

Time course of ERP generators to syllables in infants: A source localization study using age-appropriate brain templates

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ABSTRACT

Event-related potentials (ERPs) have become an important tool in the quest to understand how infants process perceptual information. Identification of the activation loci of the ERP generators is a technique that provides an opportunity to explore the neural substrates that underlie auditory processing. Nevertheless, as infant brain templates from healthy, non-clinical samples have not been available, the majority of source localization studies in infants have used non-realistic head models, or brain templates derived from older children or adults. Given the dramatic structural changes seen across infancy, all of which profoundly affect the electrical fields measured with EEG, it is important to use individual MRIs or age-appropriate brain templates and parameters to explore the localization and time course of auditory ERP sources. In this study 6-month-old infants were presented with a passive oddball paradigm using consonant–vowel (CV) syllables that differed in voice onset time. Dense-array EEG/ERPs were collected while the infants were awake and alert. In addition, MRIs were acquired during natural non-sedated sleep for a subset of the sample. Discrete dipole and distributed source models were mapped onto individual and averaged infant MRIs. The CV syllables elicited a positive deflection at about 200 ms followed by a negative deflection that peaked around 400 ms. The source models generated placed the dipoles at temporal areas close to auditory cortex for both positive and negative responses. Notably, an additional dipole for the positive peak was localized at the frontal area, at the anterior cingulate cortex (ACC) level. ACC activation has been reported in adults, but has not, to date, been reported in infants during processing of speech-related signals. The frontal ACC activation was earlier but smaller in amplitude than the left and right auditory temporal activations. These results demonstrate that in infancy the ERP generators to CV syllables are localized in cortical areas similar to that reported in adults, but exhibit a notably different temporal course. Specifically, ACC activation in infants significantly precedes auditory temporal activation, whereas in adults ACC activation follows that of temporal cortex. We suggest that these timing differences could be related to current maturational changes, to the ongoing construction of language-specific phonetic maps, and/or to more sensitive attentional switching as a response to speech signals in infancy.

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1. Introduction

Long before children utter their first meaningful words, they accumulate a wealth of auditory perceptual knowledge by selectively and involuntarily attending to their auditory environment. In order to become a proficient user of language, infants must detect and process spectral and temporal cues embedded within the acoustic spectra of ongoing speech. Fine-grained acoustic analysis in the range of tens of milliseconds is critical for decoding phonemes within the speech stream, and during language acquisition these decoding skills

are essential for the establishment of language-specific phonemic maps (Aslin, 1989; Kuhl, 2004; Tallal and Gaab, 2006). However, in the first months of life, the auditory system, particularly at the level of the cortex, continues to mature (Moore and Linthicum, 2007). Hence, it seems remarkable how efficiently infants process the dynamic spectral and/or temporal changes in auditory input essential for acquiring language. In a very short time, they begin associating sounds with the contextual information that surrounds them. Although the phonemes (consonant–vowel combinations) that combine to make words may not initially be associated with language and meaning, it is well documented that as the child becomes immersed in its native linguistic environment, these consonant–vowel (CV) combinations are used to initiate the very first steps of integrating sound and meaning to create linguistic representations (Dehaene-Lambertz et al., 2006a; Kuhl, 2010; Kuhl et al., 2008; Saffran et al., 2001; Shukla et al., 2011).

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To examine these early processing abilities, behavioral, electrophysiological and functional measures have been widely used (Kuhl and Rivera-Gaxiola, 2008). Discriminative brain responses to a frequency change have been detected as early as 28 weeks of gestation (Draganova et al., 2007) and to a vowel change at 30–35 weeks of gestation (Cheour-Luhtanen et al., 1996). Newborns and infants are able to discriminate natural and synthetic speech sounds such as vowels and consonants (Cheour-Luhtanen et al., 1995; Eimas et al., 1971; Leppänen et al., 2002, 2004; Telkemeyer et al., 2009), syllables (Friedrich et al., 2004; Imada et al., 2006; Trehub, 1976), words (van Leeuwen et al., 2007; Zangl and Mills, 2007), sentences (Dehaene-Lambertz et al., 2006b), narrative passages (Dehaene-Lambertz et al., 2002, 2010), function morphemes (Shafer et al., 1998), pseudo-words (Minagawa-Kawai et al., 2007; Vouloumanos and Werker, 2004), and word stress patterns (Weber et al., 2004).

Behavioral assessment of auditory perception in infants can be impacted in many ways, for example, by motivational and attention related factors. Therefore, electrophysiological methods, such as event-related potentials (ERP), are well suited to studies of the establishment of automatized acoustic processing in infancy (Alho and Cheour, 1997; Cheour et al., 2000). ERPs have high temporal resolution and, in addition, do not require the child to actively participate or attend to the task (Cheour et al., 2001; Kuhl, 2010). ERP responses to stimulus variations recorded at the scalp surface, measure the electrical activity of the brain by examining stimulus-locked cortical activity. For instance, auditory ERPs have been used to measure infant's ability to discriminate changes that occur in the processing of speech (Cheour et al., 1998; Dehaene-Lambertz and Dehaene, 1994; Friederici, 2005; Friederici et al., 2002; Pang et al., 1998) and non-speech signals (Benasich et al., 2006; Dehaene-Lambertz, 2000; Hämäläinen et al., 2011; He and Trainor, 2009a; He et al., 2007), and further to track developmental changes in auditory processing (Čeponienė et al., 2002; Choudhury and Benasich, 2011; Gomot et al., 2000; He et al., 2009; Lippé et al., 2009; Mills et al., 2004; Morr et al., 2002; Pang and Taylor, 2000; Ponton et al., 2000; Rivera-Gaxiola et al., 2005, 2007; Trainor et al., 2003), as well as to predict to later language outcomes (Benasich et al., 2006; Choudhury and Benasich, 2011; Guttorm et al., 2005, 2010; Leppänen et al., 2010; Tsao et al., 2004).

However, in order to have a more clear understanding of how infants process speech information, it is essential to not only consider and measure auditory change detection and speed of processing, but also to reliably determine brain areas that might sub-serve the ERP responses. Functional magnetic resonance imaging (fMRI), near infrared spectroscopy (NIRS), and magnetoencephalography (MEG) studies which have the advantage of excellent spatial resolution, have helped our understanding of the specific brain areas that are activated during speech perception in early infancy (Dehaene-Lambertz et al., 2006a, 2010; Imada et al., 2006; Kuhl, 2010; Minagawa-Kawai et al., 2007; Sato et al., 2010). For instance, in one fMRI study, 2–3 month-old infants who listened to a passage presented either forward or backward, showed bilateral activation in the superior temporal cortices (Dehaene-Lambertz et al., 2002). Activation was greater in the left than the right temporal lobe, particularly at the level of the planum temporale. In another study, 3-month-old infants listening to short sentences presented in an event-related fMRI paradigm, showed hierarchical functional organization of the superior temporal regions: faster responses were localized close to Heschl's gyrus and slower responses were identified in the posterior part of the superior temporal gyrus (STG), temporal poles, and inferior frontal regions (Dehaene-Lambertz et al., 2006b).

In the EEG/ERP domain, source localization is a technique used to identify the loci of the neural activation measured at the scalp surface. As the relationship between activity generated at neuronal level and the signals recorded from the scalp surface is not always clear-cut (Cosandier-Rimélé et al., 2008; Dalal et al., 2009; Ray et al., 2007;

Tao et al., 2005), source localization methods are better suited to detect hidden sources of neural activity that could be difficult to record with surface electrodes (David et al., 2011). But, the majority of the studies investigating localization of auditory sources have been conducted in adults (e.g. Alho et al., 1998a; Deouell, 2007; Frodl-Bauch et al., 1997; Giard et al., 1990; Ha et al., 2003; Jemel et al., 2002; Korzyukov et al., 1999; Opitz et al., 2002; Rinne et al., 2000; Waberski et al., 2001). As technology has advanced, this methodology has increasingly been applied to younger populations (Bernal et al., 2010; Dehaene-Lambertz and Baillet, 1998; Kotecha et al., 2009; Ponton et al., 2002; Richards, 2005; Roche-Labarbe et al., 2008). However, the majority of studies examining source localization in infants and children have used either, non-realistic head models or a single individual MRI for all participants, and/or adult parameters for surrounding brain structures. For example, in the auditory domain, dipole source analysis of the ERP responses to tones was investigated in children ages 5 to 16 years using a standard adult multiple dipole-model. The dipole sources of the ERP responses were located generally at the temporal lobes (Albrecht et al., 2000). In 2-month-old infants, sources of the brain responses to one-syllable words as estimated by LORETA, a distributed current source density model, were located at superior temporal auditory cortices, mainly on the left side, but using an adult template (van Leeuwen et al., 2007).

More realistic head models were used in studies examining the source localization of responses to speech stimuli in 3-month-old babies, using a two-dipole source model with realistic head tissue thicknesses; localization of the ERP generators was to the temporal lobes (Dehaene-Lambertz and Baillet, 1998). In a more recent study, sources of ERPs during processing of ungrammatical versus grammatical sentences were localized to left temporal cortex, using a weighted minimum-norm current estimate in a 3-shell head model constructed from an individual MRI from a normal 2-year-old (Bernal et al., 2010). In the visual domain, a realistic source model, based on a single 6-month MRI and using adult parameters for scalp and skull thickness, was used to explore the ERP generators of 4- and 7-month old infant's visual attention and recognition memory (Reynolds and Richards, 2005, 2009; Richards, 2005). Realistic head models were used in one interesting study, which analyzed pathological versus physiological electrical activity in five neonates with clinical medical conditions. The source localization of focal EEG events was explored using four different head models for each neonate, obtained from individual MRI scans. The authors reported differences in the magnitude of the dipoles, but no significant effect on dipole position and orientation when variations of skull thickness and bone conductivity were applied (Roche-Labarbe et al., 2008). Thus it is quite clear, that to obtain more precise source localization of ERP generators in infancy and childhood, it is important to create and use realistic head models that can reliably represent age-appropriate, normally developing brain structure, and to employ dense-array EEG recordings using a large number of electrodes evenly distributed over the head surface (Ha et al., 2003; Johnson et al., 2001).

Throughout the first years of life, the brain and its surrounding structures undergo large anatomical and histological changes that are related to electrophysiological activity and behavior including language (Nunez and Srinivasan, 2006; Ortiz-Mantilla et al., 2010a; Pujol et al., 2006; Reiss et al., 1996; Sowell et al., 2004). For instance, the degree of white matter myelination in fronto-temporal language-related areas was found to be positively associated with language production (Pujol et al., 2006). In a previous study, taking into account the developmental structural changes in the brain and its surrounding tissues, we explored the localization of the infant ERP generators to a pitch-change using 6-month ERPs mapped onto corresponding 6-month MRIs (Hämäläinen et al., 2011). Both discrete dipole and distributed models were used for source analyses. Source activity was found adjacent to the auditory cortex and in the frontal area, close to and within anterior cingulate cortex (ACC). However,

in that study using nonverbal stimuli the strength of the frontal source to the pitch change was weak and could not be successfully modeled at the individual level (Hämäläinen et al., 2011). In the present study, following the same methodology, we aimed first, to investigate in 6-month-old infants the location of the generators for ERP responses to CV syllables, and second, to analyze the strength and time course of brain activations when infants are processing speech-related information. Based on our previous results using nonverbal stimuli, we expected to find significant source activations in left and right auditory cortices as well as in frontal, anterior cingulate cortex.

2. Methods

2.1. Participants

As part of a large developmental study whose primary aim was to establish developmental landmarks across the first years of life, 42 typically developing infants were assessed at 6 months of age with ERPs and for a subset of these structural MRIs. In the present study, the participants comprised a subset of this group for a total of 28 infants (9 girls and 19 boys). All were born healthy, full-term (mean gestational age: 39.84 weeks, SD: 1.36), and with normal birth-weight (mean: 3554.6 g, SD: 409.4). Thus a total of 14 children that had participated in the larger study were excluded, 13 because of the high noise level in the ERP data, and 1 due to a medical condition unveiled in the MRI. All infants had uneventful pre- and perinatal circumstances and were born into English monolingual families. Infants were recruited from urban and suburban communities in New Jersey, and had no family history of specific language impairment, autism spectrum disorders, hearing loss, repeated episodes of otitis media, or other medical, neurological or psychiatric disorders.

Informed consent approved by the Rutgers University Human Subjects Institutional Review Board was obtained from all parents prior to their child's inclusion in the study, which was conducted in accordance with the Declaration of Helsinki. Parents were compensated for their time and infants received a toy after each visit.

2.2. Procedure

2.2.1. Event related potentials (ERPs)

Stimuli: The stimuli were consonant–vowel syllables, varying in voice-onset time (VOT). Each CV syllable duration was about 230 ms including 5 ms rise and fall times. The standard stimulus was a CV syllable (phonetically relevant in both English [da] and Spanish [ta] with VOT: +12 ms, Fig. 1). Two CV syllables were used

as deviants: a native deviant (phonetically relevant in English [ta] with VOT: +46 ms, Fig. 1) and a non-native deviant (phonetically relevant in Spanish [da] with VOT: –24 ms). The stimuli were presented in an oddball paradigm that contained a standard syllable (80%), a native deviant syllable (10%) and a non-native deviant syllable (10%) for a total of 1000 stimuli. The stimulus onset-to-onset interval was 930 ms (for a more detailed explanation of these stimuli and the paradigm used, please refer to Rivera-Gaxiola et al., 2005). Auditory stimuli were matched for intensity and presented binaurally in a sound-attenuated free field environment at 75 dB SPL.

EEG recording and data processing: Dense array EEG/ERP recordings were acquired from 6-month infants while participants were seated in their parent's lap, watching a silent movie. If necessary, infants were entertained with toys or a silent puppet show to keep them calm and engaged. EEG/ERP signals were recorded with 62 Ag/AgCl electrodes net (Electrical Geodesics, Inc.), using the vertex electrode as an online reference, 250 Hz sampling rate, and with 0.1 Hz high-pass and 100 Hz low-pass filters. After recording, the data was processed with BESA (Brain Electrical Source Analysis, BESA GmbH, Gräfelfing, Germany) using an off-line bandpass filter of 1–15 Hz and re-referenced to an average (whole head) reference. EEG data was segmented into epochs according to stimulus type (standard, native deviant and non-native deviant), with 300 ms pre-stimulus and 930 ms post-stimulus time, and 100 ms before stimulus onset used as baseline. Eye movements were corrected using the BESA software's automatic correction algorithm (PCA method). Epochs with signals exceeding $\pm 200 \mu\text{V}$ from the baseline were excluded. Minimums of 75% (average for standard: 149, range: 138–178; for native deviant: 77, range: 70–92; for non-native deviant: 75, range: 70–87) of artifact-free epochs were used for ERP averaging. In order to ensure similar signal to noise ratio between responses to standard and deviant contrasts, only the pre-deviant standard epochs were averaged for the standard response.

2.2.2. Magnetic resonance imaging (MRI)

MR images were obtained at 6–7 months of age. The visit to the MRI facility was scheduled for late afternoon or early evening so that MRIs from non-sedated, naturally sleeping infants could be more easily acquired. In the imaging suite, normal bedtime routines for the child were replicated as closely as possible by including soft lullaby music, a rocking chair, a crib, and any other objects or materials that might encourage sleeping (for a detailed explanation of the scanning procedures, see Liu et al., 2008; Ortiz-Mantilla et al., 2010a; Paterson et al., 2004). 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.

To create an MRI template for 6-month-olds, 18 MRI images were affine transformed into the MRI space of an infant with median age and combined into an average image of 19 MRIs. The MRIs were then processed using BrainVoyager QX program. Original individual and average (template) MRIs were translated and rotated into anterior–posterior commissure plane (AC–PC) and normalized into Talairach space (Fig. 2).

The skin surface was reconstructed from the individual and average template MRIs to project the ERP voltage and current density maps into realistic head shapes (Fig. 3A).

In order to increase accuracy in the source localization of the infant ERP generators, parameters for skull thickness and for subarachnoid width were estimated from the individual AC–PC aligned MRIs. Skull thickness and the width of subarachnoid space were measured in the coronal and transverse slices at four points in each slice (for detailed description refer to Hämäläinen et al., 2011). An average of the values across these 8 measurement points for each structure

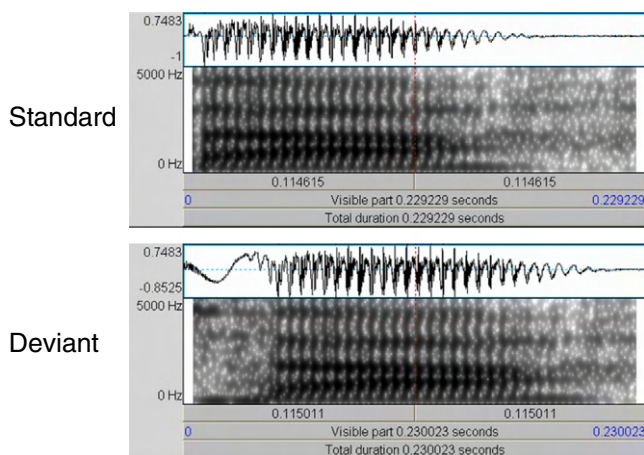


Fig. 1. Spectrogram of the syllable used as standard, phonetically relevant in English [da] VOT: +12 ms (above) and of the syllable used as deviant, phonetically relevant in English [ta], VOT +46 ms (below).

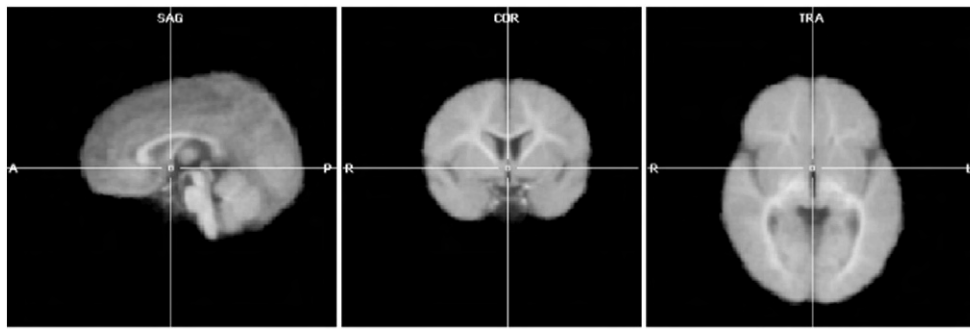


Fig. 2. Average MRI template (transverse, sagittal and coronal slices) for age 6-months aligned into anterior commissure–posterior commissure (AC–PC) plane and fitted into standard Talairach space. The crosshair is at the anterior commissure point (A: anterior; P: posterior; L: left; R: right; SAG: sagittal; COR: coronal; TRA: transverse).

was used as parameter for the source localization (average skull thickness: 1.5 mm, SD: 0.4 mm; average subarachnoid width: 1.7 mm, SD: 0.6 mm). These values were close to estimates previously reported for infant skull (Letts et al., 1988) and for width of the subarachnoid space in infants (Lam et al., 2001). As the MRI resolution was not appropriate for clear identification of the scalp, an estimate of 2.5 mm was used based on reported newborn average scalp thickness of 2 mm obtained from neonates' autopsies (Hull, 1972) and on an average scalp thickness of 3 mm measured at 2 years of age for children having cochlear implants (Raine et al., 2007). Skull conductivity was estimated by fitting an exponential function on the data available for 3–9 year old children in the BESA Research 5.3 software. The equation for the exponential function was $0.064 * e^{-0.195 * \text{age in years}}$ which gave a bone conductivity estimate of 0.0581 for the 6 month age point.

2.2.3. Source localization analyses

For the source localization analyses, the ERP data was combined with the MR images using BESA and Brain Voyager QX programs. For 16 infants, the standard electrode positions were fitted onto the individual AC–PC-aligned MRI, and the reconstructed skin surface (Fig. 3B). When the individual MRI was not available (12 infants), the average MRI template (Fig. 2) and the average reconstructed skin surface were used (Fig. 3A). The average skull thickness (1.5 mm) and subarachnoid space width (1.7 mm) and the estimated bone conductivity (0.0581) parameters were used for all subjects. Source localization analyses were carried out in BESA Research 5.3. Peaks for the responses to the standard and deviant were identified from the grand average waveform and from the individual ERPs; a time window of ± 20 ms around the peak was used for dipole fitting. A dipole source model (Scherg and von Cramon, 1985) and a confirmatory distributed source model calculated using CLARA (Classic LORETA Recursively Applied; Hoechstetter et al., 2010)

method, in a 4-shell ellipsoidal head model, were applied for the source analyses.

2.2.4. Statistical analyses

The statistical analyses were carried out using PASW Statistics 18 (SPSS, Inc) software. For the purposes of this study, only the responses to the standard and the native deviant (from now on referred to as the deviant) stimuli were included in the statistical analyses. The peak amplitudes of the ERP waveforms (positive and negative), as well as the peak amplitudes of the source waveforms (left and right temporal, and frontal), for the standard and deviant stimuli were confirmed to be significantly different from zero using one-sample t-tests (all $p < 0.001$). The source strength and latency were examined separately using repeated measures ANOVAs for the positive (Stimulus [standard, deviant] $\times$ Source [left auditory, right auditory, frontal]) and negative (Stimulus [standard, deviant] $\times$ Source [left auditory, right auditory]) responses. The source coordinates were examined separately for the x (medial–lateral), y (anterior–posterior) and z (superior–inferior) directions. For each of these variables repeated measures ANOVAs (Stimulus [standard, deviant] $\times$ Hemisphere [left auditory, right auditory] $\times$ Component [positive, negative]) were used. The significance of the contribution of the ACC-dipole to the dipole model for the positive response was examined by 2×2 (Model [two-dipole, three-dipole] by Stimulus [deviant, standard]) repeated measures ANOVAs.

3. Results

3.1. Event-related potentials (ERP)

The main ERP responses elicited by the standard and deviant syllables included a positive deflection followed by a negative deflection maximal at fronto-central areas (Fig. 4). Inversion of polarity was observed at the mastoids and for posterior channels. Measured at fronto-central channels on the grand average waveform, the positive response for the standard in the left hemisphere peaked at 164 ms (1.54 μV) and at 152 ms (1.59 μV) on the right side; for the deviant stimulus, the positive deflection peaked at 168 ms (2.12 μV) on the left and at 152 ms (2.16 μV) for the right. The negative response for the standard stimulus peaked at 380 ms (−1.26 μV) in the left hemisphere and 372 ms (−1.09 μV) on the right; and for the deviant stimulus, the peak occurred at 416 ms (−1.5 μV) and 428 ms (−1.77 μV) for left and right hemispheres, respectively. The ERP waveforms were very similar to those reported in other studies using the same paradigm but at slightly different ages (e.g. Rivera-Gaxiola et al., 2005, 2007). The voltage maps for the standard and deviant positive peak showed a bilateral frontal distribution with reversal of the polarity into negative voltages at parietal and occipital areas (Fig. 4). In addition, a clear frontal sink was identified in the surface topography. The strength of the frontal sink was tested at the frontopolar line of electrodes (Fp1, Fpz and Fp2) where a negative-going deflection

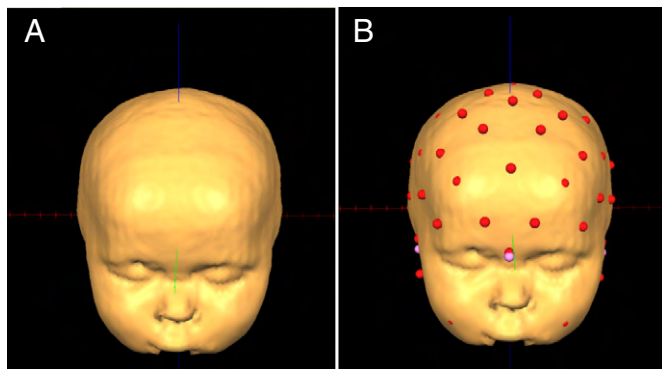


Fig. 3. A. Individual reconstructed head surface for a 6-month-old infant. B. Alignment and fitting of the standard EGI 62-channel locations with the anatomical landmarks in the individual infant MRI reconstructed head surface.

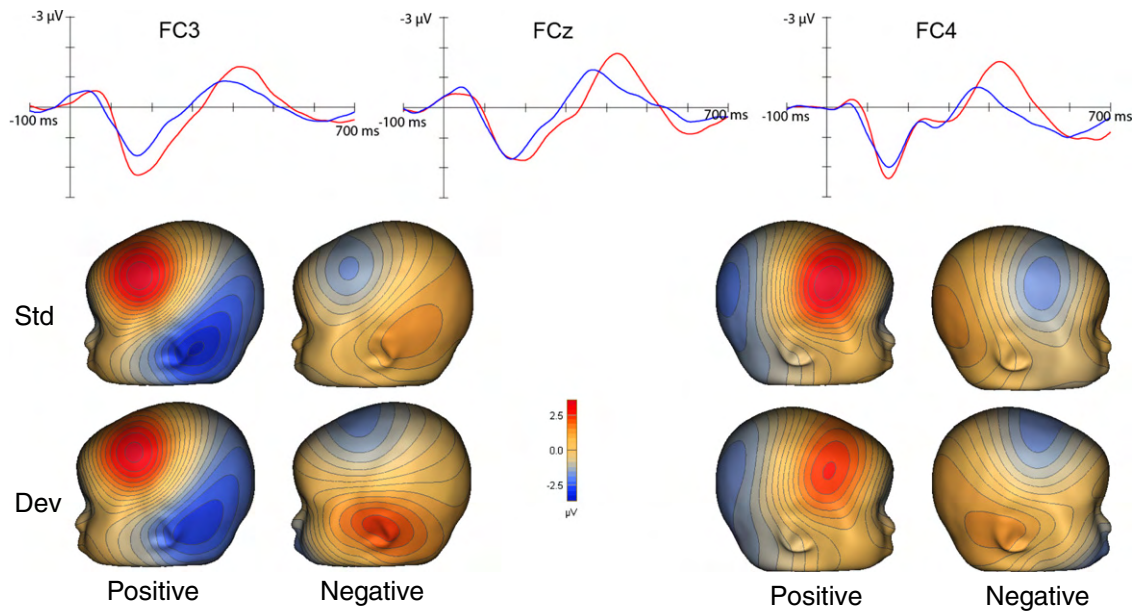


Fig. 4. Above: Grand average 6-month ERP waveforms in response to the standard (blue) and deviant (red) stimuli showing a positive deflection followed by a negative deflection at fronto-central areas (FC3: fronto-central left; FCz: fronto-central midline; FC4: fronto-central right); negativity is plotted up. Below: Voltage maps for positive and negative peaks for standard (first row) and deviant (second row) stimuli.

peaking at about 168 ms, with amplitudes at Fpz of $-1.98 \mu\text{V}$ and $-2.15 \mu\text{V}$ for standard and deviant respectively was identified (Fig. 5). One-sample t-tests showed statistically significant increases from the zero baseline in response to the standard and deviant for all three fronto-polar channels (all $ps < 0.001$). For the standard and deviant negative peak the voltage maps indicated a bilateral frontal distribution with reversal to positive voltages at posterior sites (see Fig. 4).

3.2. Source analyses based on grand average ERPs

Sources were initially examined separately for the positive and negative responses computed from the grand average of the standard and deviant stimuli. Discrete (dipole) and distributed (CLARA) source models were applied to the ERP data.

For the positive response, the CLARA distributed model showed bilateral activation to the auditory cortex near to the superior temporal gyri (STG) and to the mid-frontal area, in the anterior cingulate cortex (Fig. 6A). As a first step, a two-dipole model (residual variance 15.7% for the deviant, 12.9% for the standard) placed the dipoles at auditory cortices. However, the remaining unexplained variance showed a clear frontal distribution suggestive of a third source (see Fig. 7B). When a three-dipole model was used, the dipoles were located at auditory cortices and at the ACC leaving a residual variance of 3.9% for the deviant and 4.0% for the standard. Thus, the three-dipole model explained an additional 11.8% of variance for the deviant and 8.9% of the variance for the standard as compared to the two-dipole model. Further, after the third dipole was fitted, not only did the remaining residual variance decrease but the frontal sink was no longer seen (Fig. 7C). Fig. 7A also illustrates the temporally

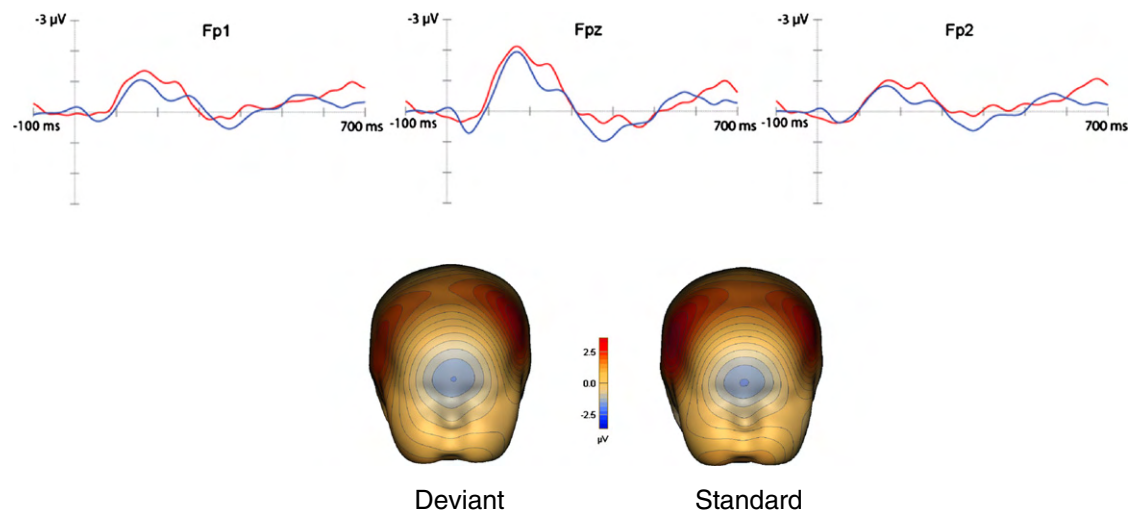


Fig. 5. Above: Grand average 6-month ERP waveforms in response to the standard (blue) and deviant (red) stimuli showing a negative deflection between 100 and 200 ms at fronto-polar areas (Fp1: fronto-polar left; Fpz: fronto-polar midline; Fp2: fronto-polar right); negativity is plotted up. Below: Scalp topography of the positive response to the deviant (left) and standard stimuli (right) shown from a frontal angle. The voltage map shows a frontal sink.

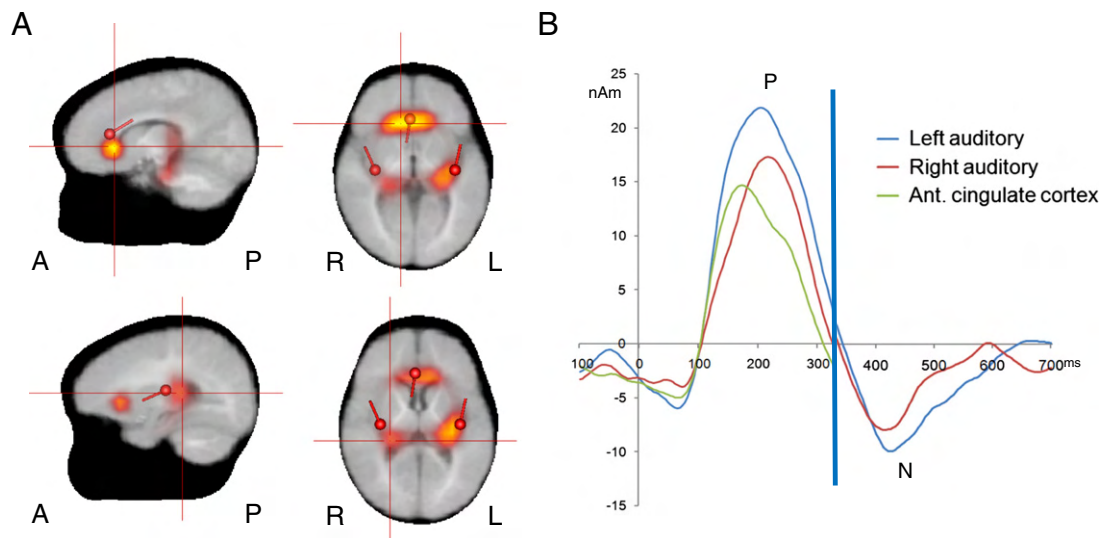


Fig. 6. A. Source locations shown by distributed CLARA and discrete dipole solutions for the deviant positive peak based on the grand average ERP at 6-months. The location of the main three sources in the left and right auditory cortices, and frontal in the anterior cingulate cortex is shown (A: anterior; P: posterior; L: left; R: right). B. Source waveforms for the deviant positive response showing earlier and smaller activation in the anterior cingulate cortex (in green) as compared to the left (in blue) and right (in red) auditory cortices. The source waveforms for the negative response have similar magnitude in the strength of activation in both hemispheres. The vertical line separates the source waveforms of the positive (P) and negative responses (N).

specific time course of the frontal sink activation in response to the deviant stimulus. Note that the frontal topography is very clear only in a small time-window (at ~200 ms).

For both the standard and deviant stimuli responses, the frontal source appeared to activate earlier and with smaller amplitude than the auditory sources (Table 1). Based on the grand averaged ERP, the main activation for the positive response to the deviant stimulus was generated in left auditory cortex (Fig. 6B), whereas for the standard stimulus the left and right auditory sources were almost equal in strength (Table 1). The source orientations in the left auditory cortex for both standard and deviant responses, showed a tangential angle, whereas in the right auditory cortex, the orientations were more oblique and closer to radial (see Fig. 8).

For the negative response, the dipole model (residual variance 10.9% for the deviant, 18.1% for the standard stimuli), and the CLARA solution also showed bilateral activation close to the STG in the temporal lobe. However, a small frontal activation near to anterior cingulate cortex (as shown by the CLARA solution) could only be dipole modeled for the response to the standard stimulus but not for response to the deviant. As shown in Fig. 6B, the source activation as a response to the deviant seemed to be larger on the left than on the right as compared to the left auditory cortex (Table 1). The source orientations were mostly tangential. All the source waveforms followed the original ERP waveforms closely indicating a good model fit to the data.

3.3. Source analyses based on individual ERPs

Subsequently, dipoles were fitted for each infant's individual ERP data. As a first step, a two-dipole model was freely fitted for deviant and standard responses. The dipoles were placed in both auditory cortices with a residual variance for the positive response of 14.07% for deviant and 14.53% for standard. As a second step, for the positive response to the standard and the deviant stimuli, a three-dipole model was used which placed the dipoles at left auditory, right auditory and anterior cingulate cortices. The dipoles located at left and right temporal hemispheres were fitted freely. However, during fitting, the location of the frontal source was fixed, based on the grand average solution, because this source, when examined at the

individual level, had less strength than the temporal sources and the signal-to-noise ratio did not allow stable free individual fitting. Conversely, the orientation of the frontal dipole was allowed to freely vary among individuals. The orientations showed a quite consistent overlay (see Fig. 9). The positive response for the deviant stimulus could be modeled for all 28 children and the response to the standard for 26 children. The variability in the dipole locations at left and right auditory cortices for the positive response to the deviant stimulus, based on each infant's individual ERP response, is illustrated in Fig. 10.

The negative response was absent in some of the children thus allowing reliable use of a two-dipole model in only 22 of the children for response to the deviant, and in 21 children for response to the standard stimulus. The small frontal activation for the standard seen for the group data could not be reliably modeled at the individual level for the negative response. The residual variance for the positive (three-dipole model) and negative (two-dipole model) responses was 11.8% (SD: 5.7) and 11.3% (SD: 5.6) for the deviant, and 10.5% (SD: 4.8) and 13.2% (SD: 6.0) for the standard stimulus. Means and standard deviations for the amplitude and latency of the source waveform peaks as a response to the standard and deviant stimuli based on individual source analyses are included in Table 1.

The contribution of the ACC dipole to the model was examined by 2×2 (Model [two-dipole, three-dipole] by Stimulus [deviant, standard]) repeated measures ANOVAs and a main effect of Model ($F_{(1,24)} = 93.49$, $p < 0.001$) was shown. Thus, a significant amount of additional variance could be explained for deviant and standard positive responses with the three-dipole model. No effect of stimulus was found. The source strength for the positive response was analyzed by 2×3 (Stimulus [standard, deviant] by Source [left auditory, right auditory, frontal]) repeated measures ANOVAs. A main effect of stimulus ($F_{(1,23)} = 36.80$, $p < 0.001$) and a main effect of source ($F_{(2,22)} = 16.33$, $p < 0.001$) were revealed. The strength of the source was larger for the deviant than for the standard stimulus by 6.92 nAm at the left auditory, by 3.95 nAm at the right auditory, and by 5.21 nAm at frontal cortices. The frontal activation was smaller than both auditory temporal activations at the left by 13.95 nAm for the deviant, and by 12.24 nAm for the response to the standard ($F_{(1,23)} = 23.48$, $p < 0.001$), and at the right, by 11.87 nAm and 13.13 nAm for the deviant and the standard respectively ($F_{(1,23)} = 35.39$, $p < 0.001$). No laterality strength effect was found. The 2×3

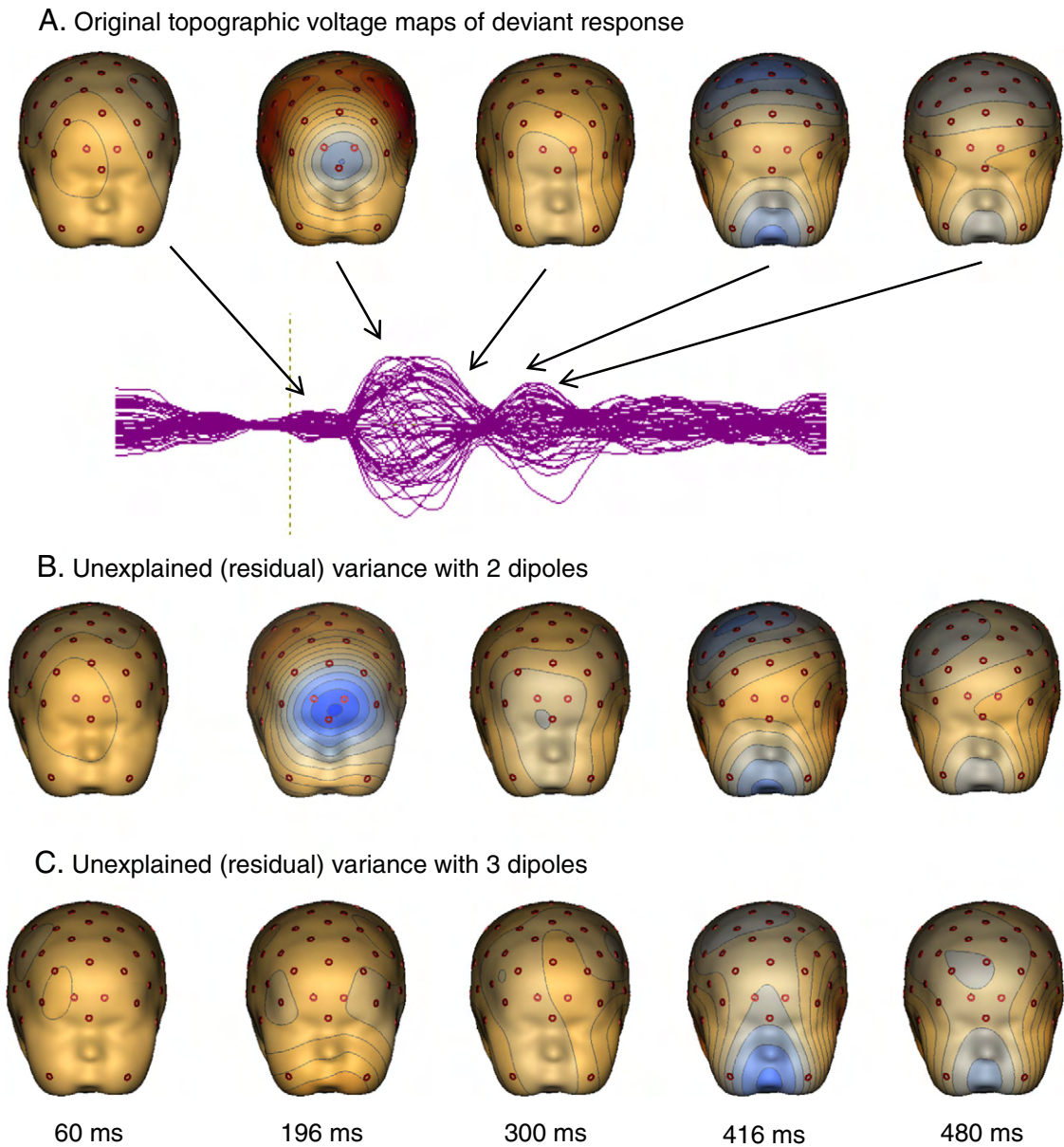


Fig. 7. Time series of the frontal sink activation in response to the deviant stimulus are shown in voltage maps. A. The original data topography shows temporally specific frontal activation around 196 ms. This time-window corresponds to the main positive activation illustrated in the butterfly plot of all channels. B. Voltage maps of the unexplained (residual) variance with 2 dipoles are shown; a frontal sink is present at 196 ms time-window. C. Voltage maps of the unexplained variance when a 3-dipole model was used. No clear frontal sink remains at any time-window after the third dipole fitting; a significant decrease of the residual variance is observed.

Stimulus by Source repeated measures ANOVA for the peak latency also showed a main effect of stimulus ($F_{(1,23)} = 24.38, p < 0.001$) and a main effect of source ($F_{(2,23)} = 8.17, p < 0.002$). The source of the response to the standard stimulus peaked earlier (by 33 ms at

left auditory, 25 ms at right auditory, and 20 ms at frontal cortices) than the source of the response to the deviant stimulus. The activation of the frontal source peaked earlier than the activation of the left auditory source, by 27 ms for the deviant, and by 13 ms for the

Table 1
Peak amplitude and latency of the sources in response to the standard and deviant stimuli based on grand average and individual source analyses.

		Grand average				Individual level			
		Deviant		Standard		Deviant		Standard	
		Amplitude (nAm)	Latency (ms)	Amplitude (nAm)	Latency (ms)	Amplitude (SD)	Latency (SD)	Amplitude (SD)	Latency (SD)
Positive peak	Left temporal	23.3	176	16.27	176	33.17 (14.76)	216.14 (40.21)	26.25 (12.71)	182.31 (24.79)
	Right temporal	17.75	208	17.25	172	31.09 (10.73)	205.71 (31.89)	27.14 (12.77)	180.77 (32.02)
	Frontal ACC	16.58	172	9.84	160	19.22 (7.39)	188.71 (47.37)	14.01 (6.09)	168.77 (28.13)
Negative peak	Left Temporal	−17.54	432	−6.96	372	−33.61 (18.01)	415.09 (54.77)	−25.27 (11.57)	372.19 (47.29)
	Right temporal	−14.14	412	−8.31	380	−28.86 (15.74)	404.18 (56.95)	−22.27 (9.38)	379.05 (39.64)

nAm: nanoamperes; ms: milliseconds; SD: standard deviation.

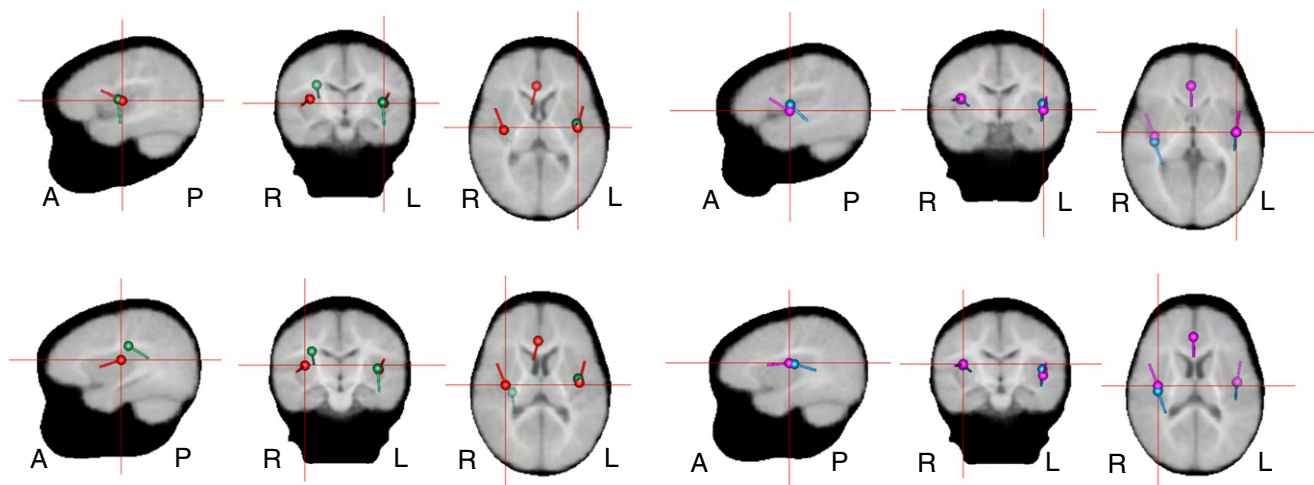


Fig. 8. Left: Dipole source solutions based on the grand average response to the deviant are shown in the average infant brain template. Dipole locations were fitted ± 20 ms around the peak of the positive (in red) and negative (in green) responses. The crosshair is at the left and right dipole locations for the positive peak. The source orientations showed tangential angle in the left hemisphere and a more oblique, closer to radial angle in the right hemisphere (A: anterior; P: posterior; L: left; R: Right). Right: Dipole source solutions based on the grand average response to the standard are shown in the average infant brain template. Dipole locations were fitted ± 20 ms around the peak of the positive (in pink) and negative (in blue) responses. The crosshair is at the left and right dipole locations for the positive peak. Similar to shown by the deviant, the source orientations for the standard showed tangential angle in the left hemisphere and a more oblique, closer to radial angle in the right hemisphere.

standard stimulus ($F_{(1,23)} = 14.51, p < 0.002$), and the activation of the right auditory source by 17 ms for the deviant, and by 12 ms for the standard stimulus ($F_{(1,23)} = 5.95, p < 0.024$).

For the negative response, the 2×2 Stimulus by Source ANOVA did not show any significant main effect or interactions for source strength. However, for the peak latency, the 2×2 ANOVA revealed a main effect of Stimulus ($F_{(1,16)} = 12.00, p < 0.004$). The source activation for the standard peaked earlier than the response to the deviant stimulus by 43 ms at the left, and by 25 ms at the right auditory cortices.

Source coordinates were examined using $2 \times 2 \times 2$ repeated measures ANOVAs (Stimulus [standard, deviant] by Source [left auditory, right auditory] by Component [positive, negative]). A main effect of source was found for the y ($F_{(1,16)} = 5.22, p < 0.036$), and for the z ($F_{(1,16)} = 4.51, p < 0.051$) coordinates. The source in the left auditory cortex was 4.9 mm anterior and 5.7 mm inferior as compared to the

right auditory source. No significant main effects or interactions were found for the x coordinate.

4. Discussion

Accurate localization of the ERP generators has the potential to inform us about when and where in the brain auditory signals are detected and processed. However, in order to obtain relatively accurate source localization of the ERP generators, it is essential to take into consideration the many variables that might impact the temporal and spatial identification of these sources. This is particularly important when ERP sources are investigated in infants since the infant brain is dynamically changing across development. Thus gray/white matter densities vary with age, as do skull and skin thickness, amount of cerebrospinal fluid, and the size of sub-arachnoid and other cortical spaces and it is clear that the electrocortical response as measured at

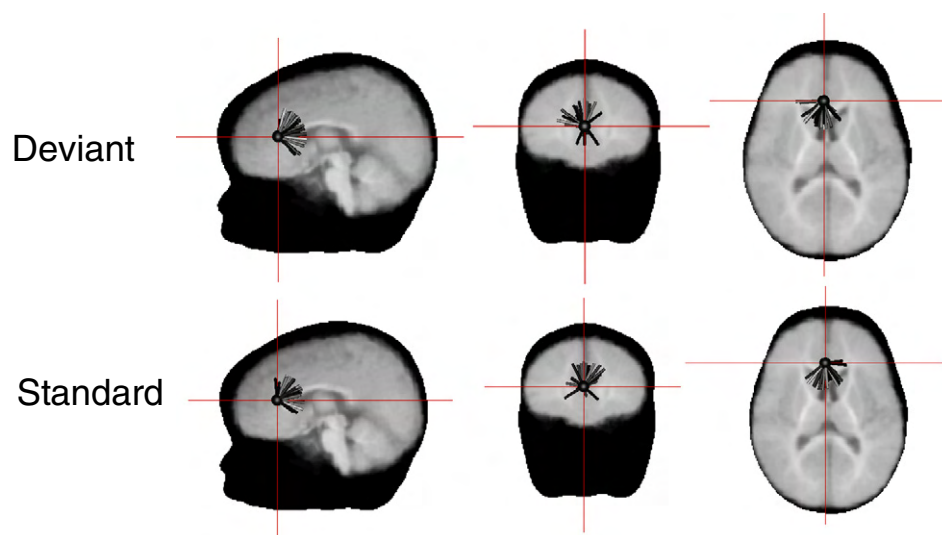


Fig. 9. Individual source orientations of the frontal source of the positive response to the deviant (first row) and to the standard (second row), plotted in the average infant brain template. The location of the frontal source was fixed based on grand average data, however the dipole orientation was allowed to freely vary.

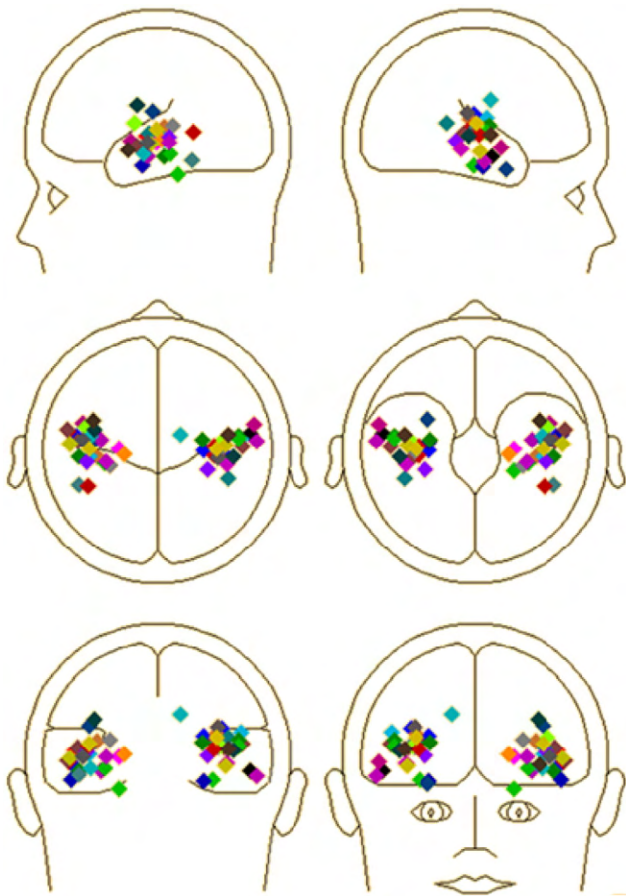


Fig. 10. Individual source locations of the positive response to the deviant for each infant at left and right temporal cortices are shown superimposed on a schematic head.

the scalp is influenced by all these changes in the brain and its surrounding structures (Nunez and Srinivasan, 2006). Therefore, the use of age-appropriate head models when attempting to localize ERP sources in infants is crucial and should ideally be taken into account in developmental studies. The findings detailed here that explicate the EEG/ERP sources in response to speech processing in infancy, as well as the techniques applied to this age group, promise to add to our understanding of the neural substrates that support early auditory processing abilities.

In this study, ERPs were mapped onto age-matched brain templates in order to: (1) examine source location of ERP generators of the response to consonant–vowel (CV) syllables in 6-month-old infants, and (2) analyze the strength and the time course of brain activations as infants process speech information. Realistic estimates were used for skull and scalp thickness, width of subarachnoid space, and for bone conductivity to facilitate accurate localization of the EEG/ERP sources. For 57% of the sample, the ERPs were mapped onto each infant's individual MRI; infants that did not have useable MRI data had their ERPs mapped onto a 6-month averaged MRI template. The main ERP responses elicited by CV syllables in 6-month-olds included a fronto-central positive deflection followed by a negative deflection. These responses were analogous to those previously reported in infant ERP studies on speech perception (Cheour et al., 1997, 1998, 2001; Dehaene-Lambertz and Baillet, 1998; Dehaene-Lambertz and Dehaene, 1994; Friederici et al., 2002; Friedrich et al., 2004; Leppänen et al., 2002; Pang et al., 1998; Rivera-Gaxiola et al., 2005, 2007; Shafer et al., 1998; Weber et al., 2004). In addition, during the fronto-central positive deflection, a frontal sink was identified that was visible at frontopolar locations as a negative deflection.

Source localization analyses identified three brain sources that were activated in infancy as a response to CV syllables: within left and right auditory temporal cortices, and notably in frontal cortex, within the anterior cingulate cortex (ACC). Therefore, the generators of ERP responses to CV syllables in infancy were localized in similar cortical areas to that reported in adults, however, ACC activation in infants significantly preceded that of the auditory temporal cortices. In adults, frontal (e.g. Deouell, 2007; Jemel et al., 2002; Opitz et al., 2002; Pulvermüller and Shtyrov, 2006; Rinne et al., 2000) and/or ACC (Crottaz-Herbette and Menon, 2006; Jemel et al., 2002; Waberski et al., 2001) activations have been found to follow that of auditory temporal cortex. We suggest that these timing differences could be related to maturation and to the construction of language-specific phonemic maps in temporal cortex. It could also be that infants, while learning their language, more easily activate attentional switching mechanisms when presented with speech signals.

4.1. Temporal auditory cortex activations

In the auditory domain, sources generated by speech processing in infants have primarily been located within the temporal lobes (Dehaene-Lambertz and Baillet, 1998), specifically, in superior temporal gyrus, (Imada, et al., 2006; van Leeuwen et al., 2007), with larger source strengths reported on the left as compared to the right (Dehaene-Lambertz and Baillet, 1998; van Leeuwen et al., 2007). Sources identified near to Heschl's gyrus have been thought to represent the activation of auditory cortex while processing transient auditory events and feature-specific sensory information (Čeponienė et al., 2002, 2003; Dehaene-Lambertz et al., 2002, 2006b; Näätänen, 1992; Näätänen and Alho, 1997; Näätänen and Picton, 1987; Opitz et al., 1999). In line with those studies, source generators of the ERP responses to CVs in the present study were located in both left and right auditory cortices. Even though the left auditory activation appeared to be larger than that on the right for the grand average distributed model (Fig. 6A), no significant laterality effect was found when statistical analyses were conducted on the source strength at the individual level. Thus, our results do not directly support a left-hemisphere advantage for processing speech information at 6-months of age.

4.2. Frontal cortex activation

Activation has been reported in frontal areas (Deouell et al., 1998; for a review, see Deouell, 2007; Giard et al., 1990; Jemel et al., 2002; Oknina et al., 2005; Opitz et al., 2002; Rinne et al., 2000; Wild-Wall et al., 2005), and in the cingulate cortex (Baudena et al., 1995; Crottaz-Herbette and Menon, 2006; Jemel et al., 2002; Oknina et al., 2005; Waberski et al., 2001; Wild-Wall et al., 2005) in adult ERP and/or fMRI auditory oddball experiments with tone stimuli. In addition, in adults processing speech stimuli, left inferior frontal (Petersen et al., 1988; for a review refer to Pulvermüller and Shtyrov, 2006; Rossell et al., 2001) and ACC activation (Petersen et al., 1988; Rossell et al., 2001) has been reported. ACC, among other structures, was also activated during word reading (Fiez and Petersen, 1998) and word generation (Crosson et al., 1999). In infants, activation in right dorsolateral prefrontal cortex was seen, using an fMRI paradigm, for 2–3 month old awake infants who were listening to forward sentences (Dehaene-Lambertz et al., 2002), and activation of inferior frontal regions was also seen in 2 and 3-month-old listening to their native language (Dehaene-Lambertz et al., 2006b; 2010). As noted, in a previous study with 6-month-olds, we identified a small ACC activation in the grand-averaged ERPs to tone doublets presented using a passive oddball paradigm (Hämäläinen et al., 2011). However, activation of ACC generators to the processing of speech signals has not, to date, been reported in infants. Using discrete and distributed source models, ACC activations on the grand average ERP were found and modeled for the positive response to both standard and

deviant stimuli but for the negative peak, only for the standard stimulus and only with the distributed source model.

The ACC has been implicated in allocation of attentional resources during the processing of cognitive and emotional information (Allman et al., 2001; Botvinick et al., 2004; Bush et al., 2000; Devinsky et al., 1995; Harman et al., 1997; Posner and Rothbart, 1998). It has 2 main subdivisions, each related to a different function but reciprocally linked: a dorsal, more superior cognitive subdivision and a rostral/ventral affective subdivision (Allman et al., 2001; Bush et al., 2000; Harman et al., 1997; Mesulam, 1998). Activation of the ACC during active auditory oddball tasks has been reported in adults, with effective connectivity analyses showing increased ACC influences on Heschl's gyrus and on superior temporal gyri (Crottaz-Herbette and Menon, 2006). The ACC was found to be a major source of the N2b-P3a attention-related components providing evidence of interaction between the ACC and auditory sensory regions (Crottaz-Herbette and Menon, 2006). ACC activation has also been reported during tasks requiring focused attention such as the generation of word associations, whereas a decrease in activation has been observed when the task becomes more automatic (Petersen et al., 1988). Additionally, generators of potentials correlated with the orienting response toward potentially significant auditory stimuli have been found in the ACC when measured with intracranial electrodes (Baudena et al., 1995).

ACC activation observed in passive paradigms has been related to involuntary switching of attention to changes occurring in the auditory environment (Waberski et al., 2001). The stronger ACC activation reported in this study for 6-month-olds presented with CV syllables in a passive oddball paradigm, in contrast to the ACC activation seen in 6-month-olds in a very similar study but using non-speech stimuli (i.e. Hämäläinen et al., 2011), might be related to involuntary switching of attention. During the early stages of language acquisition, infants show a marked preference for speech signals in their native language (Kuhl et al., 2008; Sebastián-Gallés, 2007) and prefer speech to non-speech sounds (Vouloumanos and Werker, 2004). This fact might explain why speech sounds would induce involuntary switching of attention toward speech in early infancy. Perhaps, during periods of language learning, increased levels of perceptual vigilance might enhance involuntary attention switching when additional evaluation of auditory events seems warranted. Changes that occur unexpectedly in the auditory environment do elicit an involuntary shift in attention (Alho et al., 1998b; Escera et al., 2000; Sussman et al., 2003), thus alerting individuals about potentially significant stimuli that will need further processing. This is an essential survival mechanism, and is critical for the acquisition of new skills during periods of development and learning (Gomes et al., 2000; Sussman et al., 2003). Across intensive learning periods, for example during language acquisition, infants may be more vigilant, scanning the auditory environment, ready to perceive and process auditory input in order to optimize the language learning process. Electrophysiological evidence from studies in children and adults have shown increases in the mismatch negativity (MMN), P3a (an ERP component that indexes involuntary switching of attention) and late negativity (related to reorienting of attention) during intense exposure to or learning of non-native languages (Shestakova et al., 2003), non-native contrasts (Menning et al., 2002) and tone sequences (Gottselig et al., 2004). Even when adults are learning a second language, involuntary switching of attention has been proposed as the main mechanism driving differences in ERP responses between early and late bilinguals (Ortiz-Mantilla et al., 2010b). Given that speech is the most common auditory stimulus in the infants' environment (Dehaene-Lambertz et al., 2006a), and during the first months of life infants are setting up phonemic maps, and acquiring information about the specific properties of their native language (Jusczyk, 2002; Shukla et al., 2011), it would not be surprising if speech stimuli served as a powerful trigger of infant attention.

Lastly, we consider the timing of ACC activation, one of the main findings in this study. Whereas adults activate the ACC generator

after the temporal generators when processing sounds, (speech: Pulvermüller and Shtyrov, 2006; non-speech: Crottaz-Herbette and Menon, 2006; Jemel et al., 2002; Waberski et al., 2001), 6-month infants activate the ACC earlier than auditory temporal cortices. Although the neural pathways involved in this response have not as yet been elucidated, several potential mechanisms might be suggested. These include the lack of mature inhibitory control mechanisms in the first year of life, and the faster maturational time course of the ACC as compared to the auditory areas.

Development of inhibitory control mechanisms occurs gradually throughout the first years of life. Although some primitive forms of executive control can be seen by the end of the first year, the executive attention present in infancy (Posner et al., 2007) is still quite immature at 24 months-of-age, largely maturing between 3 and 4 years (Berger et al., 2007; Posner and Rothbart, 2000). Executive functions exert slower, top-down, goal-directed attentional control. Due to young infants' lack of fully mature executive function, it is plausible that during infancy, faster bottom-up, stimulus-driven attentional mechanisms might lead sensory information processing, explaining the timing of ACC as compared to temporal lobe activation seen here. Moreover, as only minimal evidence of successful inhibitory control has been documented below the age of 3 years (Posner and Rothbart, 1998), we can posit that the inhibition of attentional processes is less well developed in young infants.

An additional mechanism that may contribute to earlier ACC activation to speech stimuli in infants as compared to adults might be the level of maturation of the auditory cortex and reciprocal pathways. Brain structures mature from posterior to anterior, inferior to superior, and medial to lateral in an ontogenically and phylogenetically organized pattern (Barkovich et al., 1988). In line with this postulate, even though auditory pathways at the brain stem level are relatively mature at birth, thalamo-cortical pathways and auditory cortices are still developing, and are less well-myelinated during the first year of life than previously thought (Moore and Guan, 2001). It has been suggested that auditory processing in infancy is primarily accomplished with a mature cochlea and brain stem, in conjunction with a cortex that only has mature axons in layer I (Hall, 2000; Moore, 2002). Thus, ERP responses in the first 6 months of life are likely conducted by immature afferent axons reaching marginal layer I, and the longer latencies observed in infants as compared to adults reflects slower conduction by relatively unmyelinated axons (Moore and Linthicum, 2007). Thalamo-cortical afferents carrying inputs from the lower levels of the auditory system will mature at around 5 years of age, while complete maturation of the auditory cortex is attained at approximately 11–12 years of age (Moore, 2002). Likewise, language related fronto-temporal regions will fully mature only at later ages, given reports that those areas have a myelinated white matter volume of 10% in 50% of 18-month-old children and in 90% of 35-month-old children (Pujol et al., 2006). Conversely, the ACC, anatomically part of the limbic system involved in the processing of emotions (Posner and Rothbart, 1998), is a structure phylogenetically older than neo-cortical areas (Kier et al., 1995; Mega et al., 1997; Posner et al., 2007; Schneider and Vergesslich, 2007), and may mature faster than the newer, more layered cortical structures. Therefore, it may not be surprising that during infancy the ACC generators activate sooner than temporal generators. As children continue to develop, and a more mature, adult-like brain structure and processing mechanisms are achieved, there may be a reversal in the activation timing of ERP generators. However, only longitudinal source localization studies can confirm this hypothesis.

In summary, this study aimed to identify, localize and investigate the time course of ERP generators to CV stimuli in infancy using age-appropriate, realistic head models. The results presented here are both novel and thought provoking and hopefully will further our understanding of infant speech processing and the putative role of the anterior cingulate cortex in speech perception.

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