NeuroImage 198 (2019) 83–92

Contents lists available at ScienceDirect

NeuroImage

journal homepage: www.elsevier.com/locate/neuroimage

Change detection to tone pairs during the first year of life – Predictive longitudinal relationships for EEG-based source and time-frequency measures

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A R T I C L E I N F O

Keywords:
Auditory processing
Development
ERPs
Infants
Phase-locking
Spectral power

A B S T R A C T

Brain responses related to auditory processing show large changes throughout infancy and childhood with some evidence that the two hemispheres might mature at different rates. Differing rates of hemispheric maturation could be linked to the proposed functional specialization of the hemispheres in which the left auditory cortex engages in analysis of precise timing information whereas the right auditory cortex focuses on analysis of sound frequency. Here the auditory change detection process for rapidly presented tone-pairs was examined in a longitudinal sample of infants at the age of 6 and 12 months using EEG. The ERP response related to change detection of a frequency contrast, its estimated source strength in the auditory areas, as well as time-frequency indices showed developmental effects. ERP amplitudes, source strength, spectral power and inter-trial phase locking decreased across age. A differential lateralization pattern emerged between 6 and 12 months as shown by inter-trial phase locking at 2–3 Hz; specifically, a larger developmental change was observed in the right as compared to the left hemisphere. Predictive relationships for the change in source strength from 6 months to 12 months were found. Six-month predictors were source strength and phase locking values at low frequencies. The results show that the infant change detection response in rapidly presented tone pairs is mainly determined by low frequency power and phase-locking with a larger phase-locking response at 6 months predicting greater change at 12 months. The ability of the auditory system to respond systematically across stimuli is suggested as a marker of maturational change that leads to more automatic and fine-tuned cortical responses.

1. Introduction

The first year of life involves large changes in brain microstructure and function (e.g., Dubois et al., 2014). One system in particular that exhibits a long period of functional maturation is the auditory system. It continues to mature well into the teenage years and, further, is constantly shaped by the acoustic environment (e.g., Ponton et al., 2000; Tervaniemi et al., 2006). Here we set out to examine maturational changes in auditory event-related potentials (ERPs), their source activity, and time-frequency decomposition during the first year of life while infants processed rapid changes in non-speech stimuli. Our main interest was in determining the major frequency bands that support the ERP response to auditory change and to examine hemispheric lateralization patterns across age. Further, we aimed to determine whether these measures of auditory change detection could be used to predict the degree of maturational change.

Auditory ERPs have a well-known developmental trajectory in childhood where the broad P1 and N2 responses shift, occurring earlier in latency and smaller in amplitude with age, finally becoming separated by the N1 and P2 responses around the age of 9 years (Albrecht et al., 2000; Ponton et al., 2000; Shahin et al., 2010; Wunderlich et al., 2006). However, during the first year of life the auditory ERPs become larger from birth for repeated sounds (Kushnerenko et al., 2002b; Lippé et al., 2009) and larger or smaller for change detection responses depending on the polarity of the ERP response (Choudhury and Benasich, 2011; Kushnerenko et al., 2002a; Ortiz-Mantilla et al., 2016). For example, one previous study using the same stimuli as the present study demonstrated that the amplitude and latency of the major ERP response to pitch change

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https://doi.org/10.1016/j.neuroimage.2019.05.034
Received 8 March 2019; Received in revised form 25 April 2019; Accepted 13 May 2019

with positive voltages over fronto-central scalp areas (termed the "mismatch response") decreased with age (Choudhury and Benasich, 2011).

In addition to changes in the ERP responses there are also developmental changes in the frequency composition of the EEG. Brain activity is predominantly stronger in the lower end of the frequency range (delta and theta bands) in early development compared to adults (Cragg et al., 2011; Gasser et al., 1988; Gómez et al., 2017; Lippé et al., 2009; Marshall et al., 2002; Tolonen et al., 2007, for reviews, see Segalowitz et al., 2010; Yordanova and Kolev, 2009). The age-related decrease in the low frequency power range is more widespread, while the changes in power in the alpha and beta ranges have more focal topography concentrated in frontal areas (Gómez et al., 2017). These changes in EEG power have been attributed to neuronal and synaptic maturation and density as well as increases in myelination (Gómez et al., 2017; Whitford et al., 2007).

Changes in the ERP amplitudes and EEG power bands with age should also be reflected in the time-frequency decomposition of the stimulus-related responses. Indeed, developmental shifts in the power within different frequency bands has been observed in response to auditory stimuli (e.g., Lippé et al., 2009; Ortiz-Mantilla et al., 2016; Segalowitz et al., 2010). Most studies examining these changes have been carried out with school-age children, thus there are few studies examining time-frequency indices during the first year of life (e.g., Bosseler et al., 2013; Lippé et al., 2009; Musacchia et al., 2013, 2017; Ortiz-Mantilla et al., 2013, 2016).

At school age, developmental changes have been quantified as increases in inter-trial phase locking from 7 years to adulthood in response to changes in tones and speech (Bishop et al., 2011), and as increases in inter-trial phase locking and spectral power from 4 years to adulthood in response to tones and musical sounds (Shahin et al., 2010). This occurs in parallel to the amplitude changes in ERPs. In young children, between the ages of 1 and 66 months, spectral power seems to increase with age, at least in higher frequency ranges, but a decrease is seen in the delta range in response to broadband noise stimuli (Lippé et al., 2009).

Based on a previous study that used speech sounds as stimuli in a subset of participants of the present study, we expected the power and phase locking in the lower frequency bands (delta and theta) to decrease and to show a narrowing time window for phase locking with age (Ortiz-Mantilla et al., 2016). This decrease in response strength was also expected to occur in the ERP amplitudes which, in infancy, produce long lasting, slow responses; these are most likely to occur in the delta and theta frequency ranges. Decreases in ERP amplitude and in power and phase locking for the positive-going change detection response may reflect a more automatic and efficient processing of auditory information or perhaps a general maturational process in infants (Choudhury and Benasich, 2011). Further, a general trend in EEG power spectra seems to include a decline in low frequency oscillatory activity and an increase in higher frequencies over development (e.g., Koroleva et al., 2002; Marshall et al., 2002; Orekhova et al., 2006; Ortiz-Mantilla et al., 2016; Segalowitz et al., 2010) suggesting these findings could be related to ongoing maturation of the nervous system. Although the neural mechanism driving the decrease in response amplitude across the first year of life still requires further investigation it could be related to changes in synaptic density and to a reduced number of neurons responding to the stimuli (Gómez et al., 2017; Whitford et al., 2007).

Differing maturational time frames for the left and right auditory cortices has been suggested for auditory ERPs generated on the lateral surface of the temporal lobe, the T-complex, with faster maturation occurring in the left as compared to the right hemisphere from 3 years to adulthood for both tone and speech stimuli (Pang and Taylor, 2000). However, a recent study using magnetoencephalography showed that the right hemisphere as compared to left shows a more mature pattern of response around 100 ms in response to sinusoidal tones in 7–8 -year-old children (Parviainen et al., 2019). The maturational pattern extracted might therefore depend on the stimulation and partly on the sensory component examined (T-complex vs. N1m; Pang and Taylor, 2000; Parviainen et al., 2019). Hemispheric specialization specific to the type of stimulus has also been suggested for the auditory cortex, with the left auditory areas capable of more precise analysis of time sensitive information while the right auditory areas appear better suited for more precise sound frequency analysis (Poeppel, 2003; Zatorre et al., 2002; Tervaniemi and Hugdahl, 2003). The ability to process tone pair stimuli with short intervals have also been shown to predict later language skills, further suggesting enhancement of left hemispheric processing (Benasich et al., 2006; Cantiani et al., 2016, 2019; Choudhury and Benasich, 2011). Thus left hemisphere involvement would be expected when auditory stimuli have rapid successive temporal changes. Overall hemispheric differences in brain responses to tones and speech stimuli have been reported at the ages of 4, 6 and 12 months-of-age (e.g. Musacchia et al., 2013; Ortiz-Mantilla et al., 2016, 2019). However, previous studies did not find significant interactions of hemisphere and age (6 months vs 12 months) for speech sounds in either ERP source strength or spectral power (Ortiz-Mantilla et al., 2016) or for tone stimuli at 4 months and 7 months (Musacchia et al., 2017). Thus this hypothesis remains to be examined for tone stimuli processing in 12 month-old infants.

Given that there are large changes in brain responses to auditory stimuli in infancy, an important question is what the predictors of these changes may be. Examining how spectral power and phase locking at 6 months can predict developmental change in response strength could give an indication of the mechanism underlying this change. Event-related changes in spectral power have often been interpreted as related to the number of neurons and synapses that are activating synchronously, and specific frequency bands have been linked to excitation and inhibition of cortical areas with differing functions (e.g., Buzsáki et al., 2012; Bonnefond et al., 2017). On the other hand, phase locking across stimulus presentations reflects the auditory system's ability to systematically respond with the same timing to each stimulus presentation. Based on the shift of spectral power from lower to higher frequencies and changes in the amount of inter-trial phase locking with development, we would expect the lower frequency range to be predictive of the amplitude change with age in both the spectral power and phase locking domains.

Previous research thus suggests that changes in ERP amplitude and source strength as well as in spectral power and phase locking within differing frequency bands are expected during maturation. These changes might occur differently in the left and right hemispheres due to differing maturational trajectories of the structure and function of the temporal lobes (Deoni et al., 2011; Pang and Taylor, 2000; Zatorre et al., 2002). To examine the neural underpinnings of developmental changes in auditory change detection processes during the first year of life, EEG was recorded using an oddball paradigm that presented fast-rate, successive tone pairs (i.e. an interstimulus interval (ISI) of 70 ms) incorporating a frequency change to a longitudinal sample of 6 and 12 month-old infants. Localization of ERP activity of the change detection response was examined in order to study lateralization differences during development. ERP amplitudes and source strength were expected to decrease for the change detection response (e.g., Choudhury and Benasich, 2011; Musacchia et al., 2017). We also expected to see a more mature pattern (more power in the higher frequencies and decrease of power in lower frequencies with age) in left auditory areas compared to right auditory areas based on suggested earlier maturation of the left auditory areas (Pang and Taylor, 2000) and a functional preference for processing rapidly changing information in the left auditory cortex (Zatorre et al., 2002; Tervaniemi and Hugdahl, 2003). Further, we examined the predictors of developmental changes in source strength in this longitudinal sample. Based on the assumption that variation in spectral power and phase locking at 6 months would already capture the maturational state of the auditory system and would therefore be associated with the rate of change in further development, we anticipated that the magnitude of spectral power and phase locking in lower frequencies at 6 months would predict the change in response strength from 6 to 12 months-of-age. Analyses carried out for the gamma frequency range were exploratory in nature, rather than based on specific hypotheses, given the limited literature on the change detection response for tones at this range and at this age.

2. Materials and methods

2.1. Participants

A longitudinal sample of infants was tested at 6 months and again at 12 months-of-age. The number of participants at 6 months was 39 (20 boys; 19 girls) full-term (mean gestational age: 40.1 weeks, SD: 1.1), normal birth weight (mean: 3563.2 g, SD: 376.9) infants. Originally 55 children were tested for ERPs but 16 were excluded due to high noise levels or neurological problems. We retained all infants that participated at 6-months in our previous study (Hämäläinen et al., 2011), with the exception of one child that was excluded due to a later diagnosis of autism, then adding one additional infant to the sample.

The number of participants at 12 months was 24 (14 boys; 10 girls) full-term (40.1 weeks, SD: 1.1) and normal birth weight (3490.3 g, SD: 388.3) infants. Longitudinal data was available from 21 of these infants.

To confirm that the infants were developing within typical range, The Mullen Scales of Early Learning (Mullen, 1995) was administered at 6 and 12 months. The Mullen Scales consists of five scales: gross motor, visual reception, fine motor, receptive language and expressive language that can be combined to generate an overall composite score that is standardized to a mean of 100 and SD of 15. The composite score was within the normal range for all infants at 6 months, mean: 98.6, SD: 12.2, min: 75, max: 133; and at 12 months, mean: 101.5, SD: 15.2, min: 70, max: 130. Although no audiometry was performed, all parents confirmed that their infants had passed the neonatal hearing screen, and had no history of otitis media, or parental observations of hearing problems.

The study was carried out in accordance with the Declaration of Helsinki. Informed consent approved by the Rutgers Human Subjects Board was obtained from all parents prior to their child's inclusion in the study. Parents received compensation for their time.

2.2. EEG

2.2.1. Stimuli

The stimuli were tone pairs 70 ms in duration with 5 ms rise and fall times. Sounds were presented at approximately 75 dB SPL. The stimulation was presented free-field from two loudspeakers located at the left and right sides of the infant.

Standard tone pairs consisted of two identical tones with a fundamental frequency of 100 Hz (15 harmonics, 6 dB roll-off per octave) and the deviant tone pairs consisted of two tones with differing pitch; the first tone having a fundamental frequency of 100 Hz, the second tone 300 Hz. There were 125 (15%) deviant tone pairs and 708 (85%) standard tone pairs presented in the EEG experiment and 3–12 standard stimuli were interposed between each deviant stimulus. The tones were presented successively at a fast-rate with an ISI between the tones in the pair of 70 ms and the offset-to-onset ITI (the interval between tone pairs) of 705 ms (for further details, see Benasich et al., 2006).

2.2.2. Procedure

EEG was recorded at 6 and 12 months-of-age while infants were awake, sitting quietly on their parents' laps, and entertained to minimize movement (for more procedural details, see Musacchia et al., 2015). The entertainment included watching a silent, age-appropriate movie and presentation of quiet toys such as bubbles, puppets and infant books.

EEG was recorded using a 62-channel EGI sensor nets (Electrical Geodesics, Inc.) with vertex as the reference electrode. The sampling rate was 250 Hz with 0.1 Hz high-pass and 100 Hz low-pass online filters.

The EEG was re-referenced off-line to an average reference and bandpass filtered at 0.5–25 Hz for event-related potentials and source analyses (this filter was only used for ERP and source analyses, see below for time-frequency analyses). The data was segmented with 300 ms pre-stimulus time and 915 ms post-stimulus time with 50 ms pre-stimulus baseline for deviant and pre-deviant standard stimuli. Eye movements were corrected using the BESA software's automatic correction algorithm (PCA method). Artifact rejection limit for the epochs was between 200 and 290 μV from the baseline, which retained a minimum of 70% of the trials.

2.3. Magnetic resonance imaging

MRIs were obtained for a subset of infants at 6–7 months and at 12–13 months of age using a non-sedated, naturally sleeping paradigm (for further details, see Raschle et al., 2012). T1 weighted 3D SPGR images were collected on a GE 1.5 T Echospeed MRI scanner using a standard head coil and with the following parameters: Field of view = 25 cm, TR/TE = 24/10 ms, flip angle = 30°, matrix size = 256 × 192, slice thickness = 1.5 mm, number of slices = 124, sagittal orientation, bandwidth = 15.63 kHz.

The individual MRIs were processed using BrainVoyager QX program. The images were aligned into the anterior commissure - posterior commissure (AC-PC) plane and normalized into the Talairach space. The head surface was reconstructed from the MRIs to project the ERP voltage maps into realistic head shapes.

To create age-appropriate MRI templates, 19 MRIs at 6-months and 9 MRIs at 12-months were affine transformed into the MRI space of an infant representing the group median age. This was performed for both age groups and the MRIs were combined into an age-group average (one for 6-month-olds and another for 12-month-olds) and further transformed into Talairach space.

2.4. Source analyses

For source analysis, we followed the protocol used for 6-month-old infants in Hämäläinen et al. (2011). Parameters for skull and scalp thickness, and for cerebrospinal fluid (CSF) width were estimated at each age (6-months: average scalp thickness: 2.5 mm, skull: 1.5 mm, average CSF width: 1.7 mm; 12-months: average scalp thickness: 2.5 mm, skull: 2.0 mm, average CSF width: 1.5 mm) and used for source localization.

The skull bone conductivity was estimated by fitting an exponential function on the data available from 3 to 9 years in the BESA 5.3 (Brain Electrical Source Analysis) software. The equation for the exponential function was 0.064*e−0.195*age in years giving an estimate of 0.0581 at 6 months and 0.0527 at 12 months. This estimate is close to that provided by the SCALE algorithm (Acar et al., 2016).

The ERP data was combined with individual MRI images (6-months, N = 21; 12-months, N = 9) or with an age-appropriate average MRI when an individual MRI was not available, using BESA Research 5.3 and BrainVoyager QX programs. The standard electrode positions were fitted onto the corresponding MRI.

Peaks were identified from the individual ERPs (based on the global field power (GFP)) across EEG electrodes, or alternatively were based on the time course of the spatial principal component factor scores provided in BESA in cases where the peak was not clearly identifiable from the GFP, and the time window of ± 20 ms around the peak was used to fit a 2-dipole model (Scherg and Von Cramon, 1985). The average residual variance of the model at 6 months was 11.13% (SD: 5.49), and at 12 months 14.55 (SD: 6.60) %. A distributed source model was calculated using the Classic LORETA Recursively Applied (CLARA; Hoechstetter et al., 2010) method at the same time window of±20 ms around the peak to confirm the results of the dipole fitting.

2.5. Time-frequency analyses

In order to examine hemispheric effects, the time-frequency analyses were carried out in source space using BESA 6.1. In the first step, the individual source solutions were applied to the raw EEG filtered at 0.5 Hz

(1 Hz was used for one 6-month-old infant to remove excess noise from the data) to transform the data into source space (Hoechstetter et al., 2004). The artifact rejection limit was between 200 and 290 μV retaining at least 70% of the trials (6-months: 94 trials for the standard stimulus, range: 88–117, and 95 trials the deviant stimulus, range: 88–111; 12-months: 92 trials the standard stimulus, range: 85–102, and 93 trials for the deviant stimulus, range: 83–109). A complex demodulation method with 1 Hz wide frequency bins and 50 ms time resolution, from −300 to 915 ms (with zero-padding of 2000 ms) in the range of 2–90 Hz was used for decomposing the single-trial EEG data into time-frequency representations (Scherg et al., 2010). To examine event-related changes in amplitude of different frequency bands relative to the baseline (Tallon-Baudry et al., 1996; Hari and Salmelin, 1997; Tallon-Baudry and Bertrand, 1999) we used temporal spectral evolution (TSE). Phase alignment between the trials was examined using inter-trial phase-locking (ITPL) values (Tallon-Baudry et al., 1996; Tallon-Baudry and Bertrand, 1999). ITPL values of 0 indicate random phase across trials and 1 perfect inter-trial phase alignment. TSE and ITPL indices were obtained at the left and right auditory cortices for the standard and deviant stimuli. Grand average time-frequency plots were generated in MATLAB.

2.6. Statistical analyses

The analyses were carried out in two stages. First, to examine differences between the responses to the standard and deviant stimuli at each age the full sample was used (at 6 months $N = 39$, at 12 months $N = 24$). Second, to examine maturational effects the longitudinal sub-set of the sample was used ($N = 21$). BESA Statistics 2.0 software was used for examining differences between the deviant and standard stimulus and between the 6- and 12-month-olds for the ERP data and time-frequency data. Source waveform data based on peak analysis was examined using ANOVAs. BESA Statistics uses permutation statistics with clustering to correct for multiple comparisons due to the large number of time points and channels (Maris and Oostenveld, 2007). The initial statistic used for the subsequent permutations is based on t-tests. For the ERP analyses all time points between 0 and 900 ms were included. For the time-frequency analyses, pre-defined frequency bands were examined separately in the time window between 0 and 900 ms (in 50 ms steps) with 3000 permutations. The frequency bands examined were delta (2–3 Hz), theta (4–7 Hz), alpha (8–12 Hz), beta (13–29 Hz), low gamma (30–69 Hz), and high gamma (70–90 Hz).

At source level, hemispheric effects were examined separately using Hemisphere (left, right) x Age (6 months, 12 months) repeated measures ANOVAs for the source peak amplitude and latency; Hemisphere (left, right) x Frequency (delta, theta, alpha, beta) x Age (6 months, 12 months) repeated measures ANOVAs were performed for the spectral power and phase locking values. The average of the values in the clusters obtained from the permutation statistics were used as input in the ANOVAs; only main effects and interactions related to the factor Hemisphere were examined. When indicated, additional post hoc t-tests were used to assess possible interaction effects between the hemispheres.

Predictive relationships between the measures were examined first by Pearson correlation coefficients between the neural indices at 6 months and the amount of change (source strength at 12 months subtracted from the source strength at 6 months) and then by using linear regression analysis to examine the unique amount of variance explained by the predictors. Alpha-level for all statistical analyses was 0.05.

3. Results

3.1. ERPs

The overall morphology of the ERPs (see Fig. 1) was similar between the 6- and 12-month-olds, and aligns to results reported earlier using the same stimuli but in an independent sample (Benasich et al., 2006; Choudhury and Benasich, 2011). At both ages the infants showed clear differentiation of the responses to the deviant and standard stimuli as evidenced by the permutation statistics (Fig. 2). At 6 months, the cluster with the largest differences was located in the fronto-central channels at 208–900 ms; larger positive responses for the deviant than the standard stimuli were identified (cluster $p < 0.0001$). As the change detection response was inverted in polarity at posterior areas, the parieto-occipital channels at 216–548 ms showed similarly larger negative-going responses for the deviant than the standard stimuli (cluster $p < 0.0011$). At 12 months, the cluster with the largest differences was again located fronto-centrally at 316–672 ms and showed larger positive responses for the deviant than the standard stimuli (cluster $p < 0.029$). In the parieto-occipital channels, similarly larger negative-going responses for the deviant compared to the standard stimuli were evident at 332–560 ms (cluster $p < 0.037$). See Table 1 for a summary of the ERP results and cluster descriptions.

When the ERP responses to the deviant stimuli were directly compared between 6- and 12-month-olds, using the longitudinal sample ($N = 21$), the largest maturational differences were present in the parietal channels at 180–468 ms with larger negative responses seen at 6 months than at 12 months (cluster $p < 0.0054$). In a second cluster, larger positive responses occurred at 6 than at 12 months (cluster $p < 0.018$) with the largest difference evident at 492–852 ms, first in the occipital channels through 620 ms and then continuing in the fronto-central channels (Fig. 2). No significant differences between the ERP amplitudes across age were observed in response to the standard stimulus.

3.2. Source analysis

Source analyses for these 6 month-olds were reported in Hämäläinen et al. (2011). However, in the present study, we did not include the third mid-frontal source in the model because it explained only a small amount of variance for the 6-month grand average and could not be accurately localized at the individual level. Further, no mid-frontal activation was identified at 12 months. The source analysis showed major activation in the left and right auditory areas as shown in Fig. 3.

The localized ERP activity was examined between hemispheres and

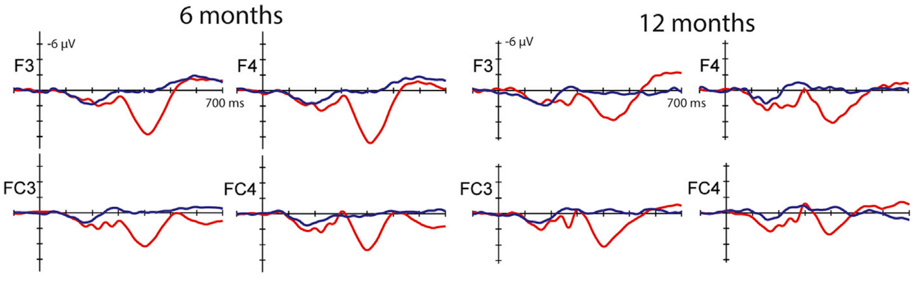

Fig. 1. Event-related potentials to tone pairs in 6 (left, $N = 39$) and 12 (right, $N = 24$) month-old infants. Response to the standard tone pair is in blue, and to the deviant tone pair in red. One vertical tick mark is 2 μV, one horizontal tick mark in 100 ms. Negativity is plotted up. F3: frontal left, F4: frontal right, FC3: frontocentral left, FC4: frontocentral right.

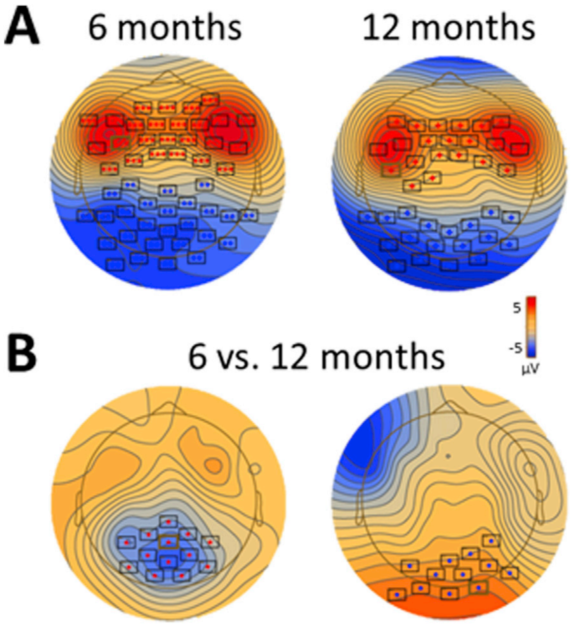

Fig. 2. Topographic difference maps between the responses to the deviant as compared to (A) the standard stimuli at 6 months (left, 400 ms) and 12 months (right, 412 ms), and (B) the difference maps of the response to the deviant stimulus between 6 and 12 months at the maximal points for the difference (cluster 1, left, 344 ms; cluster 2, right, 536 ms). Channels forming a cluster (red stars, cluster 1; blue stars, cluster 2) based on the permutation statistics are marked with rectangles. Red indicates positive voltages, blue indicates negative voltages.

Table 1

Summary of the channel level cluster-based permutation statistics.

Contrast, cluster	Time	Cluster p-value	Direction
S vs. D at 6 m, cluster 1	208–900 ms	<0.0001	D > S
S vs. D at 6 m, cluster 2	216–548 ms	0.001	D > S
S vs. D at 12 m, cluster 1	316–672 ms	0.027	D > S
S vs. D at 12 m, cluster 2	332–560 ms	0.034	D > S
6 vs. 12 m for D, cluster 1	180–468 ms	0.0053	6 m > 12 m
6 vs. 12 m for D, cluster 2	492–852 ms	0.017	6 m > 12 m

Note. S = Standard stimulus, D = Deviant stimulus.

age to determine possible differences in maturation. A Hemisphere x Age ANOVA for the peak source strength in response to the deviant stimulus showed only a main effect of age ($F(1,20) = 8.584$, $p < 0.009$, $\eta_p^2 = 0.300$). Source strength decreased with age (6 months, mean: 92.7 nAm, SD: 25.3; 12 months, mean: 67.6 nAm, SD: 23.8) as shown in Fig. 4. No significant effects were found for source peak latency.

To examine whether the developmental difference in ERP amplitudes at the posterior electrodes was due to a combined source strength and dipole orientation effect, the voltage topographies generated by the dipole models were plotted for both ages. Fig. 5 shows that the dipole orientations (see Fig. 3c) indeed caused the observed topographic difference in the ERPs, as shown in Fig. 2, because the topography for the dipole model of the 6-month data clearly shows that the negative voltages at the posterior scalp areas extend more superiorly than those in the model topography for the 12-month data.

3.3. *Time-frequency analysis*

3.3.1. *Spectral power*

Changes in spectral power were examined separately for the predefined frequency bands as follows: delta (2–3 Hz), theta (4–7 Hz), alpha (8–12 Hz), beta (13–29 Hz), low gamma (30–69 Hz), and high gamma (70–90 Hz).

At 6 months, the responses to the deviant compared to the standard stimulus elicited more power mostly in the lower frequency bands up to 20 Hz in a wider time window for the lower frequencies and in a narrower time window for the frequencies from 8 Hz upwards (Table 2 and Fig. 6). No differences were observed in the gamma band power at 6-months.

At 12 months, the responses to the deviant stimulus compared to the standard stimulus elicited more power mostly in the lower frequency bands up to 7 Hz (Table 3 and Fig. 6). No differences were observed in the gamma band power.

Longitudinal comparison of the 6- and 12-month-olds (N = 21) showed more power in the lower frequency bands (up to 12 Hz) for the 6- compared to the 12-month-olds for the deviant stimulus responses (Table 4 and Fig. 6). No age differences were observed for the standard stimulus responses.

Laterality effects, examined in an Age (6 m, 12 m) x Frequency (delta, theta, alpha, beta) x Hemisphere (left, right) repeated measures ANOVA did not yield any effects with hemisphere.

3.3.2. *Inter-trial phase locking*

At both ages similar differences in ITPL were found between the responses to the deviant and standard stimuli. At 6 months, ITPL to the deviant stimulus as compared to the standard stimulus were larger primarily in the lower frequency bands up to 25 Hz in a wide time window that became narrower for frequencies from 8 Hz upwards (Table 2 and Fig. 7).

At 12 months, a similar increase in ITPL was observed in the lower frequency bands up to 29 Hz and in a wide time window that became narrower for the frequencies from 8 Hz upwards (Table 3 and Fig. 7).

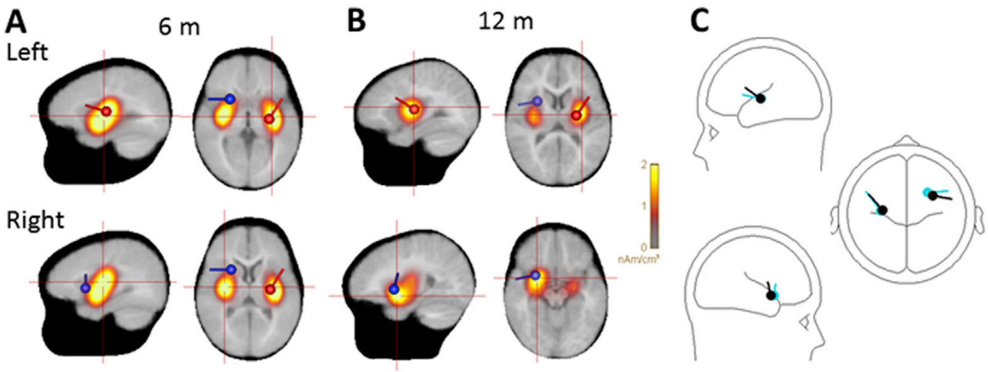

Fig. 3. Dipole and distributed (CLARA) source solutions shown in an age-appropriate average infant MRI template (A) at the time window of ± 20 ms around the peak of the deviant stimulus grand average ERP response at 6 months (N = 39) and (B) at 12 months (N = 24). On the far right, (C) the dipole source models at 6 months (light blue) and 12 months (black) are shown overlaid in a schematic head.

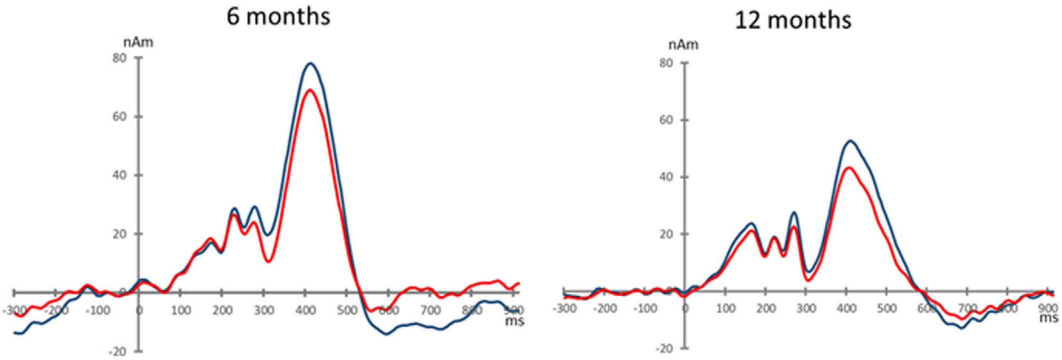

Fig. 4. Grand average source waveforms to the response to the deviant stimulus from left (blue) and right (red) auditory cortices at 6 (N = 39) and 12 (N = 24) months of age. Positivity is plotted up. Strength of the response is given in nanoamperes (nAm) in the y-axis and time in miliseconds (ms) in the x-axis.

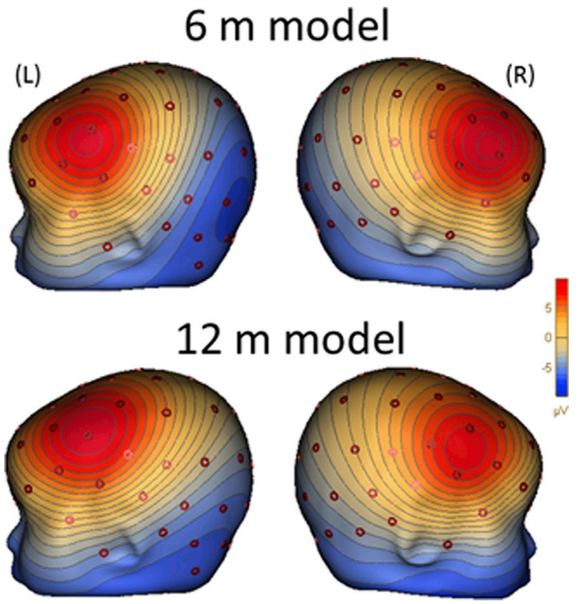

Fig. 5. Voltage map topographies generated by the dipole models at 6 months and 12 months are shown at left and right hemispheres on the 6-month head surface. The same head surface was used for both ages to avoid confounding the dipole orientation effect with differences in head shape.

Table 2
Differences between the deviant and standard stimulus responses at 6 months in spectral power and inter-trial phase locking (ITPL), N = 39.

Frequency	Cluster time	Hemisphere	Cluster p-value	Direction
Power				
Delta (2–3 Hz)	150–900 ms	Left	0.0001	D > S
Delta (2–3 Hz)	150–900 ms	Right	0.0003	D > S
Theta (4–7 Hz)	100–900 ms	Left	0.0007	D > S
Theta (4–7 Hz)	100–850 ms	Right	0.0003	D > S
Alpha (8–12 Hz)	150–400 ms	Right	0.0077	D > S
Beta (13–29 Hz)	0–350 ms	Right	0.038	D > S
ITPL				
Delta (2–3 Hz)	250–900 ms	Left	0.0003	D > S
Delta (2–3 Hz)	300–900 ms	Right	0.0001	D > S
Theta (4–7 Hz)	200–900 ms	Left	0.0003	D > S
Theta (4–7 Hz)	50–900 ms	Right	0.0001	D > S
Alpha (8–12 Hz)	100–500 ms	Left	0.0003	D > S
Alpha (8–12 Hz)	100–500 ms	Right	0.0001	D > S
Beta (13–29 Hz)	0–350 ms	Left	0.0001	D > S
Beta (13–29 Hz)	100–400 ms	Right	0.0003	D > S

Note. D = response to the deviant stimulus, S = response to the standard stimulus.

Longitudinal comparison of the two ages showed stronger phase-locking predominantly in the low frequency bands (up to 12 Hz) for 6-month-olds as compared to 12-month-olds for the deviant stimulus responses (Table 4 and Fig. 7). In addition, at 12 months there was an increased ITPL in high gamma compared to 6 months. For the standard stimulus responses, phase locking was stronger at 6 months than 12 months but only in the right hemisphere at 2–3 Hz at 550–700 ms (cluster $p < 0.021$) (Fig. 7).

Comparing the hemispheres in an Age (6 m, 12 m) x Frequency (delta, theta, alpha, beta) x Hemisphere (left, right) repeated measures ANOVA revealed an Age x Frequency × Hemisphere interaction ($F(3,60) = 3.403$, $p < 0.023$, $\eta_p^2 = 0.145$). The interaction was examined by separate Age x Hemisphere ANOVAs for each frequency band. The Age × Hemisphere interaction was significant only at the delta frequency range ($F(1,20) = 8.568$, $p < 0.008$, $\eta_p^2 = 0.300$); no other hemisphere main effects or interactions were found. Further, a paired samples *t*-test comparing the 6-month minus the 12-month difference score in ITPL between the hemispheres was significant ($t(20) = -2.927$, $p < 0.009$), indicating a larger change in phase locking values in the right compared to the left hemisphere (6 month, left: 0.25, right: 0.27; 12 month, left: 0.20, right: 0.18).

3.4. *Longitudinal correlations*

To study what might be driving the reduction in response strength from 6 to 12 months, correlations between the 6-month measures and the amount of change in source strength between 6 and 12 months were examined. The amount of change was strongly correlated with the initial source strength and moderately correlated with the 6-month delta and theta frequencies phase locking values as shown in Table 5. The larger the source strength or ITPL value at 6 months the larger the change in source strength (i.e., the smaller the response) from 6 months to 12 months.

To take into account the initial source strength at 6 months and the developmental change in source strength, regression analyses were carried out separately for the left and right hemispheres. The amount of change in source strength was examined in a two-step analysis. In step one the independent measure was the initial source strength at 6 months, and in step two the independent measures were spectral power and ITPL in the four frequency bands, which were entered into the model using a stepwise method. For the left hemisphere, only the initial source strength explained significant variance in the amount of change (Standardized Beta = 0.845, $p < 0.001$, $\Delta R^2 = 0.714$, $p < 0.001$). For the right hemisphere both the initial source strength (Standardized Beta = 0.778, $p < 0.001$, $\Delta R^2 = 0.605$, $p < 0.001$) and ITPL values in the delta frequency range (Standardized Beta = 0.763, $p < 0.001$, $\Delta R^2 = 0.102$, $p < 0.023$) explained significant amounts of variance. The larger the phase locking values at 6 months the larger the change in source strength

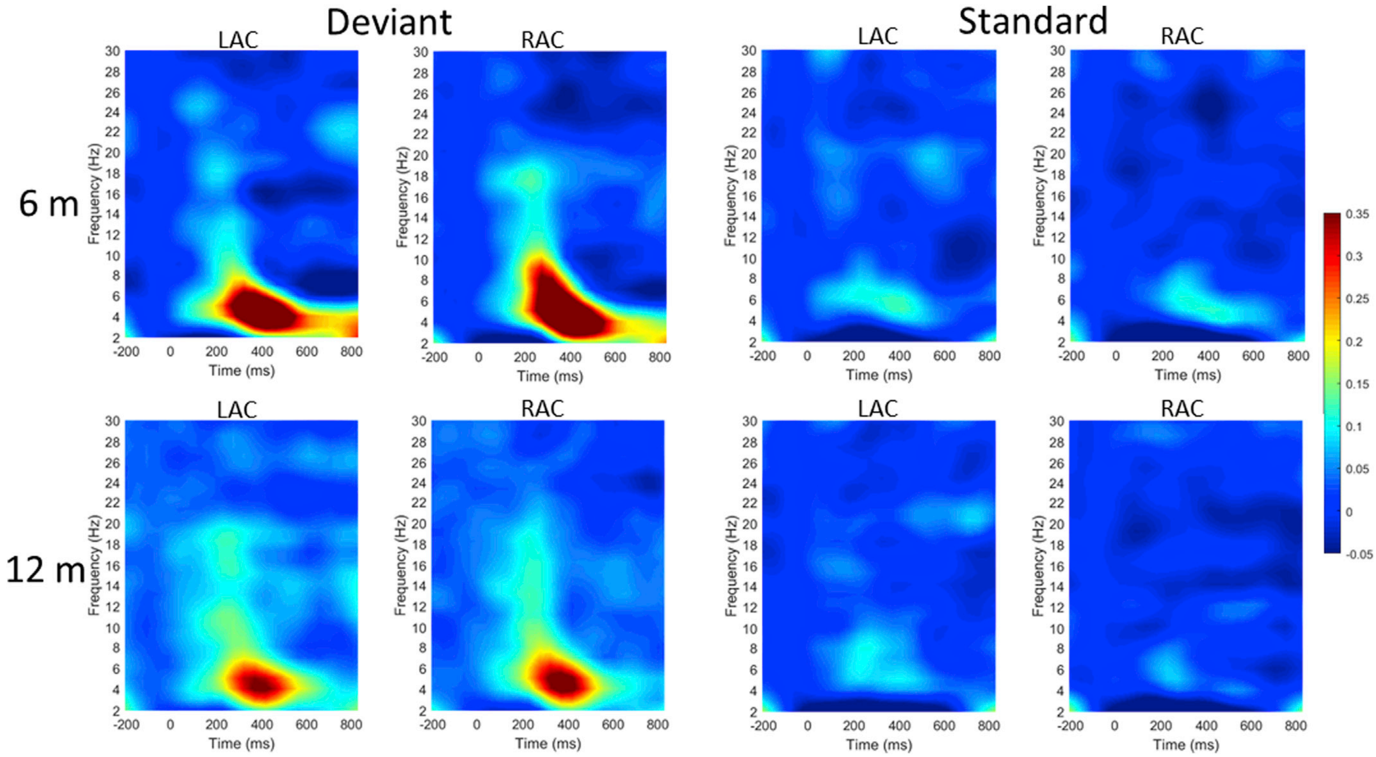

Fig. 6. Spectral power changes (temporal-spectral evolution) in left (LAC) and right (RAC) auditory cortices in different frequency bands in the low range (2–30 Hz) in comparison to the baseline. Top row: Power changes at 6 months, bottom row: Power changes at 12 months in response to the deviant stimulus pair (left) and standard stimulus pair (right).

Table 3
Differences between the deviant and standard stimulus responses at 12 months in spectral power and inter-trial phase locking (ITPL), N = 24.

Frequency	Cluster time	Hemisphere	Cluster p-value	Direction
Power				
Delta (2–3 Hz)	250–600 ms	Left	0.021	D > S
Theta (4–7 Hz)	150–750 ms	Right	0.0047	D > S
ITPL				
Delta (2–3 Hz)	250–900 ms	Left	0.0001	D > S
Delta (2–3 Hz)	300–650 ms	Right	0.0007	D > S
Theta (4–7 Hz)	300–750 ms	Left	0.0001	D > S
Theta (4–7 Hz)	300–650 ms	Right	0.0003	D > S
Alpha (8–12 Hz)	0–400 ms	Left	0.0001	D > S
Alpha (8–12 Hz)	250–400 ms	Right	0.016	D > S
Beta (13–29 Hz)	100–450 ms	Left	0.0001	D > S
Beta (13–29 Hz)	100–400 ms	Right	0.0007	D > S

Note. D = response to the deviant stimulus, S = response to the standard stimulus.

Table 4
Longitudinal differences between the 6-month-olds and 12-month-olds in spectral power and inter-trial phase locking (ITPL) for the deviant stimulus, N = 21.

Frequency	Cluster time	Hemisphere	Cluster p-value	Direction
Power				
Delta (2–3 Hz)	350–900 ms	Right	0.005	6 > 12
Theta (4–7 Hz)	250–500 ms	Right	0.032	6 > 12
Alpha (8–12 Hz)	200–400 ms	Right	0.044	6 > 12
ITPL				
Delta (2–3 Hz)	350–850 ms	Right	0.0001	6 > 12
Theta (4–7 Hz)	300–600 ms	Left	0.019	6 > 12
Theta (4–7 Hz)	200–850 ms	Right	0.0023	6 > 12
Alpha (8–12 Hz)	150–450 ms	Left	0.027	6 > 12
Alpha (8–12 Hz)	200–450 ms	Right	0.020	6 > 12
High gamma (69–90 Hz)	550–700 ms	Right	0.041	12 > 6

from 6 months to 12 months, i.e., the smaller the source strength became.

4. Discussion

Brain activity related to auditory processing exhibits large changes during infancy and childhood (e.g., Choudhury and Benasich, 2011; Pang and Taylor, 2000; Ponton et al., 2000). Further, the first year of life has been suggested as a crucial period when representations for speech sounds are being assembled and thus efficient auditory processing is critically important at this age (Benasich et al. 2014; Kuhl, 2010). Here, development of auditory change detection processes were examined in a longitudinal sample at 6 months and 12 months using EEG-based measures. The main finding was a robust predictive relationship that emerged between phase locking values and source strength at 6 months and the amount of change in response strength from 6 to 12 months. Further, a decrease in ERP amplitude and source strength from 6 months to 12 months was observed in both left and right auditory areas, which were accompanied by a decrease in spectral power and inter-trial phase locking in the lower frequency ranges. Phase locking values in the 2–3 Hz delta range also exhibited a maturational effect, specifically a larger decrease in the right hemisphere when compared to the left.

We used multiple indices of EEG-based brain activity including ERPs, source localization of ERP generators, and time-frequency analysis at source level to examine in depth the auditory change detection response across the first year of life. Each technique provides specific temporal, spatial and/or spectral information. For instance, examination of ERP responses allowed comparability to previous studies conducted with a different sample of infants (Benasich et al., 2006; Choudhury and Benasich, 2011), whereas use of the source localization protocol for infants (Hämäläinen et al., 2011; Ortiz-Mantilla et al., 2012, 2013; 2016, 2019; Musacchia et al., 2013, 2015; 2017; Cantiani et al., 2019) facilitated separation of neural activity originating from different cortical areas, in order to examine our hypothesis on hemispheric differences in maturation. The scalp level ERPs cannot be easily interpreted with regard

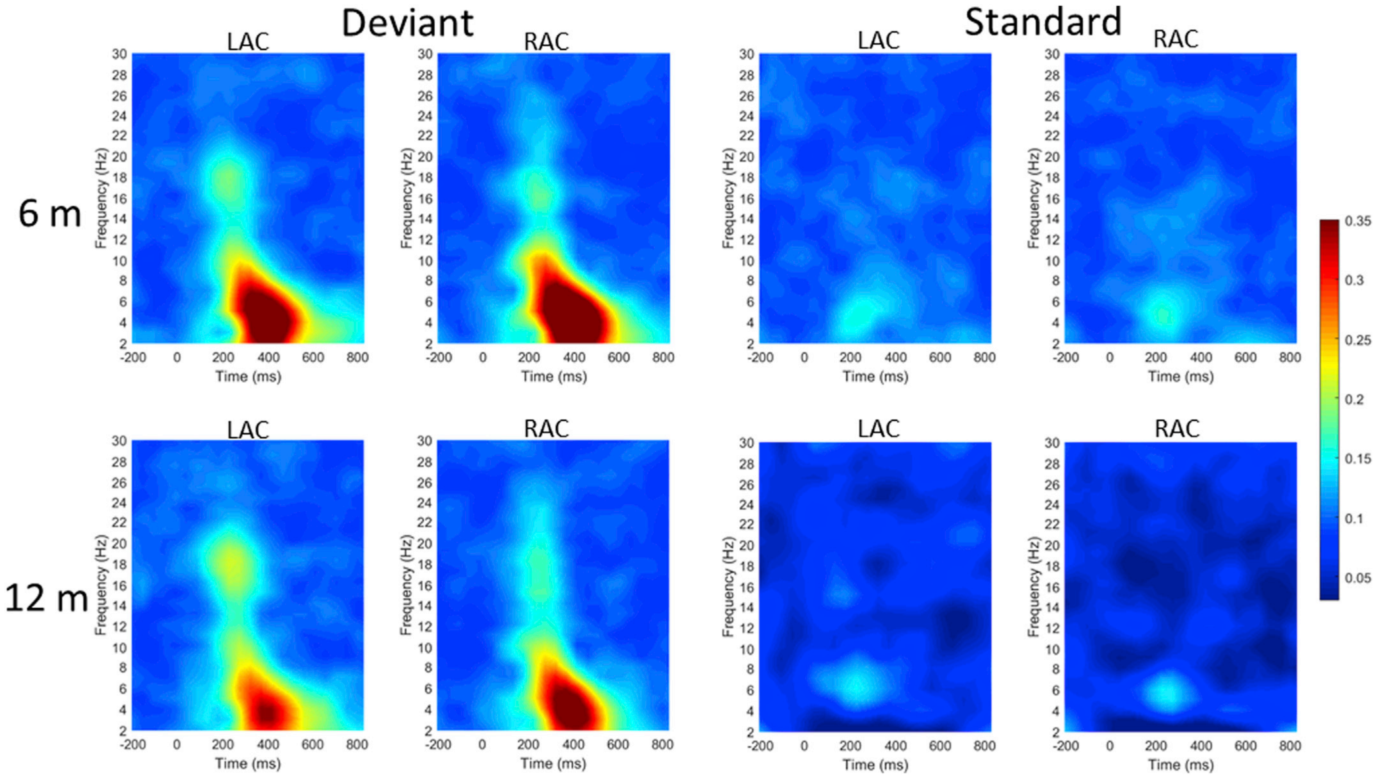

Fig. 7. Inter-trial phase locking (ITPL) values in left (LAC) and right (RAC) auditory cortices in different frequency bands in the low range (2–30 Hz) in comparison to the baseline. Top row: ITPL at 6 months, bottom row: ITPL at 12 months in response to the deviant stimulus pair (left) and standard stimulus pair (right).

Table 5
Correlations (and corresponding p-values) between left (L) and right (R) source strength, inter-trial phase locking (ITPL), and spectral power (TSE) at 6 months and the change in source strength from 6 to 12 months (N = 21) for each frequency band. Significant correlations are marked in bold.

Measure at 6 m	Change in left source from 6 to 12 months	Change in right source from 6 to 12 months
Source L	**.845 (.000)**	-.019 (.935)
Source R	.045 (.848)	**.778 (.000)**
ITPL delta L	.299 (.188)	.421 (.058)
ITPL theta L	**.519 (.016)**	**.458 (.037)**
ITPL alpha L	.210 (.360)	.314 (.165)
ITPL beta L	-.135 (.560)	.084 (.718)
ITPL delta R	.340 (.132)	**.471 (.031)**
ITPL theta R	.348 (.122)	**.544 (.011)**
ITPL alpha R	-.088 (.703)	.209 (.364)
ITPL beta R	.113 (.626)	.227 (.322)
TSE delta L	.371 (.098)	.035 (.879)
TSE theta L	.429 (.052)	.165 (.475)
TSE alpha L	.248 (.278)	.254 (.266)
TSE beta L	-.130 (.575)	-.212 (.355)
TSE delta R	.099 (.669)	.010 (.967)
TSE theta R	.315 (.164)	.392 (.079)
TSE alpha R	-.070 (.764)	.279 (.220)
TSE beta R	.244 (.286)	.207 (.368)

to hemisphere effects due to volume conductance and electrical field projections across hemispheres. Time-frequency decomposition on the other hand, provided specific spectral information on the frequency band contribution to spectral power and phase stability.

The ERP amplitudes at both the parietal and occipital sites and the source strength were larger at 6 months than at 12 months showing a similar decrease as a function of age. The ERP amplitude decrease for the change detection response is in line with earlier studies with the same or similar age ranges (Choudhury and Benasich, 2011; Musacchia et al., 2017). Although the source locations were very similar between the two ages there was a noticeable difference in the dipole orientations. This could be the reason that the ERP amplitude change was visible only in the parietal and occipital electrodes as the orientation change was in the direction of more superior areas at 12 months compared to 6 months. No differences in source strength were seen between hemispheres at either age. This is in line with our earlier report in infants of the same age with a partly overlapping sample, whose ERP responses were examined during speech processing (Ortiz-Mantilla et al., 2016).

The time-frequency decomposition of the ERP responses showed that the ERP and source amplitude decrease was accompanied by a reduction in spectral power and phase locking in the 2–12 Hz range between 6 and 12 months of age. This is also in line with our earlier report in a partly overlapping sample at the same ages (Ortiz-Mantilla et al., 2016), confirming that over maturation infants become more automatized and require less allocation of neuronal resources (as reflected in the amount of spectral power) and phase synchrony to process auditory information. Evidence for a difference in the developmental time course of the hemispheres was identified for phase locking values in the lowest frequency band (2–3 Hz). This finding is at odds with previous studies (Musacchia et al., 2017; Ortiz-Mantilla et al., 2016). However, these differences could be due to differing stimuli employed as well as the different ERP responses examined in these studies. In the current study the focus was on the positive change detection response at a rather late time window, whereas in previous studies using similar tone pairs that differed in spectral content, earlier ERP responses were examined (Musacchia et al., 2013, 2017). It is possible that the hemispheric difference observed in the present study reflects the emergence of functional differentiation of the hemispheres after 6 months of age, but primarily for auditory processing at later processing stages. The later processing stage could reflect demands on both change detection and attention switching (Hämäläinen et al., 2011).

Interestingly, we found a larger change in ITPL values for the right hemisphere as compared to the left from 6 to 12 months indicating a larger decrease in phase locking for the right hemisphere with age. This is at odds with the suggestion that auditory processing in the right hemisphere matures later than in the left (Pang and Taylor, 2000), if lower phase locking values are considered a signature of maturation at this age. However, there are also observations of more mature pattern of brain activity in school-age children in the right compared to the left hemisphere (Parviainen et al., 2019). Further, the maturation of phase locking might also interact with the stimulus parameters. In that case, a smaller change in the left hemisphere could be due to the rapid presentation (i.e., a shorter interstimulus interval) of the two tones in the tone pair. This would imply that the left hemisphere is timing the onset of the second tone more precisely than the right at 12 months. A second alternative explanation could be that the left hemisphere at 6 months had a faster rate of maturation than the right and therefore the change found from 6 to 12 months was smaller in left than right auditory areas. Further research will be necessary to clarify differences in the maturation rate of auditory cortices.

The findings for phase-locking values in general, are aligned with a previous study which examined the development of speech perception (Ortiz-Mantilla et al., 2016). In that study the phase-locking values in the lower frequency bands were also found to decrease with age, although the change appeared to be due to an increase in processing speed of the native as compared to non-native syllables, as reflected by a decrease in ITPL from 6 months to 12 months at a later time window. However, also a small increase in the frequency band was seen at an earlier time window. In the current study there was no indication of a latency shift in the phase-locking values, perhaps suggesting a different developmental trend for speech and basic sound processing.

A small difference in ITPL at a late time window (550–700 ms) with larger values at 12 months than 6 months was also identified in the high gamma range. Although this result is difficult to interpret it could be related to maturational mechanisms that begin to emerge at older ages. It is known that over development, oscillatory activity at lower frequencies gradually shifts into higher frequency bands (Koroleva et al., 2002; Marshall et al., 2002; Orekhova et al., 2006; Cragg et al., 2011). We have reported a similar finding observed during processing of native speech sounds that started at a much earlier time window (Ortiz-Mantilla et al., 2016). However, to our knowledge, there are no previous comparable findings for processing of non-speech stimuli in infants or children.

Finally, we examined the longitudinal relationships between auditory processing indices at 6 months and the amount of change in source strength from 6 to 12 months. By exploring these associations we can begin to understand the neural mechanisms which underlie maturational changes. Identification of developmental predictive relationships have been scarce in the extant literature as most developmental studies use cross-sectional rather than longitudinal designs. Moreover, the majority of developmental studies have examined ERP amplitudes and latencies alone, whereas in the current study we examined spectral power and phase locking as well, in order to tease apart the neural mechanisms that underpin auditory cortical maturation (e.g., Albrecht et al., 2000; Ponton et al., 2000). Source strength was selected as the outcome measure as it is closely related to both ERP amplitude and the time-frequency measures that were calculated within source space. We found that the initial strength of the auditory response at 6 months was most strongly correlated with the amount of change in source strength from 6 to 12 months. This was expected given that the change in amplitude is likely to be proportional to the strength of the responses, due to a number of factors including skull bone and tissue thickness, source orientations, the number of neurons responding to the stimulation etc. On the other hand, the predictive associations for the 6-month source strength were hemisphere specific. The lack of cross-hemisphere predictive associations suggests that the general factors mentioned above do not explain the relationship fully, and the two hemispheres are developing relatively independently despite the same general maturational mechanisms. This could be related to, for example, the hypothesized functional specialization of the left and right auditory cortices for more precise temporal and frequency processing, respectively (e.g., Tervaniemi and Hugdahl, 2003; Zatorre et al., 2002), as well as to the anatomical differences between the hemispheres that are already present in infancy (e.g., Deoni et al., 2011; Dubois et al., 2014; Witelson and Pallie, 1973).

Interestingly, phase locking to stimulation at 6 months also robustly predicted the amount of change in source strength. This association remained significant at the right hemisphere even after removing the variance of the initial source strength at 6 months. This suggests that ability to phase lock systematically to repeated stimuli at 6 months can index the rate of maturational change in the auditory system. We speculate that the ability to systematically phase lock to repeated stimulation at 6 months may well be an important measure of the efficiency of processing in the auditory system. A somewhat similar finding has been reported in the visual domain in older children (Uhlhaas et al., 2009). Specifically, reaction times to correct decisions on a visual target correlated with phase locking across development in a wide frequency range from theta to gamma bands, thus, better phase locking was linked to better performance. In our case, the ability of the auditory system to phase lock to repetitive stimulation would lead to larger maturational changes in response strength, indicating that less neuronal resources are needed to process the same stimuli, and therefore more automatic processing can be achieved at the next developmental stage.

Given the relatively short epoch used in the time-frequency analysis, it should be noted that the estimation of the lowest frequencies may not be optimal. However, for the within group comparisons between conditions this estimation error should remain the same for each comparison. It is possible that some developmental effects at the lowest frequencies might be difficult to detect due to this limitation and to clarify this, further studies may be needed using longer inter-trial intervals. A second possible source for variation might arise from variability in the hearing sensitivity of the infants. None of the available indices showed any hearing problems, but it is possible that within this random sample of typically developing infants there could be variability in hearing levels. This should not, however, limit interpretation of the current data because we are reporting typical variation of brain responses at these ages.

2Overall, our study shows a robust decrease in the amplitude, source strength, spectral power and phase locking in the lower frequency range of the change detection response occurring to tone-pairs from 6 months to 12 months of age. Maturational changes were pinpointed to phase locking values that began to show hemispheric differences at 12 months. Phase locking at 6 months predicted a significant amount of the variance in the magnitude of change in source strength from 6 to 12 months-of-age. Therefore the ability of the auditory system to respond systematically and accurately to rapidly presented successive sound onsets may well be a valuable predictive index of central nervous system maturation.

Declarations of interest

None.

Acknowledgements

This work was supported by the Academy of Finland (Multilete #292466) to J.A.H, and National Science Foundation Grant SMA-1041755 to the Temporal Dynamics of Learning Center, an National Science Foundation Science of Learning Center, to A.A.B. with additional funding from the Elizabeth H. Solomon Center for Neurodevelopmental Research and the Santa Fe Institute Consortium.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuroimage.2019.05.034.

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