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Same but different: Nine-month-old infants at average and high risk for autism look at the same facial features but process them using different brain mechanisms

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Abstract

Lay Abstract—Reduced attention to the eyes and/or increased focus on the mouth have been described as features of atypical face processing in individuals with autism spectrum disorders (ASD). In this study, we examined whether 9-month-old infants at average vs. high risk for ASD differ in their detection of changes in individual facial features (eyes vs. mouth) and whether this ability is related to infants' social and communicative skills. Eye tracking data and electrical brain activity were recorded while infants viewed repeated presentations of a smiling unfamiliar female face. Occasionally, the eyes or the mouth of that face were replaced with corresponding parts from a different face. There were no group differences in the number or duration of fixations on the eye or mouth regions for any of the face stimuli. Brain activity data revealed that all infants detected both eye and mouth changes, and that these changes were associated with changes in activity of the face-specific perception mechanisms for average-risk infants only. For all infants, the size and speed of brain responses correlated with parental reports of communication use and understanding, suggesting that differences in brain processing of faces and their features in infants are associated with individual differences in early communication skills.

Scientific Abstract—The study examined whether 9-month-old infants at average vs. high risk for autism spectrum disorder (ASD) process facial features (eyes, mouth) differently, and whether such differences are related to infants' social and communicative skills. Eye tracking and visual event-related potentials (ERPs) were recorded in 35 infants (20 average-risk typical infants, 15 high-risk siblings of children with ASD) while they viewed photographs of a smiling unfamiliar female face. On 30% of the trials, the eyes or the mouth of that face were replaced with corresponding features from a different female. There were no group differences in the number, duration, or distribution of fixations, and all infants looked at the eyes and mouth regions equally. However, increased attention to the mouth was associated with weaker receptive communication skills and increased attention to the eyes correlated with better interpersonal skills. ERP results revealed that all infants detected eye and mouth changes but did so using different brain mechanisms. Changes in facial features were associated with changes in activity of the face perception mechanisms (N290) for the average-risk group, but not for the high-risk infants. For all infants, correlations between ERP and eye tracking measures indicated that larger and faster ERPs to feature changes were associated with fewer fixations on the irrelevant regions of stimuli. The size and latency of the ERP responses also correlated with parental reports of receptive and

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expressive communication skills, suggesting that differences in brain processing of human faces are associated with individual differences in social-communicative behaviors.

Keywords

Face processing; ERP; eye tracking; infants; ASD; Vineland

Prospective longitudinal studies of infant siblings of children with autism spectrum disorders (sibs-ASD), who are at higher than average risk for receiving the diagnosis themselves, are becoming the approach of choice for identifying early markers of risk for the diagnosis (Ozonoff et al., 2010; Rogers, 2009). Types of markers range from measures of head growth and sensory sensitivities to social, emotional and communicative behaviors, and the current consensus is that behavioral differences between sibs-ASD who do and do not receive a later ASD diagnosis emerge during the first year of life and become more evident at 12 months of age or later (Elder et al., 2008; Nadig et al., 2007; Ozonoff et al., 2010; Rozga et al., 2010; Zwaigenbaum et al., 2005).

Social-communicative deficits, including reduced attention to others and poor eye contact, may be among the earliest signs of ASD (Osterling & Dawson, 1994, Young et al., 2009). Although altered face scanning in persons with ASD is not universal (Bar-Haim et al, 2006, Rutherford & Towns, 2008; van der Geest et al, 2002) and may be limited only to certain cognitively demanding tasks (Jemel, Mottron, & Dawson, 2006; Volkmar et al, 2004), a number of studies in children and adults with ASD demonstrated fewer fixations on eyes and/or a relative proficiency in processing the mouth region (Dalton et al., 2005; Joseph & Tanaka, 2003; Klin et al., 2002) or chins and cheeks (Pelphrey et al., 2002). Moreover, atypical face processing appears to be more pronounced in younger children with autism (Klin et al., 1999; Langdell, 1978). Prior studies in high-risk infants and retrospective analyses of video data for children diagnosed with ASD report reduced looking to the eyes (Baranek, 1999; Maestro et al., 2002; Osterling, et al., 2002; Werner et al., 2000; Wetherby et al., 2004) to be present by 12 months in those later diagnosed with ASD (Zwaigenbaum et al., 2005). Therefore, examining processing of facial features (specifically, eye and mouth regions) in young infants may be a productive direction for identification of early markers of risk for adverse social-communicative outcomes.

While the interest in the early markers of risk for ASD is increasing, the number of standardized behavioral measures suitable for use with young infants is limited (Elsabbagh & Johnson, 2010), due in part to a limited repertoire of reliable behavioral responses at this age. Psychophysiological measures, such as event-related potentials, and eye tracking methods offer an opportunity to quantify early social behavior by documenting individual differences in face processing. Similar to other physiological measures, eye tracking can be obtained in the absence of verbal or other explicit behavioral responses, and therefore can be useful in the study of infant behavior. Eye tracking studies in typical populations have revealed that the preference for individual facial features changes as a function of development. For example, the distribution of typical infants' fixations shifts between 3.5 – 6.5 months of age from being equally divided between the eyes and mouth of the mother's face (48% vs. 45%) to focusing on the mouth for nearly twice as long as the eyes (57% vs. 30%), possibly due to increased interest in language (Hunnius & Geuze, 2004). Goal-related differences in the distribution of fixations were also reported in typical adults, who tended to look more at the mouth when identifying words and at the eyes when assessing prosody of speech (Lansing & McConkie, 1999). Thus, the existing data suggest that fixating on individual facial features may serve multiple purposes in addition to basic face perception.

Furthermore, the relative efficiency in processing information from the eyes vs. mouth may be related to language and social functioning. Indeed, face processing ability has been correlated with social competence in persons with ASD (e.g., Dawson et al., 2005; Klin et al., 1999; Volkmar et al., 1989). However, such associations have not yet been investigated extensively in infants at high risk for ASD. A recent eye tracking study comparing 6-month-old typical infants and high-risk siblings of children with ASD reported no group differences in face scanning patterns during a still-face paradigm but noted greater frequency of preferential attention to the mouth of the mother's face in high-risk group (Merin et al., 2007). In the combined sample, increased fixations on the mouth were associated with better language outcomes at 24 months but did not predict ASD diagnosis (Young et al., 2009), consistent with the notion that behaviors considered to be atypical at one age may be appropriate and beneficial at a different age (Rogers, 2009).

While differences in behavior between average- and high-risk infants may take time to manifest, measures of brain function could offer evidence of atypical processes before the emergence of overt behavioral deficits (Elsabbagh & Johnson, 2010). Event-related potentials (ERP), or scalp-recorded changes in electrical brain activity in response to a specific stimulus, can be obtained using paradigms that do not require any overt behavioral responses. This methodology has been used successfully to document cognitive processing, including that of faces, in typical infants and more recently, in sibs-ASD. To date, only three ERP studies of face processing in sibs-ASD have been published. McCleery et al. (2009) compared 10-month-old high-risk infants to typical infants and found accelerated N290/P400 brain responses to objects but no group differences in response to faces. Elsabbagh et al. (2009) found longer P400 latencies to faces with direct gaze in 10-month-old high-risk siblings relative to those at average risk, which is consistent with previous reports of slower processing in adolescents and adults with autism (McPartland, Dawson, Webb, Panagiotides, & Carver, 2004). Finally, Luyster et al. (2011) compared face recognition in 12-month-old high-risk and typical infants in response to their mother vs. a stranger, and found no group differences in N290/P400 or Nc responses; however, results suggested possible developmental delays in attentional processes of high-risk infants.

Although these studies provide valuable information about brain mechanisms supporting face perception in infants, many questions remain. In particular, these studies did not specifically examine processing of the mouth or the eyes of the faces, nor did they examine the results in reference to functional aspects of infant social or communicative behavior.

The purpose of this study was two-fold: (1) to examine how infants at average and high-risk for ASD process eyes and mouth facial features as measured by eye tracking and ERP data, and (2) to examine whether preferential looking at these features, as reflected in the number and duration of fixations and brain responses to eyes and mouth changes, are associated with infants' social and communicative behaviors. The purpose of eye tracking was to facilitate interpretation of the ERPs by disambiguating whether potential group differences could be attributed to differences in underlying brain mechanisms vs. different stimulus input because infants in the two study groups looked at different parts of the face stimuli.

If changes in eyes and/or mouth features invoke face-specific brain mechanisms, we expected such evidence to be present in amplitude and/or latency of the occipito-temporal N290 and P400 peaks (infant precursors of the adult N170; see de Haan, Johnson, & Halit, 2003, for a review). In particular, relative to the standard face, eye changes were expected to elicit larger and/or faster N290/P400 over the left hemisphere typically associated with featural processing (Scott & Nelson, 2006). If the changes in facial features do not affect the brain's face-specific perceptual mechanisms per se but attract attention as rare novel/unfamiliar stimuli, we expected to observe an increased fronto-central Nc component (see de

Haan et al., 2003 for review) to altered stimuli. Furthermore, given recent behavioral evidence of association between language outcomes and preferential fixation on the mouth region of a face (Young et al., 2009), we anticipated that ERP characteristics sensitive to changes in the mouth would correlate with behavioral measures of infants' communicative abilities.

Method

Participants

A total of 35 infants, age 9 months, participated in the study. The *average-risk group* included 20 infants (7 females; $M\text{ age} = 9.01 \pm .34$ months) reported by parents to have typical development, no concerns about their social skills, and no family history of ASD or developmental disabilities. The *high-risk group* of sibs-ASD was recruited through community referrals as well as university-based diagnostic clinics and ongoing research projects involving sibs-ASD. The final sample included 15 infants (6 females; $M\text{ age} = 9.19 \pm .44$ months) who had an older sibling diagnosed with ASD. All diagnoses were made by licensed psychologists, and 11/15 (73%) of the sample received the ADOS either alone or in combination with the ADI-R to support the clinical diagnosis. Data were collected from additional 4 typical and 2 high-risk infants, but were excluded from analyses due to insufficient number of ERP trials retained after artifact detection. The two groups did not differ in proportion of males, age, receptive communication or interpersonal skills; however, the average-risk group had higher expressive communication skills as reported by parents using Vineland Adaptive Behavior Scales-II Parent/Caregiver Rating Form (VABS-II; Sparrow, Cicchetti, & Balla, 2005). The summary statistics for the sample are presented in Table 1.

Stimuli

The stimuli included three color photographs of an unfamiliar smiling female face: one represented the standard face, one represented the same face with different eyes, and one represented the same face with a different mouth (see Key, Stone, & Williams, 2009). The novel features were obtained from a photograph of a different smiling female and introduced changes in the overall shape (including the degree of openness) of the eyes and mouth (Figure 1). The photographs subtended a visual angle of 20.93° (w) x 16.75° (h) with the eyes and mouth features occupying 5.4° x 1.43° and 3.82° x 1.43° , respectively. Thus, the on-screen stimuli were close to life-size and all facial features were clearly visible.

All stimulus alterations were made using Adobe Photoshop CS (v.8.0) and the novel features were placed at the corresponding locations in order to minimize changes to the original configural characteristics. While changes of such magnitude are not possible in real life, this stimulus set was designed specifically to target processing of the eyes and mouth regions. Changes in either feature were expected to elicit a change in ERPs if the original feature was processed in sufficient detail (see Bentin et al., 2006 for a conceptually similar approach to stimulus manipulation).

Procedure

This study was reviewed and approved by the Institutional Review Board of Vanderbilt University, and parents provided written informed consent prior to the initiation of any research procedures. All data were collected in a single visit, with the eye tracking procedure preceding the ERP recording. The eye tracking procedure was kept brief to avoid excessive familiarization with the stimuli that could have attenuated their attention to the stimuli in the ERP task. Infants completed both procedures in the same darkened sound-attenuated room while seated in the parent's lap.

Eye tracking procedure—Data were collected using a table-top camera (Tobii x50 series) positioned 20" in front of the infant. Infants viewed the same face stimuli as used for the ERP recording. Using ClearView software, each face was presented for 5 seconds with a 3-second interstimulus black screen, with a total of 2 presentations for each stimulus. The faces were presented in fixed order: standard face, eyes change, mouth change. Prior to the recording of eye gaze data, a 5-point calibration using infant-friendly moving images (colorful toys presented against black background) was performed to ensure accuracy of eye tracking data. Similar to the procedures described in Merin et al. (2007), calibration data were collected while a researcher in the room with the participant observed that the infant was looking at the screen and an eye-tracker operator in the control room verified that the eye tracker camera was detecting infant's eyes. After calibration, the plot of gaze data was examined and points with poor quality data were re-calibrated until usable calibration was obtained for each of the five regions of the screen.

ERP Procedure—A high-density array net of 124 Ag/AgCl electrodes embedded in soft sponges (Geodesic Sensor Net, EGI, Inc., Eugene, OR) was used to record infant ERPs. Electrode impedance levels were adjusted to below 40 kOhm. Data were sampled at 250Hz with filters set to 0.1–30Hz. During data collection, all electrodes were referred to Cz (re-referenced offline to an average reference).

ERPs were obtained using a passive (i.e., not requiring an overt behavioral response) oddball paradigm with two blocks of 100 trials. The original face served as the standard stimulus in both blocks and was presented on 70% of the trials in each block. The eye- or mouth-change stimuli served as the deviant stimuli and were presented on 30% of the trials within their respective blocks. The order of the blocks was counterbalanced across the participants. Each trial began with a 500 ms black plus sign on a white background followed by a 1000 ms presentation of the face stimulus. The stimuli were presented against a black background in the center of the computer screen positioned 90 cm in front of the participant. While the change in the screen background color was used as an additional means to attract infants' attention, the plus sign alerted the researcher in the room to check that the infant is looking at the monitor. Interstimulus interval varied randomly between 1100–1600 ms to prevent habituation to stimulus onset. Recording of the brainwaves was controlled by Net Station software (v. 4.1; EGI, Inc., Eugene, OR). Stimulus presentation was controlled by E-Prime (v. 1.2, PST, Inc., Pittsburgh, PA). During the entire test session, a researcher in the control room continuously monitored infant's electroencephalogram (EEG) while another researcher present in the testing room observed infant's behavior. Stimulus presentation occurred only when the EEG was free of motor artifact and the infant was quiet and looking at the monitor. During periods of inattention and/or motor activity, stimulus presentation was suspended and the researcher present in the testing room redirected infants to the computer screen using a battery-operated toy wand with flashing spinning lights. If that was not sufficient to attract infant's attention, a baby-friendly video (Baby Einstein series) was presented briefly on the monitor and replaced by the face stimuli as soon as the infant looked at the screen. Because the study stimuli and the attention-grabbing videos were presented on the same screen and controlled by a switch-box, there was minimal lag associated with transitions between the visual displays.

Behavioral data—To assess infants' social-communicative skills, mothers of the infants completed three subscales of the Vineland Adaptive Behavior Scales-II Parent/Caregiver Rating Form (VABS-II; Sparrow, Cicchetti, & Balla, 2005): Receptive Communication, Expressive Communication, and Interpersonal Relationships. These subscales were selected a priori because they measure constructs that are most directly related to social-communicative functioning. The Receptive Communication subscale includes questions about how the infant listens and pays attention, as well as which words or concepts he/she

understands. Questions on the Expressive Communication subscale focus on the sounds and gestures used by the infant to make his/her wants known. The Interpersonal Relationships subscale assesses how the infant interacts with others, including how he/she expresses and recognizes emotions, responds to others, shows affection, and demonstrates social imitation. These subscales yield standardized v-scores with a mean of 15 and a standard deviation of 3. All infants in the study obtained v-scores within the average range (see Table 1). Two out of 35 infants (5.7% of the sample) had missing VABS data for two of the three subscales, and one infant (2.8% of the sample) had missing data for one of the three subscales. Missing data were single-imputed with the EM algorithm (Rubin, 1987). After imputation, the ratios of old to new means and standard deviations for each subscale were all between 98.8% and 102.1% suggesting that the imputation introduced no large changes in variance.

Data Analysis

Eye tracking—Using ClearView software analysis tools, each infant's eye gaze data were automatically scored as the number and duration of fixations within the following regions of interest: eyes (including eyebrows), mouth, face (other than eyes and mouth), hair, body (visible neck and upper shoulders), and background (Figure 1). Together, these regions encompassed the entire stimulus. A fixation was defined as having a radius of at least 50 pixels (visual angle of approximately 2.5 degrees) and the minimum duration of 100 ms. Data for the number and duration of fixations within regions of interest were expressed as proportion of the total fixations for each stimulus face. Also, to better reflect individual differences in looking to the eyes versus the mouth region, an eyes-mouth index (EMI) was computed as a ratio of fixations to the eyes to the total fixations to the eyes and mouth combined, following the approach outlined by Merin et al. (2007). EMI values above .5 indicate more fixations on the eyes than the mouth region, while values below .5 indicate greater visual preference for the mouth than the eyes. The number and duration of fixations within regions of interest were analyzed using a repeated measures ANOVA with Face (3) x Region (6) as the within-subject variables and Group (2) at the between-subject factor. Additionally, because the fixed stimulus order (necessitated by the software limitations) could affect the amount of attention devoted to the stimuli presented later in the sequence (due to habituation or short attention span), total looking time was calculated as the percentage of the total possible time (10 sec) for each condition and entered into a repeated measures ANOVA with Face (3) x Group (2) factors.

ERP analysis—Individual ERPs were derived by segmenting the ongoing EEG on each stimulus onset to include a 100-ms prestimulus baseline and a 900 ms post-stimulus interval. To avoid biasing the results due to a largely uneven number of standard and deviant trials presented in an oddball design (Thomas, Grice, Najm-Briscoe, & Miller, 2004), only the standard trials preceding a deviant stimulus were selected for the analysis. Resulting segments were screened for artifacts using computer algorithms included in NetStation and then followed by a manual review. The automated screening criteria were set as follows: for the eye channels, voltage in excess of 140 μ V was interpreted as an eye blink and voltage above 55 μ V was considered to reflect eye movements. Any channel with voltage exceeding 200 μ V was considered bad. Trials contaminated by eye or movement artifacts or containing more than 15 bad channels (12% of the electrodes) were excluded from the analysis. For the remaining trials, data from bad channels were reconstructed using spherical spline interpolation procedures. Next, ERPs were averaged, re-referenced to an average reference and baseline corrected. For a data set to be included in the statistical analyses, individual condition averages had to be based on at least 10 trials. Trial retention rates were similar across stimulus conditions and groups (average-risk group: M standard = 19.50 $\pm$ 6.28, M mouth change = 14.70 $\pm$ 4.54, M eye change = 15.10 $\pm$ 4.32; high-risk group: M standard = 18.11 $\pm$ 5.76, M mouth change = 14.11 $\pm$ 4.02, M eye change = 14.34 $\pm$ 3.90).

To reduce the number of variables in the statistical analyses, only electrodes corresponding to the a priori defined regions of interest were analyzed. These electrode clusters were selected based on the scalp locations identified in previous studies as the optimal sites for face-sensitive N290 and P400 peaks and the novelty-sensitive Nc peak (de Haan & Nelson, 1997; de Haan et al., 2003; Halit, de Haan, & Johnson, 2003; Key, Stone, & Williams, 2009; Scott & Nelson, 2006). The graphic representation of the selected electrode clusters is presented in Figure 2. Next, latency and amplitude measures were obtained for N290 (250–350ms) and P400 (350–500ms) peaks, and mean amplitude measures for Nc (500–800ms) using the NetStation statistical extraction tool. These data were derived for each selected electrode and then averaged within each cluster. Latency windows were determined based on the examination of the grand-averaged waveform and the intervals used in prior studies. Separate repeated measures ANOVAs with Face (3) x Electrode (2) x Group (2) factors and Huynh-Feldt correction were conducted for mean amplitude and latency measures of the N290, P400, and Nc responses.

Additionally, the relation between eye tracking variables (relative number and duration of fixations on the eyes, mouth and face regions of interest), ERP data (amplitude and latency of N290/P400 and Nc), and VABS-II v-scores on the Receptive Communication, Expressive Communication, and Interpersonal Relationships subscales were examined using Pearson's r correlation coefficients. To control for multiple significance tests of the correlations, the false discovery rate (FDR) measure (Benjamini & Hochberg, 1995) was used. This approach was selected over the Bonferroni correction (Hochberg, 1988) because it accounts for non-independence among ERP variables and therefore avoids the biased loss of statistical power. This resampling-based correction (Westfall & Young, 1993) was performed using SAS PROC MULTTEST (Westfall, Tobias, Rom, Wolfinger, & Hochberg, 1999) and all correlations reported below remained significant ($p < .05$ family-wise).

Results

Eye Tracking Results

Due to hardware failures or lack of infant cooperation (i.e., no fixation data for two of the three stimulus types), eye tracking data were available for 14 of the 20 typical infants (70%) and 14 of the 15 infants in the high-risk group (93%). Means and standard deviations for the relative number and duration of fixations (expressed as proportion of the total number/duration of fixation for each stimulus) are presented in Table 2. The repeated measures ANOVA identified a main effect of Region of Interest for fixation number and duration, $F(5,105)=19.212$, $p<.0001$ and $F(5,105)=19.249$, $p<.0001$, respectively. As evident in the table, all infants fixated most frequently and for the most time on the eyes, mouth, and other face regions than hair, body, and background (all post-hoc pair-wise t -test p 's $<.0001$). There were no significant group differences or stimulus-related effects for the number or duration of fixations, or for the EMI variables. There were no significant group or face differences in the total looking time for the three stimulus types.

Correlations between eye tracking data and the parental reports of social and communicative behaviors revealed specific associations between individual faces and social-communicative functioning. Infants who spent more time looking at the stimuli (total looking time across all ROIs) during the standard and eye change faces scored higher on the Interpersonal Relationships scale ($r=.412$, $p=.029$ and $r=.468$, $p=.012$, respectively). For the mouth change face, increased number and duration of fixations on the mouth region were observed in infants with lower scores on the Receptive Communication scale ($r=-.475$, $p=.016$ and $r=-.486$, $p=.041$). In contrast, greater number and duration of fixations on the eye region of the mouth change face were related to higher scores on the Interpersonal Relationships scale ($r=.428$, $p=.033$ and $r=.412$, $p=.041$). These effect sizes were medium-to-large, according to

conventional guidelines for Pearson's r (i.e., r s of .10/.30/.50 correspond to small/medium/large effect sizes; Cohen, 1992).

ERP Results

Mean amplitude and latency data for the two infant groups are presented in Table 3.

N290 Amplitude—A Face x Electrode interaction was significant, $F(2,66)=3.849$, $p=.026$, partial $\eta^2=.104$, but follow-up tests revealed only a trend toward a more negative N290 in response to eye change compared to the standard face, $t(34)=1.918$, $p=.064$, $d=.32$. Hemisphere differences were present for the standard face with larger N290 recorded at the right than left locations, $t(34)=2.461$, $p=.019$, $d=.42$, and a trend toward similar differences was observed for the mouth change stimuli, $t(34)=1.936$, $p=.061$, $d=.33$.

In the combined sample, more negative left N290 response to mouth changes was associated with better receptive communication ($r=-.330$, $p=.053$) and interpersonal relations ($r=-.467$, $p=.005$) scores on VABS-II. In the average-risk group, larger left N290 response to the standard face was associated with higher Receptive Communication ($r=-.469$, $p=.037$) and Expressive Communication ($r=-.762$, $p<.001$) scores, indicating higher levels of communication understanding and use. Higher Receptive Communication scores were also related to a larger left N290 response to mouth changes ($r=-.503$, $p=.024$). None of these ERP measures correlated significantly with eye tracking data.

In high-risk infants, a larger left N290 to mouth change was associated with higher Interpersonal Relationships score, $r=-.699$, $p=.004$. The size of this ERP response was also related to the number and duration of fixations on the face region of the mouth change condition: more numerous and longer fixations were associated with a smaller N290 ($r=.653$, $p=.021$ and $r=.664$, $p=.018$, respectively).

N290 Latency—A Face x Electrode x Group interaction was present, $F(2,66)=5.343$, $p=.007$, partial $\eta^2=.139$. Follow-up analyses revealed that group differences were due to average-vs. high-risk infants generating shorter left N290 latencies in response to eye (283.2 vs. 301.1 ms, $F(1,33)=4.028$, $p=.053$) and mouth changes (274.9 vs. 299.6 ms, $F(1,33)=8.612$, $p=.006$, respectively), while there were no group differences in the N290 latency to the standard face ($p>.46$). Furthermore, post-hoc analyses indicated that only average-risk infants demonstrated shorter left N290 latencies to eye and mouth changes than the standard face, $t(19)=2.573$, $p=.019$, $d=.575$ and $t(19)=2.995$, $p=.007$, $d=.670$, respectively (Figure 3). Shorter left N290 latencies to the eye change stimuli were also related to fewer and briefer fixations on the face region of the eye change stimulus ($r=.624$, $p=.023$ and $r=.610$, $p=.027$, respectively). Concurrently, longer right N290 latency for the standard face was related to shorter duration of fixations on the mouth region of the standard face ($r=-.594$, $p=.032$). No correlations with VABS scores reached significance.

No stimulus-related differences were detected for the high-risk group, but shorter left N290 latency for eye changes was related to higher Expressive Communication scores ($r=-.549$, $p=.034$). Right N290 latency to mouth changes became shorter as the number of fixations on the mouth region increased ($r=-.579$, $p=.048$).

P400 Amplitude—A Face x Electrode interaction was significant, $F(2,66)=4.752$, $p=.012$, partial $\eta^2=.126$. Follow-up analyses indicated that compared to the standard face, eye change stimuli elicited a smaller left P400 in all infants, $t(34)=2.079$, $p=.045$, $d=.351$. A trend toward a Face x Electrode x Group interaction was present, $F(2,66)=2.837$, $p=.066$, observed power=.539, but follow-up analyses were not significant.

In the combined sample, a smaller left P400 response to mouth changes was associated with better receptive communication ($r = -.351$, $p = .038$) and interpersonal relations ($r = -.424$, $p = .011$) scores on VABS-II. Within the average-risk group, in addition to the smaller mouth change responses being associated with higher Receptive Communication scores ($r = -.487$, $p = .029$), a smaller left P400 to the standard face was related to higher Expressive Communication scores ($r = -.477$, $p = .033$), while a smaller P400 amplitude over the right hemisphere in response to the eye change faces correlated with higher Interpersonal Relationships scores ($r = -.461$, $p = .041$).

In high-risk infants, a smaller left P400 to mouth changes and a larger right P400 to eye changes were related to better Interpersonal Relationships scores ($r = -.780$, $p = .001$ and $r = .548$, $p = .034$, respectively). The amplitude of the left P400 to mouth changes decreased as the number and duration of fixations on the eyes of the mouth change face increased ($r = -.627$, $p = .029$ and $r = -.614$, $p = .034$, respectively).

P400 Latency—No main effects or interactions reached significance for P400 latency. In average-risk infants, the left P400 latency became shorter as the number and duration of fixations on the eyes increased ($r = -.579$, $p = .038$ and $r = -.615$, $p = .016$). A similar relationship was present between the left P400 latency and the number and duration EMI for the eye change face ($r = .651$, $p = .022$ and $r = -.712$, $p = .009$), indicating the looking more at the eyes than the mouth of the face was associated with shorter latency. There were no correlations with VABS scores. In the high-risk group, shorter latency of the right P400 to standard face was related to higher Expressive Communication scores ($r = -.706$, $p = .003$).

Nc mean amplitude—There were no significant ANOVA effects for the fronto-central Nc (Figure 4). In average-risk infants, a smaller (less negative) left Nc to standard face was associated with higher Expressive Communication scores ($r = .546$, $p = .013$). In the high-risk group, a larger left Nc to mouth change was associated with higher Receptive Communication scores ($r = -.691$, $p = .004$). No correlations between these ERP variables and eye tracking data reached significance.

Discussion

This study examined whether increased risk of ASD (due to genetic vulnerability) is associated with different processing of facial features (eyes vs. mouth) in 9-month-old infants as measured by eye tracking and ERPs. The data were also used to investigate the association between individual differences in these psychophysiological responses and infants' social and communicative functioning.

Eye tracking data did not reveal any group differences in face scanning behavior between average- and high-risk infants. Both groups spent similar amounts of time looking at each of the stimuli, attended more to the faces and their features than to hair, body, and background, and fixated on the eyes and mouth areas of the faces at comparable frequencies and for similar durations. Nevertheless, distinct patterns of associations between eye tracking data and behavioral characteristics emerged. In particular, lower Receptive Communication scores were associated with increased duration and number of fixations on the mouth of the mouth change stimulus. Conversely, increased fixations on the eyes region of the same stimulus were related to better Interpersonal Relationship skills.

The lack of group differences in eye tracking data is not entirely surprising given the number of recently published papers identifying age 12 months as the time point after which behavioral symptoms of autism are more clearly and consistently present (Zwaigenbaum et al., 2005; Nadig et al., 2007). The lack of group differences could also be due to the analytic

approach. Merin et al. (2007) did not observe any group differences in fixation patterns of 6-month-olds with and without family history of ASD when using a repeated measures ANOVA approach, yet post-hoc cluster analysis revealed a greater number of infants at high risk for ASD who spent more time looking at the mouth (i.e., falling in the low-EMI cluster). However, our sample size was too small to perform similar follow-up analyses.

Increased preferential looking to the mouth has been observed previously in younger (6 month old) typical infants and associated with increased interest in language (Hunnius & Geuze, 2004). In a combined sample of 6-month-olds at average and high risk for ASD, looking at the mouth was predictive of better language skills at 2 years of age (Young et al, 2009). The availability of visual information (mouth movements) that is temporally synchronous with the auditory input (speech) may facilitate early perceptual learning (Bahrick, Netto, & Hernandez-Reif, 1998). However, between 6 and 12 months of age, typically developing infants rapidly acquire proficiency in speech sound processing as reflected in their increasing ability to discriminate sounds present in their native language but not in the other languages (Cheour et al., 1998; Kuhl et al., 2006). Improved native speech processing should reduce the need for concurrent visual information from the mouth, freeing attentional resources for processing of other inputs (e.g., eye region, emotional content). Therefore, increased looking at the mouth observed in 9-month-old infants with weaker receptive communication skills may reflect a compensatory strategy necessitated by a less mature language processing ability. A follow-up study to specifically address this possibility is currently in preparation.

While we did not observe any overt behavioral evidence of group differences in face scanning behavior, there were differences in brain mechanisms of face processing. Analysis of the brain responses to the facial stimuli revealed that in accordance with previous infant studies on face processing (de Haan et al., 2003; Nelson, 2001; Pascalis, de Haan, & Nelson, 2002), occipito-temporal N290/P400 peaks as well as fronto-central Nc responses were present in all infants. At the level of an omnibus ANOVA, group differences were observed for the latency of the N290 response, where shorter latencies were recorded for the change stimuli in the average-than high-risk infants, but there were no group differences in the speed of N290 response to the standard face. Also, only the average-risk group showed condition differences, with faster N290 responses to change stimuli compared to the standard face. There was an additional trend toward group differences for the P400 amplitude, but we did not have sufficient statistical power to pursue this effect.

A shorter latency of the left N290 in the average-risk group in response to the eye change is consistent with the observations from adult studies that information in the eye area of a face activates face-specific perceptual mechanisms (Bentin et al., 2006) and the reports that brain mechanisms for processing eye information may mature faster than those for general face perception (Taylor et al., 2001). Analysis of correlations between ERPs and eye tracking data further revealed that latencies of the left N290 responses to change stimuli were delayed when more time was spent fixating on change-irrelevant regions. Evidence of similar left N290 acceleration in response to mouth changes suggests that typical infants attended to both features and processed them in sufficient detail.

In contrast to average-risk infants, in high-risk siblings of children with ASD, neither changes in the eyes nor the mouth features resulted in latency alterations of the N290 response. One of the reasons could be increased inter-infant variability in ERP characteristics, as many of these infants may not develop ASD or any features associated with the broader phenotype. The group difference in N290 latency effects is at odds with recent reports of no group differences in ERP responses to faces between typical and high-risk infants (Luyster et al., 2011; McCleery et al., 2009), but this could be attributed to

procedural differences. In the other studies, stimulus contrasts were potentially easier to process as the stimuli were much more distinct (faces vs. objects or mother vs. stranger), while in the present study, stimulus manipulations were more subtle, requiring greater attention to stimulus features. The lack of acceleration of the N290 in response to change stimuli may be similar to the reports of reduced attention to faces as indexed by the delayed N170 response to faces in adolescents and adults with ASD (McPartland et al., 2004). However, the lack of group differences in the N290 latency to the standard face argues against the possibility that the high-risk infants did not attend to the stimuli at all or were slower to habituate to the standard face and thus unable to detect featural changes.

This interpretation of reduced attention to stimulus features is further supported by correlations between ERPs and eye tracking variables in the high-risk group. This sample demonstrated an overall pattern similar to that of the typical infants, in that increased fixations on irrelevant parts of the face were associated with slower ERP responses. Moreover, correlations between ERPs and parental reports of social-communicative functioning revealed associations between more typical-like N290 characteristics and higher scores on the Interpersonal Relationships scale, which includes a number of attention-related items (e.g., “looks at face of parent”, “follows with eyes someone moving by”, “imitates simple movements”, etc.).

The absence of stimulus discrimination effects for the Nc amplitude in all infants suggests that single featural changes in a familiarized face were not sufficient to change the overall salience of the stimuli. The Nc response is considered to reflect attention (Courchesne et al., 1981; de Haan et al., 2004) and is also modulated by stimulus familiarity (Reynolds & Richards, 2005). It is also possible that at 9-months of age there might be increased variability in social attention, as the transition between a focus on familiar faces to increased attention to novel stimuli has been reported to occur between 9 and 12 months of age (Burden et al., 2007). Similar lack of group differences in the amplitude of the Nc response to a familiar (mother) vs. novel (stranger) face was reported in 12-month-old typical and high-risk infants (Luyster et al., 2011).

In sum, our results extend prior findings in the area of facial processing in infants. Although the 9-month-olds in our study fixated mainly on the internal facial features (as could be expected based on prior eye tracking studies in children and adults; e.g., Schwarzer, Huber & Dummler, 2005), individual differences in face-scanning behaviors may not only reflect perceptual strategies (e.g., determining face identity) but also help disambiguate other sensory inputs (e.g., spoken language). This possibility is supported by the finding that those 9-month-old infants who fixated more on the mouth of the mouth-change face were more likely to have weaker Receptive Communication scores. Group differences in ERPs were limited to the speed of the face-specific N290 response to change stimuli, suggesting reduced processing of facial details in high-risk infants. This combination of eye tracking, ERP and parental report findings extends current understanding of face perception processes and their association with risk for ASD.

Although many of our findings are consistent with the existing literature, the present study has several limitations. It is possible that our results are stimulus-specific, as only one set of faces was used for all infants. While the single set guaranteed that the amount of change introduced by substituting eyes or mouth remained identical across participants, future studies with a wider range of stimuli are needed to replicate our current findings. Also, the link between behavioral and brain findings in the present study will need further replication as eye tracking and ERP data were acquired sequentially, in fixed presentation order, using paradigms with different numbers of trials. Capitalizing on recent technological advances allowing for concurrent registration of eye tracking and ERPs with temporal precision would

strengthen the proposed conclusions by avoiding concerns associated with stimulus repetition/familiarity and possible order effects.

The sample size for the high-risk group was relatively small and, given the estimated prevalence rates for ASD among siblings of children with the diagnosis, unlikely to have included many children who will receive a later ASD diagnosis. However, results from previous studies of siblings of children with ASD suggest that early behavioral differences are not necessarily driven by the minority who receive a later diagnosis of ASD (Stone et al., 2007) but may relate more generally to the elevated risk status/genetic vulnerability of this sample. Thus, even though most of the high-risk infants may not receive an ASD diagnosis, their brain mechanisms underlying face processing may be altered. This interpretation is also in line with the reported evidence of atypical face processing observed in parents of children with ASD (Dawson et al., 2005). Finally, it is possible that the observed pattern of group differences at 9 months of age is not predictive of either an ASD diagnosis or other cognitive or behavioral differences at later ages, as found by others (Merin et al., 2007; Young et al., 2009). A follow-up diagnostic assessment as infants in our sample get older is the only way to determine the specific relation between individual differences in looking patterns, brain responses to faces, reported communicative skills and later developmental outcomes.

In conclusion, our results contribute to the growing evidence that infants at high risk for ASD may process facial information differently from typical infants. Furthermore, the combination of our eye tracking and ERP results suggests that such differences are evident in brain measures of face processing in the absence of overt behavioral alterations in face scanning (i.e., no detectable avoidance of the eye region or increased attention to the mouth area as has been frequently reported in older children with ASD), and are observed prior to 12 months of age. Individual differences in gaze patterns and ERP responses to changes in facial features were associated with parental reports of infant interpersonal and communicative behaviors. Additional longitudinal follow-up that includes a diagnostic assessment is needed to examine the predictive value of the observed individual differences in ERPs to face stimuli as a marker of risk for autism spectrum disorders.

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Figure 1. Stimuli used for eye tracking and ERP procedures, and corresponding regions of interest used for eye tracking analyses.

Figure 2.
A priori selected electrode clusters used in the analyses.

Figure 3. N290/P400 responses to standard and altered faces recorded in average- and high-risk infants.

Figure 4.
Nc responses to standard and altered faces recorded in average- and high-risk infants.

Table 1

Sample characteristics: means (standard deviations).

	Average-risk group (n=20)	High-risk group (n=15)	p-value
Age (mos)	9.19 (0.44)	9.01 (0.34)	0.20
Receptive Communication *	15.41 (2.29)	14.64 (2.06)	0.31
Expressive Communication *	14.80 (1.51)	12.60 (1.81)	<.0001
Interpersonal Relationships *	14.23 (1.36)	13.53 (1.88)	0.21

* v-scores from the VABS, mean = 15, sd = 3

Means (standard deviations) for the number and duration of fixations (expressed as proportion of the total number/duration of fixations for each stimulus).

Table 2

	Average-risk Group			High-risk Group		
	Standard	Eye change	Mouth change	Standard	Eye change	Mouth change
Total looking time (% of total stimulus duration)	.42 (.26)	.42 (.27)	.31 (.25)	.40 (.43)	.36 (.44)	.32 (.37)
<i>Number of fixations</i>						
Eyes	.24 (.25)	.32 (.35)	.16 (.26)	.23 (.23)	.22 (.27)	.12 (.18)
Mouth	.24 (.16)	.29 (.25)	.32 (.30)	.35 (.32)	.25 (.31)	.29 (.24)
Face (other)	.40 (.26)	.26 (.22)	.35 (.30)	.34 (.27)	.41 (.30)	.50 (.33)
Hair	.04 (.09)	.00 (.00)	.01 (.05)	.00 (.01)	.02 (.04)	.01 (.03)
Body	.01 (.02)	.01 (.03)	.07 (.11)	.03 (.08)	.06 (.10)	.05 (.08)
Background	.07 (.12)	.12 (.18)	.08 (.12)	.05 (.14)	.05 (.10)	.04 (.07)
EMI (eyes/(eyes+mouth))	.42 (.36)	.45 (.41)	.34 (.41)	.43 (.40)	.49 (.44)	.27 (.35)
<i>Duration of fixations</i>						
Eyes	.24 (.25)	.35 (.37)	.17 (.26)	.25 (.28)	.25 (.32)	.12 (.18)
Mouth	.28 (.20)	.30 (.30)	.33 (.30)	.32 (.31)	.26 (.31)	.30 (.25)
Face (other)	.40 (.27)	.27 (.28)	.36 (.31)	.36 (.29)	.38 (.33)	.51 (.34)
Hair	.03 (.08)	.00 (.00)	.01 (.03)	.01 (.01)	.02 (.06)	.01 (.03)
Body	.01 (.01)	.01 (.02)	.08 (.15)	.03 (.07)	.04 (.09)	.04 (.07)
Background	.05 (.09)	.07 (.11)	.06 (.10)	.04 (.11)	.05 (.09)	.02 (.04)
EMI (eyes/(eyes+mouth))	.42 (.37)	.47 (.41)	.34 (.41)	.46 (.42)	.46 (.44)	.25 (.34)

EMI – eyes-mouth index (Merin et al., 2007).

Table 3

Amplitude and latency values for ERP peaks used in the analyses.

	Left Hemisphere						Right Hemisphere					
	Average-risk			High-risk			Average-risk			High-risk		
	<i>M</i>	<i>SD</i>		<i>M</i>	<i>SD</i>		<i>M</i>	<i>SD</i>		<i>M</i>	<i>SD</i>	
N290												
<i>Amplitude</i>												
Eye change	-2.66	6.96		-6.21	7.02		-2.02	6.33		-5.11	7.33	
Mouth change	-1.83	7.71		-1.21	8.18		-5.08	8.34		-4.11	7.78	
Standard	1.48	6.60		-4.74	8.59		-5.07	7.45		-5.13	5.12	
<i>Latency</i>												
Eye change	283.23	24.45		301.07	28.00		295.97	23.46		300.40	26.21	
Mouth change	274.87	19.62		299.60	30.21		291.70	25.10		284.80	24.14	
Standard	297.27	25.71		290.62	26.43		295.07	20.28		297.73	31.88	
P400												
<i>Amplitude</i>												
Eye change	7.99	8.53		4.85	8.81		9.20	8.10		5.69	7.87	
Mouth change	11.71	7.68		11.19	8.95		8.12	9.10		6.07	9.33	
Standard	12.60	7.18		8.15	9.09		5.62	6.61		7.95	5.57	
<i>Latency</i>												
Eye change	408.80	29.22		425.51	39.95		412.93	35.94		420.84	41.79	
Mouth change	414.83	36.44		427.56	41.96		413.93	31.31		416.49	39.72	
Standard	427.57	29.55		419.42	32.62		412.30	33.65		412.93	38.57	
Nc												
<i>Mean Amplitude</i>												
Eye change	3.34	7.04		3.37	5.85		2.46	6.52		0.04	6.23	
Mouth change	3.81	6.15		2.53	5.75		2.34	8.13		-0.48	5.78	
Standard	1.83	4.78		3.45	3.94		1.38	4.87		3.46	4.96	