster, Powell, Tager-Flusberg, & Nelson, 2014; Luyster, Wagner, Vogel-Farley, Tager-Flusberg, & Nelson, 2011], which have shown only subtle differences between the HRA and LRC groups, our coherence findings may indicate that atypical hemispheric specialization for faces occurs on a distributed, network scale. Our results add to the growing body of evidence that indicates that both face processing abnormalities [Pellicano, 2008] and atypical hemispheric specialization [Dundas et al., 2012b; McCleery et al., 2009] may be important endophenotypes in ASD. ASD is a behaviorally heterogeneous disorder with a polygenic etiology; endophenotypes represent more simplified features of the disorder and a powerful tool to facilitate the detection of common genetic risk variants [Geschwind, 2008].

More recently, ERP indices of gaze processing have been shown to be associated with ASD outcome in high-risk infants in the absence of overt attentional differences, as measured by eye tracking [Elsabbagh et al., 2012]. While in our study there is considerable overlap between the outcome groups in lateralization at 12 months (see Fig. 4) and lateralization values are low (placing considerable demand on measurement precision), the pattern of the current results suggests that infants who meet criteria for ASD show the greatest left lateralization at 12 months. Should this finding be replicated with a larger independent sample, then atypical hemispheric specialization for faces may potentially represent a marker that can distinguish infants who will ultimately develop autism from those with a familial risk.

Limitations

Phase of the EEG signal, as measured from the scalp, represents the linear sum of all sources in the brain and therefore is only a best approximation of unique underlying neural generators. While they have their own set of caveats, future research should attempt to localize distributed neural generators in source space [e.g. by using independent component analysis; Onton, Westerfield, Townsend, & Makeig, 2006] in an effort to examine source-to-source rather than channel-to-channel coherence, or, alternatively, use a measure of coherence that is not sensitive to zero-phase-lag connectivity [e.g. Vinck, Oostenveld, van Wingerden, Battaglia, & Pennartz, 2011]. A separate limitation of the current study was the hardware upgrades that took place in the middle of the project. Several steps were taken to control for this net switch, including selecting electrodes that corresponded to 10-10 locations across both nets and including net-amp combinations as a covariate in our analyses. The

later resulted in similar statistical outcome, indicating that this change did not impact our findings (see Appendix S1).

Additionally, high frequency EEG is susceptible to contamination from both eye movements [Yuval-Greenberg, Tomer, Keren, Nelken, & Deouell, 2008] and myogenic artifacts [Goncharova, McFarland, Vaughan, & Wolpaw, 2003; Pope, Fitzgibbon, Lewis, Whitham, & Willoughby, 2009]. Although these artifacts may affect gamma-band activation and coherence across the scalp, contamination is most pronounced at the periphery of the electrode net. In the current study, our ROI did not include these most peripheral electrodes. Moreover, while it remains a possibility, it is unclear how contamination could affect the lateralization index and why this should vary across group and ages. Nevertheless, if possible, future studies should attempt to more rigidly control for and/or remove these artifacts. A separate methodological limitation of the current study was the lack of procedures necessary to limit any effect of the parent on the testing session (e.g. occluding vision). Although a second experimenter was in the room to monitor the infant, subtle cues may have been introduced from the caregiver.

Finally, although the current study included over 95 infants, including 46 high-risk infants, our preliminary analysis included only ten high-risk infants that met diagnostic criteria for ASD. Given the longitudinal nature of the project, our outcome group remains small and therefore these results should be interpreted with caution. Future studies will include larger outcome samples as infants in our study complete their 36-month time point.

Conclusion

The present study examined the developmental trajectory of hemispheric specialization of face processing abilities across the first year of life in infants at risk for ASD. Although the majority of previous studies have utilized event-related potentials to investigate face processing in individuals with ASD and HRA infants, examining event-related oscillatory dynamics provides a complementary source of information regarding neurophysiological correlates of face processing. Our findings suggest HRA infants demonstrate an atypical leftward shift in lateralization of intra-hemispheric coherence across the first year of life, suggesting that the network specialized for face processing develops differently in these infants. Moreover, high-risk infants with the greatest leftward asymmetry at 12 months were those that met criteria for ASD, providing support to the growing body of evidence that atypical hemispheric specialization may be an early neurobiological marker for ASD.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

Figure S1. Scatter plot showing association between accepted trials (mother) and coherence values for left (blue; $r = -0.74$, $P < 0.001$) and right (green; $r = -0.68$, $P < 0.001$) hemisphere for 150–250 ms time window for all participants at all time points (6- or 12-months).

Table S1. Net and amplifier configurations for included participants

Table S2. Number of participants contributing 1 or 2 time points

Appendix S1. Methods