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Role of inter-trial phase coherence in atypical auditory evoked potentials to speech and nonspeech stimuli in children with autism

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HIGHLIGHTS

- Children with autism showed enhanced P1 but reduced N2 auditory evoked responses for both speech and nonspeech stimuli.
- Theta band inter-trial phase coherence values significantly predicted P1 and N2 amplitudes.
- Abnormalities in evoked potentials and oscillations in autism are time-dependent.

ABSTRACT

Objective: This autism study investigated how inter-trial phase coherence (ITPC) drives abnormalities in auditory evoked potential (AEP) responses for speech and nonspeech stimuli.
Methods: Auditory P1-N2 responses and ITPCs in the theta band (4–7 Hz) for pure tones and words were assessed with EEG data from 15 school-age children with autism and 16 age-matched typically developing (TD) controls.
Results: The autism group showed enhanced P1 and reduced N2 for both speech and nonspeech stimuli in comparison with the TD group. Group differences were also found with enhanced theta ITPC for P1 followed by ITPC reduction for N2 in the autism group. The ITPC values were significant predictors of P1 and N2 amplitudes in both groups.
Conclusions: Abnormal trial-to-trial phase synchrony plays an important role in AEP atypicalities in children with autism. ITPC-driven enhancement as well as attenuation in different AEP components may coexist, depending on the stage of information processing.
Significance: It is necessary to examine the time course of auditory evoked potentials and the corresponding inter-trial coherence of neural oscillatory activities to better understand hyper- and hypo- sensitive responses in autism, which has important implications for sensory based treatment.

1. Introduction

Sensory processing abnormality constitutes a core feature of autism spectrum disorders (American Psychiatric Association, 2013). Atypical auditory evoked potentials (AEPs) in autism have been reported with mixed findings. School-age children with autism often display prolonged neural response latency around 100 ms (N1, or M100 in magnetoencephalography) to tonal stimuli compared with typically developing (TD) children (Bruneau et al., 2003; Oram Cardy et al., 2008; Gandal et al., 2010; Roberts et al., 2010). However, the opposite pattern with the autism group showing earlier N1 response has also been found (Ferri et al., 2003). Attenuated P1 amplitude to pure tones (Orekhova et al., 2008; Donkers et al., 2015), speech and complex tonal stimuli (Lepistö et al., 2005), as well as attenuated N1c to clicks (Orekhova et al., 2009) have been discovered in children with autism. Moreover, some researchers observed attenuated N2 amplitude in children with autism in response to vowels (Whitehouse et al., 2008) and

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complex tones (Lepistö et al., 2005), whereas others did not (Čeponienė et al., 2003; Gomot et al., 2011).

The mixed AEP findings suggest the variable nature of sensory perception in individuals with autism, which may partly result from methodological differences across studies. First, the sample age range varied from study to study with the widest being 11 years. As the AEP morphology in terms of amplitude and latency of the peak components show age-dependent maturational changes, it is not surprising to see large variations in the results across individuals and studies. Second, differences in stimulus presentation rate across studies could contribute to the variations in the reported AEP results, as it is known to affect the presence and morphology of P1-N1(or N2) in children (Čeponienė et al., 1998, 2002; Cunningham et al., 2000). Third, atypical sensory perception in autism may show different hyper- or hypo-sensitive patterns depending on the category of auditory stimuli (i.e., whether the stimulus is speech or nonspeech) (Yu et al., 2015; Huang et al., 2017; Wang et al., 2017), and it is still unclear how these atypical sensory patterns as assessed by the AEP responses may change over time in child development. For instance, when tested with speech sounds, children with autism tend to display a categorical perception deficit with poorer discrimination of phonemic contrasts and enhanced sensitivity for within-category differences or allophonic variations (Wang et al., 2017; You et al., 2017). When tested with nonspeech stimuli, children with autism often exhibit enhanced discrimination of certain acoustic dimensions such as pitch (Lepistö et al., 2005; Yu et al., 2015; Wang et al., 2017) but reduced sensitivity for other dimensions such as sound duration (Lepistö et al., 2005; Huang et al., 2017). These findings point to the necessity of exercising caution when interpreting abnormal AEPs in autism, as they may reflect different neural processes of acoustic, phonetic, and phonological analysis. Fourth, abnormal AEPs in autism are often intertwined with stimulus complexity. It is suggested that the spectro-temporal complexity in verbal stimuli may compromise the neural dynamics in individuals with autism (Samson et al., 2006). Moreover, the inclusion of ASD subgroups of autistic disorder such as Asperger's Syndrome and individuals with potentially only subclinical symptomology may further introduce heterogeneity to the sample (Smith et al., 2015). The differences in subject characteristics, stimulus property, and experimental task add complexity to the synergistic interpretation of the existing AEP findings across the autism studies.

Among the frequently studied AEP components, P1 and N2 are the most prominent and reliable responses in childhood through adolescence (Sharma et al., 1997; Ceponiene et al., 1998; Ponton et al., 2000). In TD children, the auditory P1 is a stimulus-driven response peaking at around 100 ms post-stimulus. P1 latency is thought to mark the time delay of thalamocortical neural transmission in the auditory pathway (Eggermont et al., 1997). TD children's P1 amplitude increases with greater acoustic complexity (Čeponienė et al., 2001), and is affected by arousal and sound onset features (Pratt, 2012). Following the P1 is a large negative deflection N2 peaking around 250 ms (Čeponienė et al., 2002). With faster stimulus presentation (i.e., inter-stimulus interval <1 s), the fronto-centrally distributed N2 in children partially overlaps with the developmentally emerging adult-like N1 (Čeponienė et al., 1998, 2002). Unlike the P1 which reflects primarily low-level sensory detection, the auditory N2 is considered reflecting higher-level sensory integration and phonetic perception (Karhu et al., 1997; Čeponienė et al., 2001, 2008, 2009). It has been shown that N2 amplitude increases with repetition of identical sound, which might be instrumental in forming auditory-learning induced neural representations of sounds (Karhu et al., 1997; Fujioka et al., 2006).

Although the AEP results can provide insights on the neural basis of variable sensory perception in autism in terms of amplitude and latency measures, the quantification of AEP components focuses solely on the time-domain information averaged across trials while discarding the trial-by-trial variations in the time-frequency domain. It has been found that phase alignment of EEG oscillations in response to a stimulus, especially in theta (4–7 Hz) and alpha (8–12 Hz) band, drives the generation of human evoked potentials (Klimesch et al., 2007; Edwards et al., 2009). Such evoked neural synchrony or phase-locking can be computed as inter-trial phase coherence (ITPC) in frequencies of interest. Smaller ITPC values represent poorer consistency in the phase alignment of oscillations or larger amount of neural "jittering" across trials.

One prevailing theory on the neurophysiology of autism is the increased variability in cortical responses to complex sensory input (Haigh, 2017), which can be tested through the inter-trial oscillatory synchrony. Indeed, recent data have demonstrated reduced task-related ITPC across multiple frequency bands in children (Gandal et al., 2010; Edgar et al., 2015a, 2015b) and adults (Milne, 2011; Sun et al., 2012; Buard et al., 2013; Jochaut et al., 2015; van Noordt et al., 2017) with autism. Critically, such jittered oscillation rhythm may result in an overall reduction in evoked response power in the EEG signal (Simon et al., 2016). In this regard, one viable question to ask is whether attenuated AEP amplitude in autism obtained from averaging over EEG trials can be explained by increased inter-trial variability in the phase alignment of oscillations for both speech and nonspeech sounds. Answer to this question can provide insightful information regarding the neural basis of altered auditory processing.

The current study aimed to characterize atypicality in AEPs to speech and nonspeech stimuli in children with autism in the light of oscillatory variability. We focused on neural oscillations in the theta band, because theta synchrony not only is an important generator of AEP but also holds additional significance for speech and linguistic processing. In particular, infants' theta activity has been shown to be modulated by linguistic experience (Radicevic et al., 2008) and phonetic salience (Zhang et al., 2011). In adults, theta ITPC significantly predicts auditory N1-P2 amplitude to CV (consonant-vowel) syllables (Koerner et al., 2015). Furthermore, theta activities are believed to be responsible for syllable-level speech encoding, which are crucial for successful speech comprehension (Morillon et al., 2010; Giraud et al., 2012; Peelle et al., 2013; Doelling et al., 2014). In the autism literature, however, the neurobehavioral consequences of theta rhythm in the processing of speech and nonspeech stimuli have rarely been tested. We were able to find only one study, in which adults and adolescents with autism showed weak synergistic theta activity for sentence-level speech processing in the auditory cortex (Jochaut et al., 2015). The relationships between trial-to-trial variations in theta activities and the AEP components for speech and nonspeech sounds remain unknown.

For the current investigation, we aimed to have a better control of some of the confounding factors to understand the AEP characteristics in children with autism with two primary objectives. First, we examined cortical processing of simple tones and complex speech sounds in school-age (8–13 years old) children with autism and age-matched TD children. Second, we were interested in exploring the relationships between the trial-to-trial variability/-consistency of theta phase-locking measured by ITPC and the P1-N2 amplitude within each group. We targeted school-age children in order to control potential age-related confounds due to maturational AEP changes. A short passive listening procedure with a fast stimulus presentation was used to elicit auditory P1-N2 components for both speech and nonspeech stimuli in these children. Amplitude/latency of P1 and N2 and the associated ITPCs were analyzed as a function of subject group and stimulus type.

We aimed to test two main hypotheses. First, if children with autism exhibit atypical sound onset feature detection and subse-

quent higher-level sound processing, we may observe atypical AEP amplitude and theta ITPC in the autism group at the processing stages of both P1 and N2 components compared with the TDs. Moreover, as deficiency in perceptual learning of auditory patterns in autism is considered to be speech-specific (Kujala et al., 2013), we expect to find the group difference to be more pronounced in the word condition than in the pure tone condition. Second, as reduced synchrony of neuronal oscillations in autism may lead to overall reduced evoked power (Simon et al., 2016), we hypothesized that reduced theta ITPC might be significantly correlated with reduced AEP amplitude in the group of autism.

2. Methods

2.1. Participants

Fifteen children with autism (14 boys and 1 girl, age mean = 9.6 years, *SD* = 1.7 years, range 8–12.4 years) were recruited from a local school for children with autism following recruitment and screening protocols established in our previous autism studies (Yu et al., 2015; Wang et al., 2017; Huang et al., 2017). The numbers of children with autism included in data analysis were 15 for the pure tone condition and 14 for the word condition as one boy was not able to complete EEG recording for the word condition. The diagnoses were established by pediatricians according to the DSM-IV criteria for Autistic Disorder (American Psychiatric Association, 1994). As the Autism Diagnostic Observation Schedule (ADOS) (Lord et al., 2001) has not been officially validated and adopted in mainland China, we confirmed the diagnoses using the Chinese version of the Gilliam Autism Rating Scale–Second Edition (GARS-2) (Gilliam, 2006). Sixteen age-matched TD controls (13 boys and 3 girls, age mean = 9.8 years, *SD* = 1.4 years, range 7.8–12.9 years) were recruited from a local elementary school. One boy and one girl were excluded from analysis for the word condition due to noisy EEG signal, resulting in 16 children for the pure tone condition and 14 for the word condition in the TD group.

All participants were native speakers of Mandarin Chinese. They were screened for hearing loss using pure tone audiometry and met the criteria for normal hearing. All children in the autism group were verbal with limited language ability. Specifically, eight out of 15 had documented delayed onset of speech measured by their use of two-word utterances (this information was unavailable for 3 children); the average verbal IQ in the autism group was 64 (*N* = 13, information unavailable for 2 children, *SD* = 19, range 45–96) measured by the Wechsler Intelligence Scale for Children (WISC-IV) (Wechsler, 2003). All participants were native Mandarin speakers. None of the children had a known or diagnosed genetic, mental, or additional neurological condition, and were unmedicated at the time of the study. Nonverbal IQ (NVIQ) of each child was measured using the Raven's Standard Progressive Matrices Test (Raven, 1998). The autism group scored lower (mean = 88, *SD* = 19) compared to the TD group (mean = 106, *SD* = 15) ($t(29) = 3.33$, $p < .01$). The lower nonverbal scores in the autism group were expected and consistent with the reported IQ profiles in the literature (Dawson et al., 2007). Informed consent was obtained from each child's parent following a protocol approved by the local institutional review board.

2.2. Stimuli and procedure

The pure tone was a 216 Hz sinusoidal wave. The word /bai2/ ("white" in Chinese) was uttered by a female talker, recorded using Neundo 4 (Steinberg Media Technologies, Germany). The sounds were edited to have a duration of 350 ms including 10 ms rise and fall time. The sound intensity was normalized to be equal for the two stimuli. The sound editing was completed using Praat (Boersma et al., 2014) and Goldwave (http://www.goldwave.com). The two stimulus conditions were presented in two separate blocks with 500 ms inter-stimulus interval (ISI). Each block contained 500 stimuli. The stimuli were presented via AKG K518 headphones at approximately 70 dB SPL. The participants were seated and asked to watch a muted self-chosen cartoon and to ignore the auditory stimuli during the experiment.

2.3. EEG recording and data analysis

Continuous EEG data were recorded with a 32-channel BrainAmps DC amplifier system (Brain Products, Germany). The sampling rate was 500 Hz. The left mastoid and AFz were used as the reference and ground, respectively. Ocular activities were monitored with electrodes placed below the right eye and the outer corner of the left eye. Electrode impedance was kept below 10 kΩ. Data analysis was performed using EEGLAB (Delorme et al., 2004). In offline analysis, the continuous EEG data were first visually inspected before preprocessing to identify overly noisy or flat segments and remove them from analysis. The data were high-pass filtered with 0.5 Hz cut-off. Ocular and muscle artifacts were removed using independent component analysis (ICA) for AEP waveform analysis. Epochs with 800 ms length were extracted including a 200 ms pre-stimulus baseline. Trials with instantaneous values exceeding ±100 μV were rejected.

Waveform analysis of the P1 and N2 components were performed with data band-pass filtered at 0.5–30 Hz. Based on the grand mean waveforms, P1 and N2 peaks were searched within post-stimulus windows of 70–150 and 200–350 ms, respectively. Mean amplitudes of P1 and N2 were computed for a 20 ms window around the peak of each participant. The Fz electrode was used for statistical analysis based on the topographical distribution.

Trial-by-trial time-frequency analysis was carried out in EEGLAB (Delorme et al., 2004). Inter-trial phase coherence (ITPC) in the theta band (4–7 Hz) was computed using the "newtimef" function: $ITPC(f,t) = \frac{1}{n}\sum_{k=1}^{n}\frac{F_k(f,t)}{|F_k(f,t)|}$. In this function, $F_k(f,t)$ is the spectral estimate of trial k at frequency f and time t obtained using short-time Fourier transformation (STFT), and || represents the complex norm of trial k. The modified STFT (with Hanning tapers) in EEGLAB uses overlapping sliding windows that are adaptive to the target frequency bins (i.e., the time window decreases linearly as frequency increases), which is recommended to overcome limitations of conventional fixed window in estimating low frequency activities. The frequency range analyzed was 0.5–50 Hz. Zero-padding was applied to windows without sufficient number of sample points with a padratio of 16 with a frequency spacing of 0.5 Hz. ITPC value of a given frequency at a given time point can range from 0 to 1. Larger ITPC values indicate higher phase consistency across trials, and smaller values indicate lower consistency or larger neural "jittering". For the calculation of theta ITPC, the ITPC data were first averaged across the frequencies within the theta range for further processing. Then the maximum theta ITPC values within the designated time windows of pre-stimulus baseline ($-200 \sim 0$), P1 (70–140) and N2 (150–250 ms) were identified for each participant for statistical analysis. Spectral power in the theta band was also computed for both the pre-stimulus baseline and the response portion of the epochs using the *spectopo* function in EEGLAB based on Welch's power spectral density estimate (oversampling × 8). Similar time-frequency analysis procedures were used in published studies (Koerner et al., 2015, 2016). The number of trials for analysis in the autism group were 332 (range 165–466) for the pure tone condition and 300 (172–383) for the word condition. The numbers in the TD group were 309 (207–396) for the pure tone condition and 334 (234–403) for the word

condition. These numbers did not differ between groups (pure tone, $t(29) = 1.01$, $p = .321$; word, $t(26) = -1.48$, $p = .15$).

To examine the main effects and interaction of group (autism vs. TD) and stimulus condition (pure tone vs. word), linear mixed effect (LME) regression was performed for each outcome measure, namely, amplitude and latency of the P1 and N2 components, theta ITPC within the baseline and corresponding windows of P1-N2, spectral theta power in the baseline and response. The mixed-effects model approach is considered superior to traditional methods statistical analysis such as repeated measures analysis of variance and Pearson's correlation (Gueorguieva and Krystal, 2011; Koerner and Zhang, 2017). In each LME model, NVIQ, group, stimulus condition, and group * stimulus condition interaction were included as fixed effects, among which NVIQ was regarded as a controlled covariate; participant was included as a random effect. Additionally, to examine the relationships between P1-N2 amplitude and ITPC within the corresponding windows in each group, LME model with theta ITPC as a predictor variable was fit for P1 and N2 amplitude for each group separately. In each LME model, theta ITPC was entered as a fixed effect, and subject as a random effect; NVIQ was included as a covariate and stimulus condition as a blocking variable. Two-tailed significance level was used for all the statistical analyses.

3. Results

3.1. AEP amplitude and latency

The LME regression model showed significant effects of group ($F(1,54) = 5.19$, $p < .05$) and stimulus condition ($F(1,54) = 16.13$, $p < .01$) on the P1 amplitude while controlling for NVIQ ($F(1,54) = 0.12$, $p = .731$), indicating larger P1 response in the autism group compared with the TD group and increased P1 response to word stimuli compared to pure tones in both groups (Fig. 1 & Tables 1 and 4). No significant group * condition interaction was found for the P1 amplitude ($F(1,54) = 0.46$, $p = .500$). For the P1 latency, there was a significant group effect ($F(1,54) = 6.93$, $p < .05$) while controlling for NVIQ ($F(1,54) = 0.38$, $p = .538$), indicating prolonged P1 latency in the autism group compared with the TD group. No condition effect ($F(1,54) = 0.24$, $p = .624$) or group * condition interaction ($F(1,54) = 0.69$, $p = .410$) on P1 latency was observed.

Table 1
Mean and standard deviation (SD) of P1 and N2 amplitude (μV) and latency (ms) in the autism group and the TD group.

	Group	P1		N2	
		Amplitude	Latency	Amplitude	Latency
Pure tone	Autism	2.82 (1.06)	104 (19)	−7.54 (1.99)	277 (43)
	TD control	2.39 (2.00)	91 (14)	−9.50 (2.83)	279 (31)
Word	Autism	4.74 (1.83)	99 (12)	−7.09(3.30)	287 (24)
	TD control	3.75 (1.11)	92 (15)	−8.86 (3.45)	269 (16)

There was a nonsignificant trend of group effect on the N2 amplitude ($F(1,54) = 2.88$, $p = .096$) while controlling for the effect of NVIQ ($F(1,54) = 3.75$, $p = .058$) (Table 4). When the NVIQ was excluded from the regression, the group effect became significant ($F(1,55) = 6.04$, $p < .05$), suggesting a diminished N2 response in the autism group compared with the TD group. No condition effect ($F(1,54) = 0.52$, $p = .474$) or group * condition interaction ($F(1,54) = 0.12$, $p = .915$) was found for the N2 amplitude. For the N2 latency, no significant effect was found (group, $F(1,54) = 1.17$, $p = .284$; condition, $F(1,54) = 0.00$, $p = .999$; group * condition interaction, $F(1,54) = 1.43$, $p = .237$; NVIQ ($F(1,54) = 0.01$, $p = .913$).

3.2. Inter-trial phase coherence and spectral power

Group and stimulus condition effects on theta ITPC were examined separately for the P1 and N2 windows (Fig. 2 & Tables 2 and 4). In the P1 window, the LME regression model revealed significant effects of group ($F(1,54) = 11.00$, $p < .01$) and condition ($F(1,54) = 5.69$, $p < .05$) on ITPC, controlling for NVIQ ($F(1,54) = 0.30$,

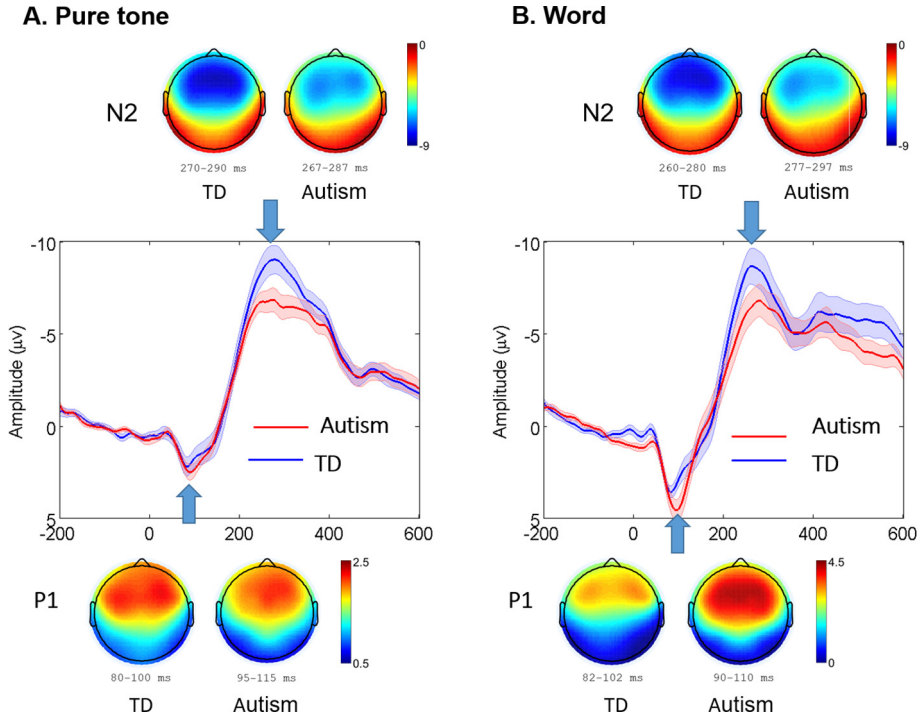

Fig. 1. Grand averaged waveforms at Fz and topographical maps of mean amplitude in the P1 and N2 windows in the pure tone condition (A) and word condition (B). Shaded areas along the waveforms represent standard error at all sample points.

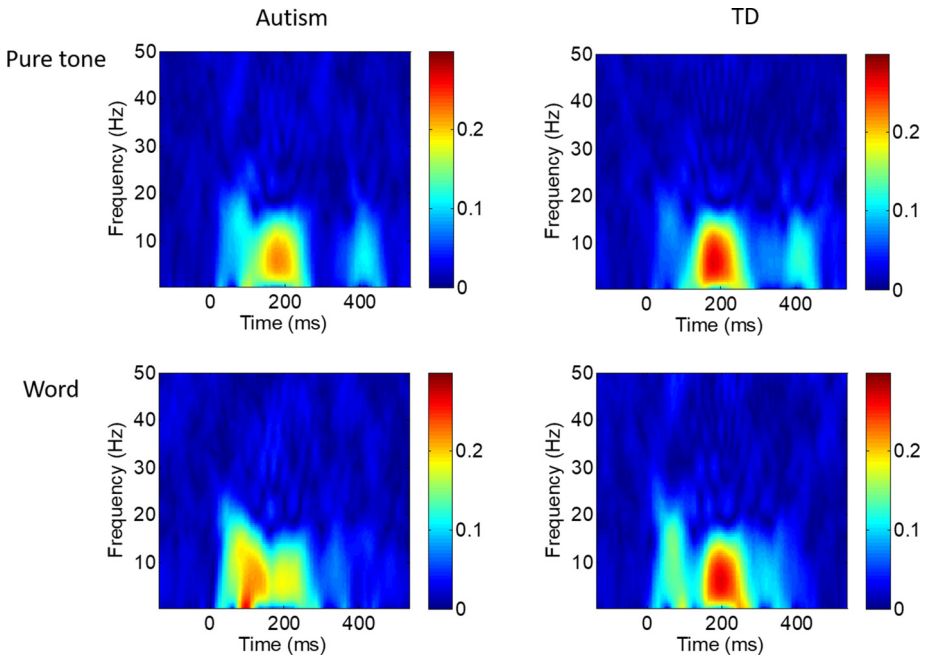

Fig. 2. Time-frequency representations showing trial-to-trial phase-locking measured by ITPC in the pure tone condition and word condition.

Table 2
Mean and standard deviation (SD) of theta ITPC in the pre-stimulus baseline and post-stimulus windows.

	Pure tone			Word		
	Baseline	P1	N2	Baseline	P1	N2
Autism	0.09(0.03)	0.19(0.08)	0.25(0.09)	0.08(0.03)	0.24(0.07)	0.22(0.09)
TD	0.09(0.02)	0.16(0.08)	0.29(0.10)	0.08(0.03)	0.19(0.05)	0.30(0.09)

$p = .587$). In particular, the autism group displayed increased ITPC in the theta band than the TD group for this early time window, and the word stimuli elicited greater theta ITPC than the pure tones for both groups. No interaction between group and condition ($F(1,54) = 0.43$, $p = .518$) was found for this window.

Analysis for the N2 response revealed a nonsignificant trend of group effect ($F(1,54) = 3.23$, $p = .078$) on the ITPC while controlling for significant NVIQ ($F(1,54) = 4.38$, $p < .05$, $\beta = -0.03$) (Table 4). Similar to the amplitude result in this window, the group effect became significant ($F(1,55) = 6.88$, $p < .05$) after excluding NVIQ from the regression model, indicating reduced N2-associated theta ITPC in the autism group compared to the TDs. No effect of condition ($F(1,54) = 0.21$, $p = .647$) or group $*$ condition interaction ($F(1,54) = 0.52$, $p = .472$) was observed for this measure. The baseline ITPC before the stimulus onset did not differ between conditions ($F(1,54) = 0.39$, $p = .537$) or groups ($F(1,54) = 0.33$, $p = .568$), nor show any group $*$ condition interaction ($F(1,54) = 0.23$, $p = .637$).

Theta power for the pre-stimulus baseline and the response was examined using similar LME regression (Tables 3 and 4). The results did not show any significant condition effect (baseline, $F(1,54) = 0.01$, $p = .933$; response, $F(1,54) = 0.21$, $p = .648$), group effect (baseline, $F(1,54) = 0.72$, $p = .399$; response, $F(1,54) = 0.01$, $p = .924$), or group $*$ condition interaction (baseline, $F(1,54) = 0.05$, $p = 826$; response, $F(1,54) = 0.10$, $p = .759$).

Table 3
Mean and standard deviation (SD) of theta spectral power (dB) of the pre-stimulus baseline and the response portion of the epochs on a trial-by-trial basis.

	Pure tone		Word	
	Baseline	Response	Baseline	Response
Autism	23.08(1.23)	11.08(1.18)	23.15(1.12)	11.29(1.01)
TD	23.30(0.81)	11.33(0.77)	23.26(0.64)	11.37(0.98)

3.3. Relationships between AEP and ITPC

The LME regression revealed that theta ITPC in the autism group was a significant predictor of P1 amplitude ($F(1,25) = 4.39$, $p < .05$)

Table 4
Summary of F-statistics of main effects and interaction on the AEP, theta ITPC and power measures, controlling for NVIQ.

	Amp		Lat		ITPC			Spectral power	
	P1	N2	P1	N2	Baseline	P1	N2	Baseline	Response
Group	5.19*	2.88†	6.93*	1.17	0.33	11.00**	3.23†	0.72	0.02
Condition	16.13**	0.52	0.24	0.00	0.39	5.69*	0.21	0.02	0.21
Group*condition	0.46	0.12	0.69	1.43	0.23	0.43	0.52	0.05	0.10

** $p < .01$.
* $p < .05$.
† $p < .1$.

Table 5
F-statistics and regression coefficients (β) indicating the relationships between AEP amplitude and theta ITPC in the autism group and the TD group.

Group	P1 amp		N2 amp	
	F	β	F	β
Autism	4.39*	7.78	6.28*	−13.81
TD	5.04*	10.47	8.43**	−16.71

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

and N2 amplitude ($F(1,25) = 6.28$, $p < .05$) across stimulus conditions regardless of NVIQ (Table 5). The regression coefficients (β) indicated positive relationships between these two types of measures, indicating stronger theta phase-locking within corresponding windows predicted larger P1-N2 response amplitude. The results were similar in the TD group that greater theta ITPC predicted larger amplitude of both P1 ($F(1,26) = 5.04$, $p < .05$) and N2 ($F(1,26) = 8.43$, $p < .01$) across stimulus conditions.

4. Discussion

4.1. AEP findings

The waveform analysis of AEPs confirmed our first hypothesis regarding abnormality in the P1-N2 components. Our first observation is the prolonged P1 latency in the autism group compared with the TD group. The amount of delay we found here is consistent with reports by other researchers examining auditory M50 and M100 to pure tones, which was approximately 10% when compared with TD children (Gage et al., 2003; Gandal et al., 2010; Roberts et al., 2010; Edgar et al., 2014, 2015b). The delayed P1 response likely indicates lower neural transmission speed along the ascending auditory pathway (Eggermont et al., 1997). Previous work has demonstrated that TD children's early auditory response (M100) shortens with increasing age, and this trend corresponds with the developmental changes in thalamocortical white matter integrity (Roberts et al., 2009). However, age-related latency shortening in individuals with autism appears to be uncoupled with thalamocortical white matter properties (Roberts et al., 2013). This uncoupling might indicate other mechanisms such as synaptic transmission and maturation as contributing factors to the latency lag in children with autism (Eggermont et al., 1997; Roberts et al., 2013). Interestingly, the P1 latency delay was observed across domains but the effect for words was not as prominent as in the pure tone condition (Table 1), which seemingly contradicts the fact that autism is often characterized with pronounced language impairment. We speculate that this result might be attributable to the robustness of stimulus onset. Unlike the pure tone, which rises sharply from silence to peak amplitude with a fixed slope at the same sound frequency, the onset of the CV syllable is not as uniformly defined as the consonant portion contains multiple spectral components and a much longer interval for the nonlinear consonant-to-vowel transition. As P1 marks the neural transmission time for sound onset detection rather than registration of fine-grain content aspect of sounds (Eggermont et al., 1997; Čeponienė et al., 2005), stimuli with more clearly defined onset acoustic features such as pure tones are expected to be more sensitive to show the between-group P1 latency differences than complex sounds that do not have the same robust onset.

The fact that words elicited larger P1 than pure tones in both groups of children indicates stronger neural activity evoked by the acoustically rich broadband signal. Interestingly, there was also a group effect that the autism group had overall increased P1 amplitude than the TD group. This finding appears to be inconsistent with previous work showing attenuated P1 to speech in school-age children with autism (Čeponienė et al., 2003; Lepistö et al., 2005; Whitehouse et al., 2008). The inconsistency might arise from coding onset differences in the physical properties of speech stimuli. Our study used a naturally recorded CV syllable starting with a less well-defined acoustic transient, whereas the previous studies used computer-synthesized steady-state vowels. P1 amplitude in adults has been found to be modulated by duration of consonant-vowel transition (CVT) (Čeponienė et al., 2008). The larger P1 to words in autism in our study might suggest a hypersensitive reaction to the acoustic transient of sound onset compared to the age-matched TD children. As syllable-evoked P1 amplitude typically decreases from childhood to adolescence (Sharma et al., 1997; Cunningham et al., 2000), enlarged P1 might also reflect delayed maturation of the auditory system in processing acoustically complex sounds. Additionally, the overall larger P1 amplitude may suggest deficits in auditory habituation to the large amount of sound repetition, as P1 amplitude reduction to repetitive stimulus can index sensory gating and habituation (Grunwald et al., 2003), which has been found impaired in adults (Buchwald et al., 1992) and children with autism (Orekhova et al., 2008).

The N2 component in the autism group was attenuated across speech and nonspeech stimulus conditions. The lack of any speech-specific difference for N2 measures seems to suggest rather domain-general atypicality in this processing stage. According to the theory by Karhu et al. (1997), children's N2 might reflect auditory "sensitization" in building up neural representations of sound features. Thus, the attenuated N2 in the autism group may reflect some basic abnormalities in auditory learning of repeating sound pattern. However, in the context of speech sounds, N2 reflects complex processes involving not only acoustic processes but also phonetic analysis of fine-grain content aspect of sounds (Fujioka et al., 2006; Čeponienė et al., 2008, 2009). In this perspective, the autism group' reduced N2 amplitude to words might indicate some phonological deficits beyond just auditory learning.

4.2. Trial-to-trial synchrony of theta oscillations

One primary finding of the current study is the increased ITPC in autism within the P1 window but reduced ITPC in the N2 window, compared with the TD children. The N2-associated ITPC clearly indicates increased neural "jittering" or variable neural response in the children with autism, whereas the increased P1-associated ITPC is counterintuitive and inconsistent with the idea that overall reduced neural synchrony may underlie the sensory and cognitive abilities in individuals with autism. For instance, individuals with autism were found to display reduced alpha ITPC during visual processing of Gabor patches (Milne, 2011), and reduced beta ITPC during picture naming (Buard et al., 2013), as well as reduced theta ITPC in feedback processing of rewards and errors (van Noordt et al., 2017). In auditory processing, reduced gamma ITPC to tones has been frequently reported in children with autism (Edgar et al., 2015a, 2015b). However, when taking into account processing stage, the literature suggests a trend that lower frequency bands below gamma generally show reduced synchrony beyond 200 ms post-stimulus but not in earlier windows (~100 ms) (Milne, 2011; Buard et al., 2013; Edgar et al., 2015a; van Noordt et al., 2017), whereas gamma bands often show reduced synchrony from early windows (Gandal et al., 2010; Edgar et al., 2015b).

Our results are the first to demonstrate increased theta ITPC during early stage of auditory processing in children with autism. More work is needed to clarify the role of neural synchrony in the different frequency bands during various tasks and stages of information processing in autism. There are some notable methodological differences across studies. While previous auditory ITPC studies on autism presented stimuli with jittered ISI, the current

study used the fixed ISI protocol as the majority of child AEP studies did. As timing regularity of auditory input influences the onset-driven phase alignment of ongoing EEG (Barry, 2003), it is possible that choice of ISI settings (i.e., jittered vs. fixed) can critically affect the inter-trial phase-locking. Unpublished EEG data in our lab using randomized ISIs in the range of 800–1200 ms did show reduced low-frequency ITPC within the P1 window in school-age children with autism, suggesting that neural phase-locking across trials in autism is subject to the modulation of stimulus timing predictability. Nevertheless, the current results of increased ITPC within the early P1 window is compatible with the sensory hyperactivity account (Mottron et al., 2013). It is proposed that synchronous cortical responses rely on thalamic regulation and thalamocortical connectivity (Winer et al., 2005; Malekmohammadi et al., 2015). The current ITPC result for the P1 response might reflect enhanced feedforward thalamocortical connectivity ascending to the primary auditory cortex. In the domain of somatosensory processing, recent work has provided indirect evidence of enhanced feedforward thalamocortical connectivity with primary sensory cortex (S1) in individuals with autism, which is linked with their enhanced response and phase-locking to the onset of somatosensory input (Khan et al., 2016).

In our study, the two subject groups differed in theta ITPC and showed opposite patterns depending on the time course of the AEP component (i.e., enhanced P1 vs. attenuated N2 in autism group). Similar results have been observed in somatosensory processing (Khan et al., 2016). In that study, individuals with autism displayed increased transient phase-locking in S1 to the onset of tactile stimulation, but decreased activities during the later steady-state portion of the response. These findings underscore the possibility that sensory hypersensitivity might negatively impact subsequent communications between sensory and higher-order brain regions (Isler et al., 2010).

4.3. Relationships between ITPC and AEPs

Consistent with our second hypothesis, theta ITPC value was a significant predictor of AEP amplitude for both P1 and N2 in both subject groups. These patterns are consistent with findings from normal adults (Koerner and Zhang, 2015). One additional piece of information is that the P1 hyper-sensitivity in the children with autism was associated with their heightened theta synchrony while their hypo-sensitivity in the N2 was associated with the reduced theta synchrony. The latter is in line with the notion that reduced inter-response synchrony in EEG oscillation may lead to overall reduced power in autism (Simon et al., 2016).

An implicated question is why there is hyper-sensitive (relative to TDs) theta oscillations for onset detection but hypo-sensitive for subsequent sound content analysis in the children with autism. In normal adults, stronger theta phase-locking tends to attenuate neural excitability during speech onset (segment-level) encoding and increase excitability during the encoding of steady-state portion of the signal, an operation fundamental for syllable-level speech parsing and encoding (Giraud et al., 2012). In the current data, it appears that the neural synchrony across trials is not universally decreased in children with autism relative to TD, but rather weighted depending on the time course of the AEP components associated with low-level vs. higher-level and segmental vs. syllabic processing. This conjecture is supported by the ITPC patterns for words in the two subject groups. Judging from the data in Table 2, word-evoked theta synchrony increased from the P1 window to the N2 window in the TD group but not in the autism group. The dynamic phase control is instrumental for efficient signal processing by the brain (Schroeder et al., 2009). Broadly speaking, individuals with autism may not have the highly organized neural rhythm to entrain to specific sensory input, which also means some sensory details or ambient signal might be unselectively amplified by the neural system.

4.4. Implications and limitations

The coexistence of hyper- and hypo-sensitive responses depending on the stage of information processing highlights the complexity of abnormal sensory perception in autism. Moreover, the fact that these hyper- and hypo-sensitivities in AEPs are associated with neural phase synchrony enhancement or attenuation in the trial-by-trial theta oscillatory activities points to a more nuanced view of disrupted underlying neural mechanisms for atypical auditory information processing in autism. The exact implication of this disruption remains to be further explored in future work. It is possible that when the timing of stimulus presentation is regular and highly predictable, children with autism are less susceptible to neural adaptation to the detection of sound onset as reflected in the P1, but their later N2 responses to processing higher-level content aspect of the auditory stimuli were not as robust as the age-matched controls. In particular, individuals with autism are subject to abnormal thalamocortical function in regulating sensory filtering (Hegarty et al., 2018). This may explain some of the sensory adaptation problems with individuals with autism. In this regard, neuromodulatory (e.g., transcranial magnetic stimulation) and neurofeedback treatment targeting oscillatory dynamics such as improving the hierarchical organization of oscillation activities might be a promising avenue for improving sensory-related behavioral issues in children with autism (Simon et al., 2016).

Several limitations of our work need to be acknowledged. First, the relatively small sample size and the inclusion of mostly male participants limit the generalizability of findings. Replications are needed with larger groups of children with more balanced sex/gender ratio and children with different language backgrounds. Second, results from the addition of a complex nonspeech stimulus condition could help tease apart the influences of stimulus complexity, social relevance, and semantic significance on cortical oscillations. Third, the current study does not provide longitudinal data to verify the maturational delay interpretation. The developmental changes in children with autism may not follow the same steps as in typical development (Mottron, 2017). Moreover, further studies are needed to examine the potential impact of these sensory atypicalities on speech and language development in children with autism.

5. Conclusions

The current study provides confirmatory AEP and novel ITPC evidence of sensory abnormalities in school-age children with autism using simple pure tones and complex speech stimuli. School-age children with autism displayed increased theta ITPC for sound onset detection in the P1 window and attenuated theta ITPC in the subsequent N2 window. The theta ITPCs in the corresponding windows were significant predictors of P1 and N2 amplitudes, indicating disrupted oscillation synchrony as a neural generator of abnormal AEPs in children with autism. These data indicate that neural synchrony in individuals with autism might be suboptimally organized depending on the stage of information processing that support low-level sensory vs. higher-level perceptual coding.

Conflict of interest statement

None of the authors have potential conflict of interest to be disclosed.

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