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RESEARCH ARTICLE

Inter-trial theta phase consistency during face processing in infants is associated with later emerging autism

Stefon van Noordt[1] | **James A. Desjardins**[2,3] | **The BASIS Team**[4] | **Mayada Elsabbagh**[2]

[1]Department of Psychology, Mount Saint Vincent University, Halifax, Canada

[2]Montreal Neurological Institute-Hospital, Azrieli Centre for Autism Research, McGill University, Montreal, Canada

[3]SHARCNET, Compute Ontario, Compute Canada

[4]Centre for Brain and Cognitive Development, Department of Psychological Sciences, Birkbeck, University of London, London, UK

Correspondence
Stefon van Noordt, 166 Bedford Highway, Halifax, Nova Scotia B3M 2J6, Canada.
Email: stefon.vannoordt@msvu.ca

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Abstract

A growing body of research suggests that consistency in cortical activity may be a promising neurophysiological marker of autism spectrum disorder (ASD). In the current study we examined inter-trial coherence, a measure of phase consistency across trials, in the theta range (t-ITC: 3–6 Hz), as theta has been implicated in the processing of social and emotional stimuli in infants and adults. The sample included infants who had an older sibling with a confirmed ASD diagnosis and typically developing (TD) infants with no family history of ASD. The data were collected as part of the British Autism Study of Infant Siblings (BASIS) study. Infants between 6 and 10 months of age ($M_{age} = 7.34$, $SD_{age} = 1.21$) performed a visual face processing task that included faces and scrambled, "face noise", stimuli. Follow-up assessments in higher likelihood infants were completed at 24 and again at 36 months to determine diagnostic outcomes. Analysis focused on posterior t-ITC during early (0–200 ms) and late (200–500 ms) visual processing stages commonly investigated in infant studies. t-ITC over posterior scalp regions during late stage face processing was significantly higher in TD and higher likelihood infants without ASD (HRA−), indicating reduced consistency in theta-band responses in higher likelihood infants who eventually receive a diagnosis of ASD (HRA+). These findings indicate that the temporal dynamics of theta during face processing relate to ASD outcomes. Reduced consistency of oscillatory dynamics at basic levels of infant sensory processing could have downstream effects on learning and social communication.

Lay Summary

We examined the consistency in brain responses to faces in infants at lower or higher familial likelihood for autism. Our results show that the consistency of EEG responses was lower during face processing in higher likelihood infants who eventually received a diagnosis of autism. These findings highlight that reduced consistency in brain activity during face processing in the first year of life is related to emerging autism.

KEYWORDS
autism, faces, infants, risk, theta coherence

INTRODUCTION

Autism spectrum disorder (ASD) is characterized by early onset symptoms that include some difficulties in social contexts, communication deficits, and atypical behavioral and neural responses to social stimuli (American Psychiatric Association, 2013). To date, research has focused on the pathophysiology of ASD in terms of structural and functional brain abnormalities as potential endophenotypes of ASD and the broader spectrum of related disorders (e.g., David et al., 2016). Particularly important for functional organization and

information processing in the brain is the temporal synchronization of neural activity (Voytek & Knight, 2015). A growing body of research suggests that reduced consistency in cortical activity may be a promising neurophysiological marker of ASD (David et al., 2016; Kovarski et al., 2019; Magnuson et al., 2020; Otto-Meyer et al., 2018; Schwartz et al., 2017). Phase coherence is a measure of the temporal consistency in the time course of oscillatory dynamics (Delorme & Makeig, 2004; Tallon-Baudry et al., 1996). Despite the fact that the temporal coordination of brain activity is critical for the development of neural networks, and a fundamental property of information processing in the brain, there are no studies examining consistency in cortical activity to social stimuli during the earliest stages of development.

Variability in spontaneous cortical oscillations is a fundamental property of information processing and neural communication (Kösem et al., 2014; Voytek & Knight, 2015). Various lines of work have found links between the single-trial phase consistency in evoked activity and cognitive performance (Cohen & Cavanagh, 2011), behavioral accuracy (Eidelman-Rothman et al., 2019), and response speed and variability (Papenberg et al., 2013; Zareian et al., 2020). Some of this work suggests that a combination of state and trait factors impact the degree to which on-going oscillations are phase consistent across trials, including neurodevelopmental disorders such as ASD (David et al., 2016; Milne, 2011; van Noordt et al., 2017). Thus, reduced consistency in neural responses may represent a core mechanism of atypical information processing in the autistic brain.

Evidence from several studies shows that children and adults with ASD have reduced consistency in neural activity across a wide range of contexts, including task-related (e.g., early visual evoked ERPs) and resting-state EEG paradigms, in multiple frequency bands, in EEG, MEG, and fMRI measures, and multiple sensory and cognitive modalities (Kovarski et al., 2019; Magnuson et al., 2020; Milne, 2011; Otto-Meyer et al., 2018). Although initial interest focused on consistency in high frequency oscillations, particularly in the gamma range as these oscillations had been linked to stimulus binding, integration, and association (Miltner et al., 1999), and excitation/inhibition imbalance (Orekhova et al., 2007), other findings suggest that phase coherence in lower frequencies is also reduced in ASD (Milne, 2011; van Noordt et al., 2017). Given that reduced consistency in ASD is observed developmentally and across multiple brain systems, intra-individual variability in neural activity could negatively affect learning and development by disrupting information processing and forming representations of the environment and therefore be an early developmental marker of ASD (David et al., 2016; Schwartz et al., 2017).

The neural dynamics of phase consistency could reveal fundamental mechanisms of information processing that are not observed in the fixed-latency average amplitude ERP approach. At the neural level, basic orienting mechanisms from around birth onward facilitate biases to social stimuli, which subsequently give rise to experience-dependent development across several brain networks (Elsabbagh & Johnson, 2016). A growing body of research focuses on typically developing (TD) infants and infants who are at higher likelihood by virtue of having an older sibling with a confirmed diagnosis of ASD, which suggests that, despite some difficulties in social awareness and communication in ASD, higher likelihood infants and control groups exhibit similar behavioral responses to faces, including orienting responses to faces (Elsabbagh et al., 2013; Ozonoff et al., 2010), gaze to faces (Ozonoff et al., 2010), scanning facial features in social contexts (Elsabbagh et al., 2014), and preference for maternal faces (Nele et al., 2015). In addition to these behavioral findings, several studies on the neural correlates of face processing suggest that atypicalities in ASD are moderated by contextual factors and heterogeneous variation that impact the emergence the broader phenotype (Shephard et al., 2020; Tye et al., In press).

Several ERP components that mediate basic visual and more specialized face processing have been examined in the context of familial ASD risk and/or outcome and vary along contextual and developmental factors. One of the earliest evoked responses to visual stimuli is the P100, a robust brain response detected over posterior occipital regions that reflects the initial stages of visual orienting/processing and is observed in a variety of visual paradigms. The P100 is highly sensitive to low-level stimulus properties (e.g., differences in color, contrast, amplitude spectrum; Johnson & Olshausen, 2003; Rousselet et al., 2008) and has a time course of activation that overlaps with independent projections from the later "face-specific" N170 ERP component (Colombatto & McCarthy, 2017; Desjardins & Segalowitz, 2013; Taylor et al., 2004).

In the face processing and ASD literature, some studies suggests that the P100 is sensitive to faces and is associated with ASD outcome (Batty et al., 2011; Hileman et al., 2011; Webb et al., 2012; but see also Dawson et al., 2002; Taylor et al., 2004); however, several studies also show that earlier visual responses such as the P100 are relatively insensitive to the nature of the stimuli being presented (Elsabbagh et al., 2009, 2012; Luyster et al., 2014; McCleery et al., 2009); de Haan & Nelson, 1999; although see Conte et al., 2020). Given that the P100 in these studies is modulated by stimulus properties (e.g., inversion, gaze direction, and emotional expression) and developmental stage, and not necessarily faces per se, the mixed findings point to the P100 response as perhaps being impacted by spatial attention (Di Russo et al., 2003; Martínez et al., 1999) as opposed to being specifically sensitive to faces.

The subsequent cascade in the visual processing stream in infants is reflected in the N290 and P400 ERP components and early developmental studies point to

functionally distinct roles for the P100 and these later face-specific components. The sensitivity of these later stage components show similarities to the N170 face-sensitive effects that are seen in adults. For example, within the first year of life the N290 exhibits sensitivity to human faces (Halit et al., 2004) and the P400 is modulated by face inversion and emotional expression (Leppänen et al., 2007), similar to the N170 seen in older children and adults. In a previous ERP study with a sample that overlaps with the current study, effects for the P100 were related to peak latency except for TD infants who had larger amplitudes for dynamic averted gaze shifts (Elsabbagh et al., 2012). The amplitude of the N290 was found to differentiate between TD and higher likelihood infants who did not develop ASD (HRA−) from higher likelihood infants who showed clinical signs of ASD at 24 months (HRA+) for dynamic gaze shifts. The effects for the P400 were even more pronounced, showing that amplitudes to dynamic gaze shifts differentiated between TD and HRA− infants from HRA+ infants who showed clinical signs of ASD at 24. Atypical visual processing at later stages involving higher level integration are therefore associated with ASD risk and diagnosis and more consistently differentiate ASD diagnosis compared to the early visual P100. These findings have led to the suggestion that the N290 and P400 in early development reflect a developmental precursor of face-sensitive N170 (Halit et al., 2003).

To date, research on the early and late stages of visual processing in at-risk infants has focused on fixed-latency measures (Elsabbagh et al., 2009, 2012; Key & Stone, 2012; Luyster et al., 2011; McCleery et al., 2009) in averaged ERP responses, but have yet to look at single-trial activation as a measure of cortical consistency. The consistency of phase oscillations reveals intra-individual variability in the timing of evoked brain responses, which may be important for understanding the mechanisms of rapid face processing in ASD. Despite the evidence for increased neural variability in ASD, currently there are no known studies that have examined perturbations in phase coherence during face processing in at-risk infants. Examining phase coherence prospectively in infants will help establish whether this potential marker can be extended to the earliest stages of development and differentiate familial ASD risk or outcome.

We focus on posterior theta activity as theta has been linked to occipital activation during face processing (Sato et al., 2014), including enhanced theta intertrial coherence (t-ITC) during the timing of the N170 that predicts emotion recognition (Csukly et al., 2014). Others have also shown that theta is modulated by attention to social stimuli, particularly at posterior scalp regions (Orekhova et al., 2006). Studies in children with ASD have also found that increased theta is observed during face processing and is related to greater levels of expressive and social communication (Dawson et al., 2012). Greater developmental changes in theta power during the first years of life has been during observed during processing social scenes, particularly in higher likelihood infants who received an intervention aimed at promoting social interactions (Jones et al., 2017). Although Jones et al. (2017) focused on frontal theta during free viewing of social videos, changes in theta were most prominent over bilateral posterior-occipital channels. The current study on face processing focused on posterior evoked responses as these are robust markers of early (P100) and late (N290/P400) stages of visual processing. We expected that TD infants would show greater t-ITC to faces than noise stimuli during the later stages of visual processing. Although in general we expected that higher likelihood infants would have reduced t-ITC and less differentiation between faces and noise, we did not have explicit a priori hypotheses about whether t-ITC during face processing would predict ASD diagnosis at 36 months in higher likelihood infants.

METHODS

Sample and paradigm

The data used for the current study was collected as part of the British Autism Study of Infant Siblings (BASIS) study and been used in previous ERP studies on gaze processing (Elsabbagh et al., 2012).

The initial sample included task-related EEG data from 104 infants, 50 TD and 54 at higher likelihood for ASD, who completed the face processing task between 6 and 10 months of age. Higher likelihood infants were followed up for subsequent assessments at 24 and 36 months. During the 24 months visit, the Autism Diagnostic Observation Schedule - Generic (ADOS-G; Lord et al., 2000) was administered in order to identify early signs of ASD symptoms. In addition to the ADOS, a battery of clinical measures including the Autism Diagnostic Interview - Revised (ADI-R; Lord et al., 1994), ICD-10 criteria, and expert clinical assessment were collected during the 36 months visit to ascertain diagnosis. From this assessment battery, 17 of the higher likelihood infants were diagnosed with ASD. Four participants were excluded due to insufficient EEG data quality and three due to unknown ASD outcome. In order to ensure stability in the estimates of individual t-ITC, we excluded participants with less than 10 artifact-free trials ($n = 25$). Due to differences in EEG pre-processing and minimal trial cut-offs required for t-ITC, the final sample size for the current study is smaller than the original ERP study by Elsabbagh et al. (2012) which included 104 infants. There were no significant differences between those participants who were excluded versus included in terms of risk status ($\chi^2(1) = 1.74$, $p = 0.19$), diagnostic outcome ($\chi^2(1) = 0.026$, $p = 0.87$), biological sex ($\chi^2(1) = 0.52$, $p = 0.47$], or age in months ($t(70) = 0.037$, $p = 0.97$]. The final sample therefore consisted of 72 infants; 32 TD,

TABLE 1 Demographic and clinical summary

	TD	HRA−	HRA+	Mann–Whitney *U* tests
n	32	28	12	
Mean age (months)	7.35 (1.20)	7.37 (1.11)	7.25 (1.54)	
ASD assessment 24 months				
ADOS communication		1.75 (1.38)	3.82 (1.72)	$z = -3.30$**
ADOS social		3.75 (2.44)	7.27 (2.79)	$z = -3.76$**
ADOS total		6.50 (4.54)	14.09 (5.66)	$z = -3.81$**
ADOS CSS		3.00 (2.02)	5.81 (2.14)	$z = -3.44$**
ASD assessment 36 months				
ADOS communication		2.67 (1.90)	3.82 (1.72)	$z = -1.81^{\dagger}$
ADOS social		3.57 (3.08)	7.42 (3.23)	$z = -3.43$**
ADOS total		6.39 (3.89)	13.33 (5.45)	$z = -3.85$**
ADOS CSS		3.14 (2.22)	6.33 (2.64)	$z = -3.63$**
ADI communication		2.96 (3.82)	9.54 (4.46)	$z = -4.14$**
ADI social		2.39 (3.52)	11.36 (5.46)	$z = -4.84$**
ADI repetitive behavior		0.68 (1.09)	4.09 (2.38)	$z = -4.79$**

Abbreviations: ADI, Autism Diagnostic Interview-Revised (Lord et al., 1994); ADOS, Autism Diagnostic Observation Schedule-Generic (Lord et al., 2000); ADOS CSS, Autism Diagnostic Observation Scale Calibrated Severity Score.
**$p < 0.001$. $^{\dagger}p = 0.07$.

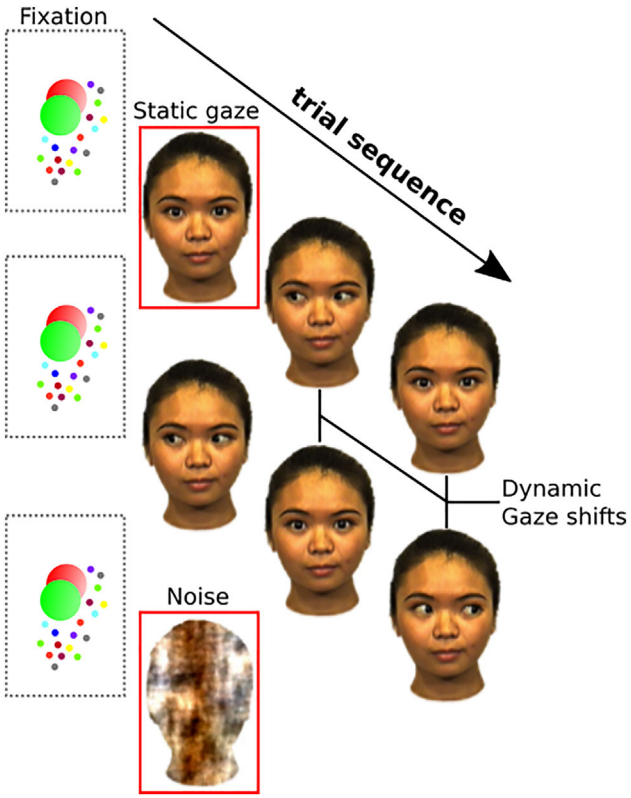

FIGURE 1 Schematic of trial sequence that initiates with color fixation followed by static face or noise stimulus. Trials with a static face were followed by 3–6 trials where eye gaze was dynamically shifted between direct and averted gaze directions

28 higher likelihood without ASD (HRA−), and 12 with ASD (HRA+). See Table 1 for a descriptive summary of the final sample.

For the current study, we examined static faces with direct gaze and a noise control stimulus for a comparison of face/non-face processing. Infants sat 60 cm from the computer screen (40 × 29 cm). Each trial began with a static color fixation for a variable duration between 800 and 1200 ms, subtended approximately 1.6 × 1.6 degrees, followed by a color image of a face stimulus. Face stimuli were aligned to the center of the screen and were subtended 21 × 14 degrees of visual angle. The groups did not differ in terms of average number of trials in either the face (TD: $M = 18.03$, SD = 4.43; HRA−: $M = 17.10$, SD = 5.51; HRA+: $M = 20.17$, SD = 7.68; p's < 0.05) or noise stimulus conditions (TD: $M = 23.66$, SD = 9.47; HRA−: $M = 23.16$, SD = 8.02; HRA+: $M = 26.46$, SD = 11.49; p's < 0.05). We also failed to find evidence that age (in months) and trial numbers were associated with t-ITC measures in either the face or noise stimulus conditions (all p's > 0.12). See Figure 1 for a schematic of the paradigm and Elsabbagh et al. (2012) for example of face stimuli used in the task.

EEG acquisition and pre-processing 2019b

EEG data were acquired using Electrical Geodesics (Eugene, OR) Net Station software with a 128 channel Hydrocel net. EEG pre-processing was performed using the EEG-IP Lossless pipeline (EEG-IP-L; Desjardins et al., 2021), which minimizes data manipulation and includes comprehensive annotations regarding signal quality for channels, time, and independent components. EEG-IP-L uses a series of criteria functions to compute metrics (e.g., voltage variance) and build distributions to

assess whether channels, time periods, or independent components are outliers.

The signal properties of the scalp channels were first examined by epoching the continuous EEG into 1 s non-overlapping windows. The standard deviation of the voltage across channels was calculated across each 1 s window. A channel was flagged for the duration of the recording if, in more than 20% of the 1 s epochs, the voltage is more than six times the 0.3–0.7 inter-quantile range. Similarly, a 1 s epoch was flagged if more than 20% of the channels are outliers based on voltages that are more than six times the 0.3–0.7 inter-quantile range. The windowed data were then concatenated back into the continuous time series. A 1 Hz high-pass filter was applied given that Independent Component Analysis (ICA) is sensitive to non-stationary artifacts generated by large low-frequency oscillations (e.g., movement artifact and sweat artifacts), and ICA decompositions have been shown to be more reliable when a high-pass filter is applied to the data (Winkler, Haufe, & Tangermann, 2011).

Scalp signals were then assessed to identify channels that have unreliable activity or are bridged with neighboring channels. Again the continuous data were windowed into 1 s non-overlapping epochs and the maximum correlation between each channel and its three spatially nearest neighbors was calculated. A channel was flagged for the duration of the recording if, in more than 20% of the duration, it showed a maximum correlation that was six times more than the 0.3–0.7 inter-quantile range. Similarly, each 1 s epoch was flagged if more than 20% of the channels are outliers based on maximum neighbor correlation coefficients that are less than six times the 0.3–0.7 inter-quantile range. To identify bridged channels, the median of the maximum correlation coefficient was divided by the interquartile range for each channel across time. This yielded a composite value that accentuates high and invariable correlations across time. Channels were flagged as bridged if the composite value exceeded six standard deviations (40% trimmed) from the mean (40% trimmed) across the channels.

The windowed data were concatenated back into the continuous time series and any channels or time periods that were not flagged were submitted to Adaptive Mixture Independent Component Analysis (AMICA; Palmer et al., 2011) for decomposition. Similar to the procedures for scalp channels, following AMICA, the data were windowed into 1 s non-overlapping epochs, and the standard deviation of IC activations was calculated to determine time periods of relative non-stationarity. Each 1 s epoch was flagged if more than 20% of ICs were outliers based on values that are more than six times the 0.3–0.7 inter-quantile range. A subsequent AMICA was performed, ignoring these time periods in which too many ICs have outlying voltage values, to generate a more reliable decomposition.

A single dipole was then fit to each IC weight topography and each IC was then classified into seven common categories (brain, eye, muscle, heart, channel noise, line noise, and other) using the ICLabel EEGLAB extension (Pion-Tonachini et al., 2019a, 2019b). The ICLabel extension examines the spatiotemporal measures in the ICLabel database, which contains more than 200,000 ICs sourced from over 6000 EEG recordings.

The final quality control was carried out by an expert review of the classification of ICs into the phenomena they capture paired with IC properties (e.g., topographical projection, spectral dynamics, dipole fit residual variance, and classification accuracy) and the comprehensive data annotations overlaid on the continuous time series of scalp and component activations. For a complete description of EEG-IP-L and a summary of data diagnostics, see Desjardins et al. (2021) and van Noordt et al. (2020).

EEG post-processing and signal extraction

The cleaned continuous data were segmented into epochs of −800 to 1800 ms to ensure appropriate time-frequency resolution for the duration of the trial, time-locked to stimulus onset. The single-trial data were convolved with complex Morlet wavelets using the newtimef function in EEGLAB, with cycles increasing in 0.5 increments from 3 Hz (1 cycle) to 30 Hz (14.5 cycles). ITC was introduced by Tallon-Baudry et al. (1996) and is a time-frequency measure of the consistency in phase activity across trials that are time-locked to a specific event. The measure ranges from 0 to 1, where 0 represents a completely random phase (at a particular frequency and latency) across trials and 1 represents EEG phase that is identical (at a particular frequency and latency) across trials. The complex vector in the 2-D Cartesian coordinate frame is normalized so that the magnitude (i.e., length) of the vector is equal to 1 across trials and only the phase information of the spectral estimate is retained. ITC is then taken as the complex average of these normalized vectors across trials (see Equation 1).

$$\mathrm{ITC}(f,t) = \frac{1}{n}\sum_{k=1}^{n}\frac{F_k(f,t)}{|F_k(f,t)|} \quad (1)$$

Two time windows of interest were selected based on previous work showing that the cascade of visual processing in infants is characterized by early P100 responses and later visual components that reflect high level integration (Elsabbagh et al., 2012; McCleery et al., 2009). Studies suggest that neural responses distinguish early (P100) and late stages (N170 in young adults) of visual processing are functionally distinct (Desjardins & Segalowitz, 2013; Rousselet et al., 2007, 2008), and the grand average waveforms showing that visual processing

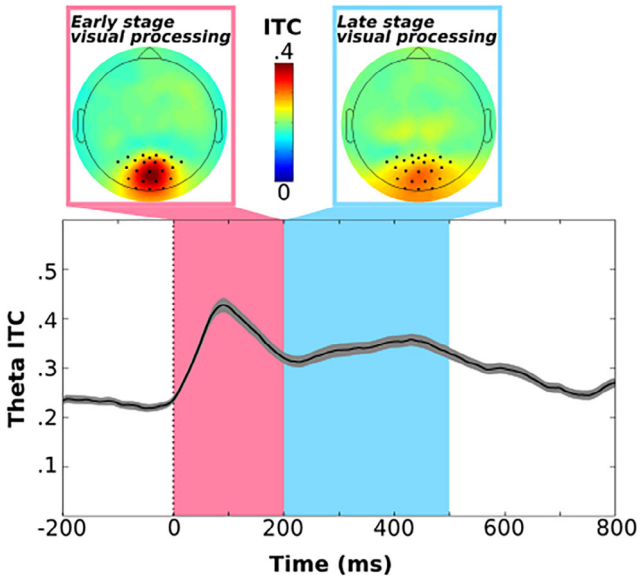

FIGURE 2 Grand average theta ITC topographical maps and waveforms, collapsed across groups and conditions, show two distinct perturbations during the early (pink, 0–200 ms) and late (blue, 200–500 ms) stages of visual processing. Black circles on topographic maps indicate the bilateral posterior channel cluster used to extract theta ITC

is marked by two distinct perturbations in posterior t-ITC. We defined "early stage visual processing" as the mean t-ITC measured from 0 to 200 ms post-stimulus onset and "late stage visual processing" as the mean t-ITC from 200 to 500 ms post-stimulus onset. The theta range was defined from 3 to 6 Hz, as is commonly used in infant EEG studies (Jones et al., 2020; Orekhova et al., 2006; Tierney et al., 2012). A bilateral posterior region-of-interest was used and corresponded to locations previously used for ERP analyses in this sample (see Figure 1) and in other studies on face processing in ASD (Elsabbagh et al., 2012; Guy et al., 2018; Jones et al., 2016; Key & Stone, 2012; Luyster et al., 2014). See Figure 2.

Statistical analyses

To minimize the impact of issues related to distribution characteristics, particularly in small samples of unequal size and variance, we used a robust estimation approach to assess group differences in t-ITC. Main effects were tested using *spmcpa* and *spmcpb* functions for a 2 (condition) × 3 (group) mixed designs in Hypothesize using 2000 bootstrap re-samples with 10% trimmed means with a sequentially rejective method to control family wise error (Campopiano & Wilcox, 2020). Interactions were examined with percentile bootstrap tests using 2000 re-samples and 10% trimmed means. Pairwise contrasts were assessed via Yuen's test (Mair & Wilcox, 2020) with 2000 bootstrap re-samples with 10% trimmed means. We also examined group differences in terms of quantiles to gain a more thorough representation of the underlying distributions. These analyses used an adaptation version the robust shift function for independent groups, using the Harrell-Davis quantile estimator in conjunction with a percentile bootstrap approach (Rousselet et al., 2017; Wilcox et al., 2014). The shift function reveals how much one distribution would need to be moved in order to align with another distribution, thus providing an estimate of similarity in addition to a single measure of central tendency. Specifically, the quantile difference between groups (e.g., group 1 minus group 2) are plotted against the quantiles of one group (e.g., group 1). Family-wise error rate was controlled via Hochberg's method. These analyses were carried out using the *matrogme* MATLAB toolbox (available here: https://github.com/Grousselet/matrogme).

RESULTS

Early stage visual processing

We did not find evidence that posterior t-ITC during early stage visual processing varied by condition, *difference* = −0.04, $p = 0.37$, 95% CIs [−0.11, 0.041], group, *differences range* = −0.03 to 0.06, p's < 0.22, 95% CI's range [−0.11 to 0.16], or the interaction between condition and group, *differences range* = −0.027 to 0.019, p's < 0.19, 95% CIs range [−0.06, 0.005]), indicating that increased t-ITC reflects a general cortical marker of an early visual response.

Late stage visual processing

For later stage visual processing we observed significant effects of condition and group on posterior t-ITC. Specifically, posterior t-ITC was greater for faces compared to noise stimuli, *difference* = 0.077, $p < 0.01$, 95% CIs [0.03, 0.13]. The group effect demonstrated that HRA+ infants have lower posterior t-ITC compared to TD, *difference* = 0.06, $p = 0.019$, 95% CIs [0.012, 0.12]) and HRA− infants, *difference* = 0.064, $p = 0.029$, 95% CIs [0.005, 0.12), with no reliable difference between TD and HRA−, *difference* = 0.008, $p = 0.84$, 95% CIs [−0.07, 0.076]). These main effects were superseded by a condition by group interaction, indicating that the difference between face and noise was significantly greater for TD, *difference* = 0.056, 95% CIs [0.035, 0.076]) and HRA−, *difference* = 0.041, 95% CIs [0.022, 0.06]) compared to HRA+. Follow-up contrasts confirmed that the TD $t(42) = 3.34$, $p = 0.002$, 95% CIs [0.036, 0.14], and HRA− $t(68) = 3.01$, $p = 0.006$, 95% CIs [0.026, 0.13]) infants show a larger increase in t-ITC to faces stimuli compared to HRA+ infants. TD and HRA− infants showed similar differentiation between face

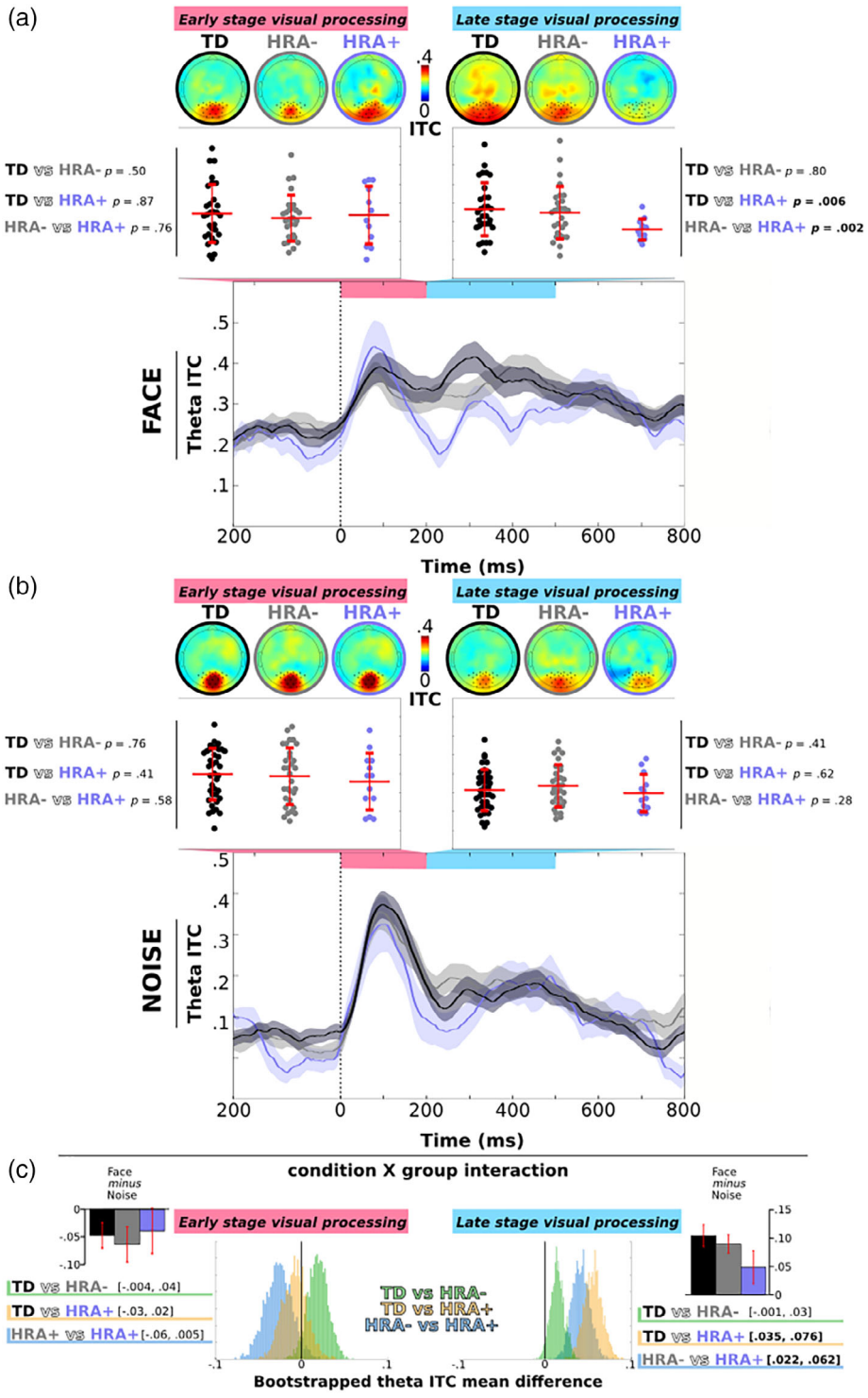

FIGURE 3 Group topographies and scatter plots of mean posterior theta ITC during early (pink, 0–200 ms) and late (blue, 200–500 ms) stages of visual processing for face (panel a) and noise (panel b) stimuli. Mean and 95% confidence intervals shown in red on scatter plots. Shaded areas around waveforms represent standard error of the mean. Panel (c) bar graphs show mean condition difference (face – noise). Histograms show the distribution of the bootstrapped trimmed means for the condition-by-group interaction for the typically developing (TD) versus higher likelihood no ASD (HRA−) in green, typically developing (TD) versus higher likelihood ASD (HRA+) in orange, and higher likelihood no ASD (HRA−) versus higher likelihood ASD (HRA+) (blue). Significant effects are shown in bold

and noise stimuli $t(68) = 0.24$, $p = 0.80$, 95% CIs [0.05, 0.07]). Given that ITC can be affected by the magnitude of the evoked response (van Diepen & Mazaheri, 2018), we examined group and condition differences in ERP amplitude and signal-to-noise ratio. We failed to find evidence that ERP magnitude or signal-to-noise ratio vary by condition or group (see Supplementary materials). See Figure 3 for the summary of the results.

Examining results of the shift function, group differences in the distributions between TD and HRA+, and HRA− and HRA+, were observed for mid and upper quantiles, indicating that the theta coherence in HRA+ across individuals was consistently low (see Figure 4). In other words, the distribution of t-ITC in HRA+ would need to be shifted, specifically in the upper quantiles, in order to be similar to TD and HRA− groups.

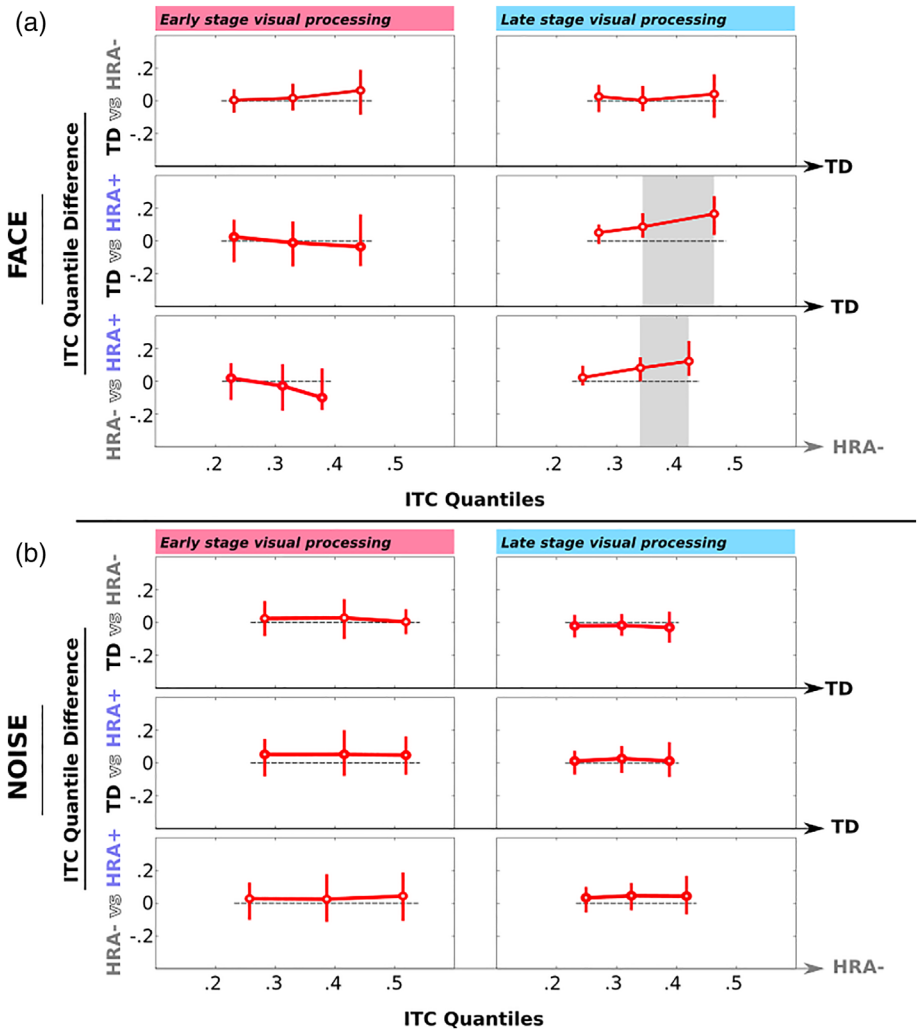

FIGURE 4 Shift function plots with bootstrapped confidence intervals. Group ITC quantiles (*x*-axis) plotted against pairwise group differences in quantiles (*y*-axis) for early (pink, 0–200 ms) and late (blue, 200–500 ms) stages for face (panel a) and noise (panel b) stimuli. Shaded areas highlight significant differences and indicate that the HRA+ infants had consistently low t-ITC compared to TD and HRA− infants

DISCUSSION

In this study we tested whether t-ITC during face processing is associated with ASD outcome in infants. We found that higher likelihood infants who eventually receive an ASD diagnosis had reduced posterior t-ITC during the later stages of face processing, in a time window that corresponds to high level integration and is thought to be a developmental precursor to the face sensitive N170 (Halit et al., 2003; Shephard et al., 2020). These findings suggest that aspects of intra-individual variability in neural responses during infancy reflect processing atypicalities of emerging ASD.

The early visual response is dominated by the P100, which is maximal at posterior-occipital channels and modulated by low-level stimulus properties (color, contrast, and amplitude spectrum) and spatial attention (Di Russo et al., 2003; Martínez et al., 1999). The evidence for face specificity of the P100 has yielded mixed findings in both infant and adults studies on face processing (Elsabbagh et al., 2009, 2012; Luyster et al., 2014; McCleery et al., 2009); de Haan & Nelson, 1999; although see Conte et al., 2020; Desjardins & Segalowitz, 2013), perhaps due a combination of differences across experimental paradigms and overlapping activities from independent stages of visual processing (see Desjardins & Segalowitz, 2013). In the current study we did not observe any robust effects for the P100 in terms of differentiating groups for faces or noise stimuli. In a previous ERP study using an overlapping sample (Elsabbagh et al., 2012), P100 amplitude was sensitive to dynamic gaze shifts only in TD infants and did not differ between groups for static faces or noise stimuli, similar to the current findings related to posterior t-ITC during the early stages of visual processing.

Later stages of visual processing reveal brain dynamics that are sensitive to face stimuli, most notably the N170 face-specific ERP component that is well-established in children and adults. In infants, the N290 and P400 ERPs are found during the later stages of visual processing and show characteristics similar to the N170 in older individuals, including sensitivity to face inversion and modulation by emotional expression (Halit et al., 2003, 2004; Leppänen et al., 2007). Similar to previous findings in this sample, we found that TD and HRA−

infants show comparable neural responses during early and late stages of visual processing. Although the effects observed in the current study did not reach statistical significance between TD and HRA− infants, the direction of the effects suggest that increases posterior t-ITC to faces compared to noise is a graded response whereby it is reduced in higher likelihood infants, but significantly more so in those higher likelihood infants who received an ASD diagnosis at 36 months (i.e., TD > HRA− > HRA+). This pattern suggests an additive effect in higher likelihood infants who are diagnosed with ASD as these infants do not show the same increase in t-ITC during the later stages of face processing.

Related to the current study, greater intra-individual variability in oscillatory phase coherence during the later stages of visual processing in HRA+ infants could reflect a physiological marker of atypical brain development. A number of studies have shown that ASD is linked to greater intra-individual variability in overt behavioral responses (Geurts et al., 2008; Van Belle et al., 2015), as well as brain responses measured by both EEG and fMRI (David et al., 2016; Dinstein et al., 2015; Haigh & Heeger, 2015; Lushchekina et al., 2016; van Noordt et al., 2017). Given that the timing of responses in sensory cortices are especially sensitive to stimulus properties, the functional significance of variability in oscillatory coherence at basic levels of sensory processing could have downstream effects on learning and social communication (Webb et al., 2017). These findings are in line with current models suggesting that early perceptual and attention capacities may differentially impact the processing of complex social information in typical and atypical development (Elsabbagh, 2020). Further support comes from several studies highlighting that atypical face processing is associated with functional deficits as reflected by more severe ASD symptoms (Kovarski et al., 2019; Neuhaus et al., 2016; Tye et al., In press; Weigelt et al., 2013), which may subsequently contribute to impaired social competence and communication.

Evidence has accumulated to suggest that greater intra-individual variability in ASD is not restricted to high frequency activity (Buard et al., 2013; Edgar et al., 2013; Milne, 2011; Schneider et al., 2008; van Noordt et al., 2017). The role of ITC in low frequency activity has been largely unexplored in the pathophysiology of ASD during the earliest stages of development. Studies on earlydevelopment suggest that theta is modulated by attention to social stimuli, particularly over posterior scalp regions (Orekhova et al., 2006), and is reduced to social stimulation in infants at-risk for ASD (Jones et al., 2017). Posterior t-ITC during the face-specific N170, which is thought to emerge from the maturation of visual responses reflected in the N290 and P400, has also been linked to emotion recognition in adults (Csukly et al., 2014). Whereas high frequency oscillations have gained much attention due to their role in intra-regional integration, low frequency oscillations in the theta range could play a role in facilitating long-range inter-regional communication that subsequently entrains localized high frequency oscillations. Some evidence supports this cross-coupling between low (theta) and high (gamma) frequencies in the inferior occipital gryus, particularly during the rapid process of faces (Canolty & Knight, 2010; Liebe et al., 2012; Sato et al., 2014), possibly reflecting network communication between visual cortex and subcortical limbic structures (Sato et al., 2017). Taken in the context of other reliable indicators, perturbations in posterior theta dynamics to social stimuli may be an informative transdiagnostic marker of the broad ASD phenotype.

Our findings also suggest that single-trial EEG measures have the utility for capturing developmental markers of ASD which may otherwise be obscured with a traditional ERP averaging approach. Using an overlapping set of participants from the current study, two previous analyses did not find evidence that the P400 amplitude to static faces differentiates ASD risk or outcome in 6–10 months old infants (Elsabbagh et al., 2012; van Noordt et al., 2020); however, in the current study we found that intra-individual variability in posterior theta coherence is greater in at-risk infants who eventually receive a diagnosis of ASD (despite similar ERP amplitudes and signal-to-noise ratios during the N290/400 time window—see Supplementary materials). Similarly, both EEG and fMRI studies have found that, although overall amplitude are similar between groups, intra-individual variability in amplitude, latency, phase coherence, and BOLD signals is greater in individuals with ASD (Dinstein et al., 2015; Haigh & Heeger, 2015; Milne, 2011; Weinger et al., 2014). Given that, in early development, the temporal integration of neural activity can shape the maturation of structural and functional networks (Uhlhaas et al., 2010), atypicalities in the temporal consistency of neural responses may result in poor "signal-to-noise ratio," which could subsequently impact the maturation of cortical networks. Moving beyond the fixed-latency ERP average approach, future studies should aim to exploit repeated single-trial measures to unpack the links between neural variability, performance, and ASD symptomatology.

We add to the literature on intra-individual variability in ASD and extend previous research by demonstrating that posterior visually evoked theta coherence during later stages of face processing is reduced (i.e., more variable) in 6–10 month old infants with higher likelihood who later receive a diagnosis of ASD. Prospective studies of higher likelihood infants are valuable as they can help distinguish neural markers that may play an important role in the development of ASD. In relation to the current findings, atypical face processing, as indexed by reduced consistency in neural responses, reflects an early marker of ASD that may play an important role in subsequent deficits in social information processing and social functioning. Due to constraints with longitudinal studies on infants with higher likelihood for neurodevelopmental

disorders, the current study contains a relatively small sample size of infants who eventually receive an ASD diagnosis. Our results reported here therefore need to be replicated in larger independent samples, ideally with longer recordings and comparable tasks. These studies will be necessary to help clarify the links between neural and behavioral variability, and whether the nature of these associations are relevant in a broader neurodevelopmental context beyond ASD.

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CONFLICT OF INTERESTS

The authors declare no potential conflict of interest.

ETHICAL APPROVAL

Ethical approval (UK National Health Service National Research Ethics Service London REC 08/H0718/76) was made available through BASIS.

DATA AVAILABILITY STATEMENT

Research data are not shared.

ORCID

Stefon van Noordt https://orcid.org/0000-0001-8413-1320

Mayada Elsabbagh https://orcid.org/0000-0002-7311-9059

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