



Source localization of event-related potentials to pitch change mapped onto age-appropriate MRIs at 6 months of age

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ABSTRACT

Auditory event-related potentials (ERPs) have been used to understand how the brain processes auditory input, and to track developmental change in sensory systems. Localizing ERP generators can provide invaluable insights into how and where auditory information is processed. However, age-appropriate infant brain templates have not been available to aid such developmental mapping. In this study, auditory change detection responses of brain ERPs were examined in 6-month-old infants using discrete and distributed source localization methods mapped onto age-appropriate magnetic resonance images. Infants received a passive oddball paradigm using fast-rate non-linguistic auditory stimuli (tone doublets) with the deviant incorporating a pitch change for the second tone. Data was processed using two different high-pass filters. When a 0.5 Hz filter was used, the response to the pitch change was a large frontocentral positive component. When a 3 Hz filter was applied, two temporally consecutive components associated with change detection were seen: one with negative voltage, and another with positive voltage over frontocentral areas. Both components were localized close to the auditory cortex with an additional source near to the anterior cingulate cortex. The sources for the negative response had a more tangential orientation relative to the supratemporal plane compared to the positive response, which showed a more lateral, oblique orientation. The results described here suggest that at 6 months of age infants generate similar response patterns and use analogous cortical areas to that of adults to detect changes in the auditory environment. Moreover, the source locations and orientations, together with waveform topography and morphology provide evidence in infants for feature-specific change detection followed by involuntary switching of attention.

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Introduction

Detecting subtle changes in the auditory environment is a crucial ability for laying down foundations for language. During the first year of life infants must attend to meaningful change in the auditory environment in order to associate initially meaningless utterances with semantic context to form their mental lexicon. In line with this premise, several studies using behavioral testing techniques have shown that perception of non-speech as well as speech auditory stimuli during the first year of life is highly associated with and predictive of later language skills (Benasich et al., 2002; Choudhury et al., 2007; Kuhl, 2004; Tsao et al., 2004).

However, it can be difficult to reliably assess infants' auditory perception using only behavioral methods. An alternative and converging method of investigating auditory information processing

abilities is to measure the electrical activity of the brain by examining stimulus-locked cortical activity, i.e. event-related potentials (ERPs) to varying acoustic stimuli. Corroborating the usefulness of infant electrocortical measures, a number of studies have found that EEG/ERPs in early infancy to both non-speech and speech stimuli reliably predict to later language outcomes (Benasich et al., 2006; Choudhury and Benasich, 2010; Guttorm et al., 2005, 2010; Leppänen et al., 2010). In order to better understand the relationship between auditory perception and language it is important to investigate the neural processes that underlie the processing of language-associated auditory information. Just as important as measuring auditory change detection and processing speed is the ability to identify which brain areas are actively involved in this process as maturation progresses. Until recently, it has been quite difficult to reliably estimate which brain areas contribute to the EEG/ERP response as recorded from the scalp, given that age-appropriate templates from normally developing, healthy infants were not readily available. In the visual domain, infant visual attention and recognition memory has been explored with source localization techniques (e.g. Reynolds and Richards, 2005, 2009) that take important steps toward using appropriate developmental head models. However, age-appropriate infant brain

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templates have not been available to aid developmental mapping of auditory information processing. In the present study, the results of source localization of EEG/ERPs were mapped to age-appropriate magnetic resonance images (MRIs) to identify auditory change detection processes in 6-month-old infants.

A change in the auditory environment elicits an ERP component termed the mismatch negativity (MMN; Näätänen et al., 1978; Näätänen, 1992). In adults, the MMN occurs approximately 150–200 ms after the onset of a rarely occurring deviant sound feature compared to sounds (or sound features) repeated often. The MMN is negative in voltage at frontal and central scalp areas with reversal into positivity below the Sylvian fissure. Most studies have localized generators of the MMN to the superior temporal gyrus near Heschl's gyrus (e.g. Frodl-Bauch et al., 1997; Ha et al., 2003; Huotilainen et al., 1998; Korzyukov et al., 1999; Opitz et al., 1999a,b, 2002; Rinne et al., 2000; Waberski et al., 2001; for a review, see Näätänen et al., 1978). Further, some studies have shown activation in frontal areas (e.g. Deouell et al., 1998; Giard et al., 1990; Rinne et al., 2000; for a review, see Deouell, 2007), with this activation localized to the right inferior frontal gyrus (e.g. Jemel et al., 2002; Opitz et al., 2002), however, generators have also been identified in anterior cingulate cortex (Waberski et al., 2001) or cingulate cortex (Jemel et al., 2002). Other sources have also been suggested, based on isolated findings, for example, in the inferior temporal gyrus (Waberski et al., 2001).

The sources identified near Heschl's gyrus have been thought to represent the activation of auditory cortex in processing feature-specific sensory information (Näätänen, 1992; Näätänen and Alho, 1997). The frontal source has been hypothesized to represent activation of processes related to the initiation of an attention switch to the sound (Näätänen, 1992) or to represent a stimulus contrast enhancement process (Opitz et al., 2002).

The MMN response is followed by a P3a component when the change in the auditory environment is large in magnitude. The P3a is thought to reflect an attention switching process in the brain (Polich, 2007). This component has a positive voltage at frontal areas. The generators for this response have not been definitively localized but the main generators have been suggested to lie in the dorsolateral frontal cortex and temporo-parietal junction, with several other sources reported in, for example, supramarginal and cingulate gyrus, based on lesion studies and intracranial recordings (Escera et al., 2000; Friedman et al., 2001; Halgren et al., 1998; Polich, 2007). Several studies using ERP, MEG and fMRI data have also shown activation in the superior temporal gyrus (Alho et al., 1998; Dien et al., 2003; Opitz et al., 1999b).

However, relatively little is known about the source structure of the mismatch response in infancy. Even though many studies have shown adult-like MMN responses in school-aged children, albeit with slightly larger amplitudes and longer latencies (e.g. Gomot et al., 2000; Hämäläinen et al., 2008; Kurtzberg et al., 1995; Shafer et al., 2000), there is much controversy concerning the MMN response during the first years of life. Some studies have found an adult-like negativity with similar latency and distribution in response to various sound changes measured during the first year of life (e.g. Alho et al., 1990; Ceponiene et al., 2002; Cheour et al., 1998; Kushnerenko et al., 2007, 2002) while others have found a large positive component with longer latency (e.g. Benasich et al., 2006; Leppänen et al., 2004, 1997; Morr et al., 2002; Sambeth et al., 2009).

The finding of opposite polarity for mismatch responses (MMRs) in infants has been speculated to be due to several different factors. One possible factor is the high-pass filter setting used in data processing. The large positive mismatch response can obscure the smaller negative response underneath it (He et al., 2007; Weber et al., 2004). Indeed, He et al. (2007) found an MMN-like negativity followed by a large positivity in the same sample of 2–4-month-old infants, when they used a 3 Hz high-pass filter, but not when they used 1 Hz high-pass filter. This finding suggests that two separate

processes may be related to change detection in infants. A second possible factor is the maturational level of the infant. For example, Leppänen et al. (2004) demonstrated that when newborns were classified according to their maturational level (estimated using gestational age and heart measures), the polarity of the mismatch response was more positive in infants that were more mature. However, at older ages the pattern of change due to maturation can be different. Thus there is uncertainty as to whether the negative and positive MMRs reflect the same process and whether this process is the same as that seen in the adult MMN (Kushnerenko et al., 2007, 2002).

Most previous studies investigating the change detection or mismatch response in infants have examined only 2–8 scalp locations and have focused mainly on changes in the waveform on these scalp locations across development (e.g. Kushnerenko et al., 2002). Other studies using larger electrode sets have examined changes in the topographical voltage maps during development (e.g. He et al., 2007). One study examined a mismatch-like response in stimulus trains to speech sounds using a dipole source model (Dehaene-Lambertz and Baillet, 1998). They found sources to be located in the posterior and dorsal temporal areas in ca. 4-month-old infants. However, to our knowledge, there are no studies on source localization of the auditory mismatch response to non-linguistic stimuli in the first year of life. In the present study we used both discrete (dipole model) and distributed (classic LORETA recursively applied; CLARA) source analyses to examine changes in source location, orientation and waveform in 6-month-old infants. Source localization could help determine whether the positive response seen is indeed similar to the adult MMN or whether it reflects attention-related responses such as the P3a. If the positive response in infants is a P3a-like response it should be preceded by a negative response. We would expect the source structure for the two responses (frontocentral negativity and positivity) to be different if they represent MMN and P3a-like processing steps.

Materials and methods

Participants

The final sample of participants in the present study was 39 (21 boys; 18 girls) full-term (mean gestational age: 40.0 weeks, SD: 1.4), normal-birth weight (mean: 3520.0 g, SD: 452.9) infants who had clean ERP data. Originally 55 children were tested for ERPs but 16 were excluded due to high noise levels or neurological problems. ERPs were obtained from infants at 6 months of age and MRIs at 6–7 months during two separate sessions. The children were in natural, unседated sleep during MRI acquisition and awake during EEG recording (see Paterson et al., 2004; Liu et al., 2008). The children were typically developing infants from urban and suburban communities in New Jersey. None of the children had hearing problems, history of language-learning impairments or repeated occurrence of otitis media.

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 were compensated for their time.

EEG

Stimuli

The stimuli were tone pairs (doublets). The tones were 70 ms in duration including 5 ms rise and fall times. The tones within each pair were separated by a 70 ms silent interval.

Standard tone doublets consisted of two identical tones with a fundamental frequency of 100 Hz (15 harmonics, 6 dB roll-off per octave) while the deviant tone doublets consisted of two different

tones; the first one having a fundamental frequency of 100 Hz, and the second 300 Hz. There were 125 (15%) deviant tone doublets and 708 (85%) standard tone doublets presented within the experiment. Between each deviant stimulus, there were 3–12 standard stimuli interposed. The offset-to-onset interval between the tone doublets in the experiment was 705 ms (for further details, see Benasich et al., 2006). The stimulation was free-field from two loudspeakers located to the left and right sides of the infant at approximately 75 dB SPL.

Procedure

The EEG was recorded from awake 6-month-old infants sitting quietly on their parents' laps. To minimize children's movement during recording silent movies were played. In addition, if necessary, an experimenter used toys and a silent puppet show to keep the children calm and engaged.

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

The EEG was re-referenced off-line to an average reference and bandpass filtered at 0.5–25 Hz. The data was segmented with 300 ms pre-stimulus time and 915 ms post-stimulus time. A hundred milliseconds before stimulus onset (i.e. before the onset of the first tone in the pair) was used as the baseline. Eye movements were corrected using the BESA software's automatic correction algorithm (PCA method). Epochs containing artifacts exceeding $\pm 200 \mu\text{V}$ from the baseline were excluded from averaging (96 trials left on average, range: 88–116). For the standard response only pre-deviant epochs were averaged to ensure similar signal-to-noise ratio between the responses to the standard and deviant stimuli. The data was also examined using a high-pass filter of 3 Hz.

Magnetic resonance imaging

MRIs 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., 2010; 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, and bandwidth = 15.63 kHz.

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

To create an MRI template for 6-month-olds, the MRI images were affine transformed into the MRI space of an infant with median age and combined into an average. The average MRI was then aligned into the AC–PC plane and transformed into Talairach space.

Source analyses

Parameters for skull thickness and subarachnoid width were estimated from the individual AC–PC aligned MRIs. The thickness was measured from four points at the coronal and transverse slices using the AC and AC–PC planes, respectively. For the transverse slice, the points were chosen to be at the level of the anterior pole of the superior frontal gyrus and at the level of the lateral occipital gyri, and for the coronal slice, the points were selected at the level of the superior frontal gyrus and superior temporal gyrus (see Fig. 1). An

average of the values across these measurement points was used as parameters in the source localization. An average of these values was used for all individuals (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 previous estimates in the literature (for skull: Letts et al., 1988; for subarachnoid width: Lam et al., 2001). Because the skin was not clearly visible from the MRIs we used an estimate of 2.5 mm based on a report from neonate autopsies showing an average scalp thickness of 2 mm (Hull, 1972).

Conductivity of the skull bone was estimated by fitting an exponential function on the data available from 3–9 years in the BESA Research 5.3 (Brain Electrical Source Analysis) software. The equation for the exponential function was $0.064 * e^{-0.195 * \text{age in years}}$ giving an estimate of 0.0581 at 6 months.

The ERP data was combined with individual MRI images (N = 21) or with an age-appropriate average MRI (based on 19 MRIs) when an individual MRI was not available using BESA and BrainVoyager QX programs. The standard electrode positions were fitted onto the AC–PC aligned MRI of the child and the reconstructed skin surface and the Talairach transformed MRI were imported into BESA.

We used two different filter settings (0.5 and 3 Hz high-pass) following the findings of He et al. (2007). For both filter settings we identified the peaks from the grand average and from the individual ERPs and used the time window of ± 20 ms around the peak for dipole fitting. In addition, peaks were picked from the individual, original ERP data at the FC3 and FC4 channels (showing maximal activation) and analyzed using paired-sample t-tests to ensure that the responses to the standard and deviant stimuli were statistically different (i.e. discriminable).

After determining the tissue thickness and conductivity parameters and importing the age-appropriate MRIs into BESA, a dipole source model (Scherg and von Cramon, 1985) was applied to the ERP data. In addition, a confirmatory distributed source model was calculated using the Classic LORETA Recursively Applied (CLARA; Hoehstetter et al., 2010) method at the time window of ± 20 ms around the peak. A 4-shell ellipsoidal head model was used for all source analyses.

Results

The ERP waveforms followed closely previously reported studies using the same paradigm but an independent sample (Benasich et al., 2006; Choudhury and Benasich, 2010).

Fig. 2 shows that the response to the standard stimuli was close to the baseline during the change detection response to the deviant stimuli. Paired-sample t-tests on the FC3 and FC4 channels showed highly significant differences between the peak amplitudes for the responses to standard compared to the deviant stimuli ($t(38) > 10.83$, $p < 0.001$ for both channels). Thus no difference wave was calculated in order to preserve the better signal-to-noise ratio of the original ERP response as compared to the difference wave. The response to the deviant stimulus showed a large positive–negative complex in response to the deviant tone at 408 and 540 ms from the tone pair onset (Fig. 2). The large positive mismatch response had a bilateral frontal distribution with reversal of polarity into negative voltages at the parietal and occipital areas as seen in the top part of Fig. 3. The bottom part of Fig. 3 displays the current source density (CSD) maps showing a similar distribution, with sources in bilateral frontocentral areas and sinks in bilateral parietal and occipital areas.

Source analyses using 0.5 Hz high-pass filter

Sources were examined first from the grand average. Fig. 4 shows the dipole locations together with the CLARA solution. Both the dipole model (residual variance (RV) 4.5%) and CLARA showed bilateral activation close to the auditory cortex. Fig. 5 shows the source waveforms from the left and right hemispheric dipoles. When

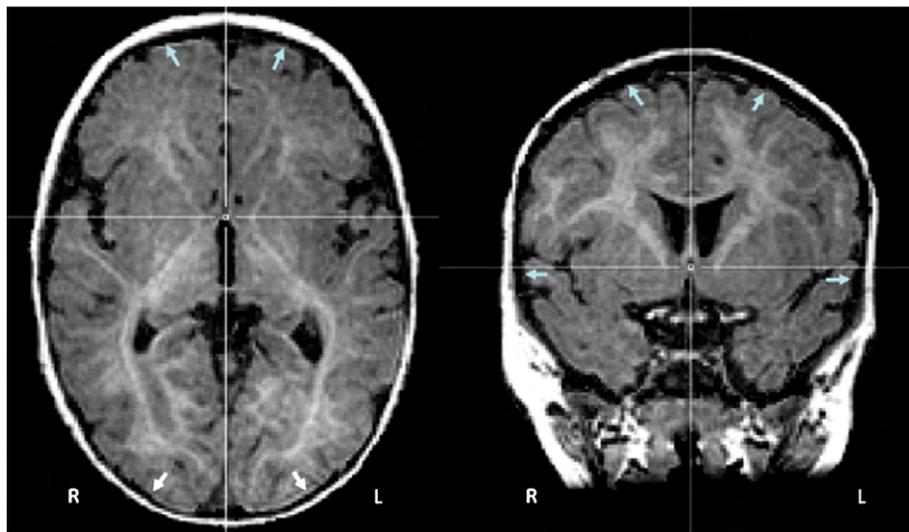


Fig. 1. An example MRI with arrows showing locations for bone and subarachnoid space measures on the transverse (left) and coronal slices (right). An average of these eight measurement points was used as estimates in source localization.

compared to the original data in Fig. 2, it can be seen that the source waveforms follow closely the original ERP waveforms indicating a good model fit to the data.

In addition, a third dipole could be fitted to the mid-frontal area (near anterior cingulate cortex, ACC) explaining an additional 3.0% of the variance (RV: 1.5%). Based on the grand average the main activation for the positive infant change detection response originates near the auditory cortex. The source orientations show an oblique relative to the supratemporal plane.

In the next step, two dipoles were fitted to the individual ERP data for each infant. Fig. 6 shows the dipole locations based on each infant's individual ERP response. Again, the dipole models showed that the main activation was near the auditory cortices with a mean residual variance of 11.0% (SD: 5.7). However, the third frontal component was unstable in the individual data probably due to the weak signal strength. Thus we did not include this component in further analyses.

Source analyses using 3 Hz high-pass filter

Using a 3 Hz high-pass filter revealed a smaller negative response occurring before the larger positive response as shown in Fig. 7. The negative peak reached maximum at 312 ms (172 ms after deviant sound onset). The peak amplitudes for the negative and positive responses showed differences between the standard and deviant

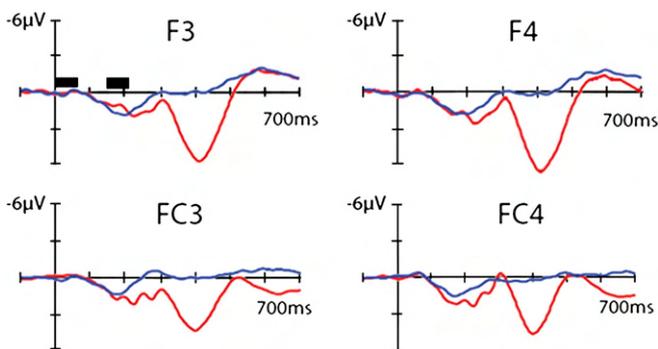


Fig. 2. Grand average waveforms at 6 months of age (N = 39). Response to the standard stimulus is in blue and to the deviant stimulus in red. Negative voltages are plotted up. The black boxes indicate the presentation time course of the tone doublet.

stimuli at the FC3 and FC4 channels ($t(32) > 8.05$, $p < 0.001$; $t(36) > 11.96$, $p < 0.001$, for the negative and positive responses, respectively, at both channels). The voltage and CSD distributions at the peak latency of the positive response were similar when either 0.5 or 3 Hz filter was used (see Figs. 3 and 8). The voltage and CSD distributions at the peak latency of the negative response showed small differences when compared to the positive response (Fig. 8) suggesting differences in source locations and/or orientations.

The grand average-based dipole solution for the generator locations for both the negative and positive responses are shown in Fig. 9. For both of the responses a dipole could be fitted into the left and right temporal areas. However, for the negative response no frontal component could be fitted whereas a frontal dipole could be fitted for the positive response. Again, the frontal dipole was close to the anterior cingulate cortex. However, the CLARA solution showed ACC activation for both of the responses. The two-dipole model for the negative response explained 80.6% (RV: 19.4%) of the data and for the positive response 93.0% (RV: 7.0%) of the data with the frontal dipole

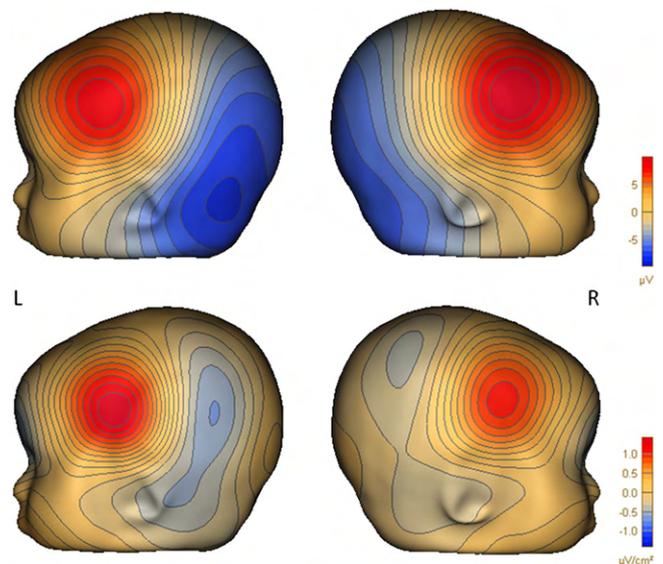


Fig. 3. Voltage (above) and current source density (below) maps at the peak of the positive response at 6 months of age plotted on the reconstructed infant head based on an average MRI.

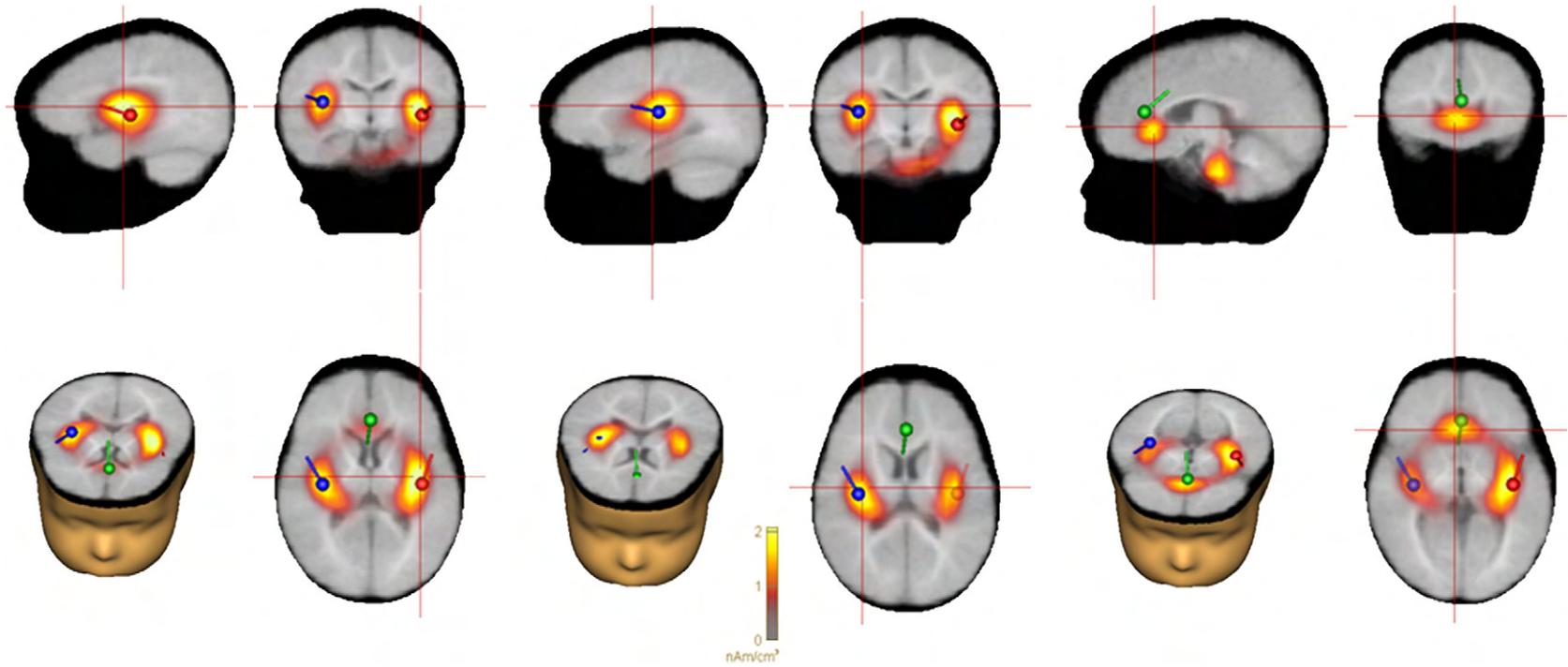


Fig. 4. Dipole and CLARA solutions for the peak (± 20 ms) of the positive deflection based on the grand average at 6 months of age. The three different source loci are highlighted in the average infant brain template.

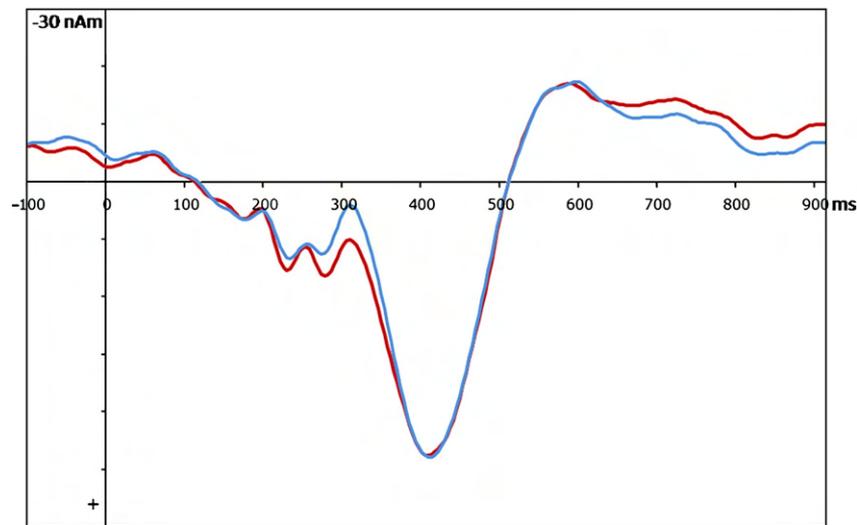


Fig. 5. Source waveforms (N = 39) for the left (blue) and right (red) dipoles close to auditory cortex. Negative is plotted up; vertical scale is in 10 nAm steps.

explaining an additional 3.0% of the data (RV: 4.0%). As can be seen from Fig. 9, the negative and positive responses revealed by the stricter high-pass filter seemed to have generator locations close to each other, adjacent to the auditory areas.

At the individual level using a two-dipole model, the negative wave could be reliably modeled in 33 infants (mean RV: 19.2%, SD: 9.4) whereas the following positive response was reliably modeled in 37 infants (mean RV: 12.2%, SD: 5.9) using the stricter filter. Data from three children were excluded because of unstable fit using the 3 Hz filter. When the source location coordinates were compared in

repeated measures ANOVAs (component [negative, positive] × hemisphere [left, right]), no differences were found between the x- and y-coordinates for the negative and positive responses. However, the z-coordinates of the negative response were inferior (by 3.9 mm on average) to those of the positive response (component main effect: $F(1,32) = 4.519, p < 0.042$). Also, the sources in the left hemisphere were inferior (by 6.5 mm on average) to those in the right hemisphere for both negative and positive components (hemisphere main effect: $F(1,32) = 9.276, p < 0.005$).

The source waveforms again closely followed the original data as shown in Fig. 10. Even though the source waveform appears to be slightly larger over the left hemisphere, repeated measures ANOVA (component × hemisphere) showed no hemispheric differences for the peak activation strength.

Discussion

Auditory change detection mechanisms in infants are not very well understood. ERPs to acoustic change have shown negative and/or positive voltages across different studies that have been recorded over the same scalp areas (e.g. Cheour et al., 1998; Leppänen et al., 2004). The negative peak has often been interpreted as an infant MMN response while the positive peak has been interpreted either as a precursor of adult MMN (e.g. Sambeth et al., 2009) or as an attention-related component (e.g. He et al., 2007). The present study showed that at 6 months, infants discriminate auditory changes as indexed by

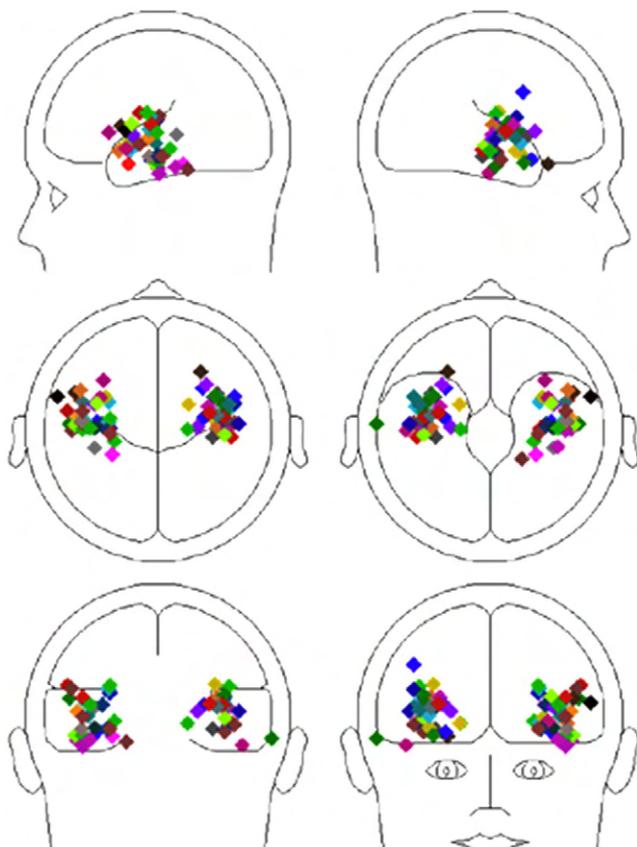


Fig. 6. Individual source locations for the positive peak with 0.5 Hz filter for the 6-month-old infants (N = 39) superimposed on the schematic head.

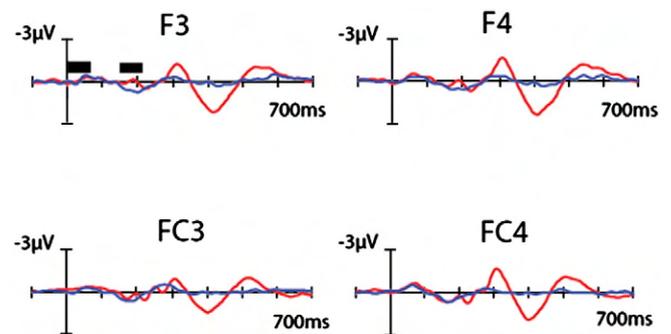


Fig. 7. Grand average waveforms with a 3 Hz high-pass filter. Response to the standard stimulus is in red and to the deviant stimulus in blue. Negative voltages are plotted up. The black boxes indicate the presentation time course of the tone doublet.

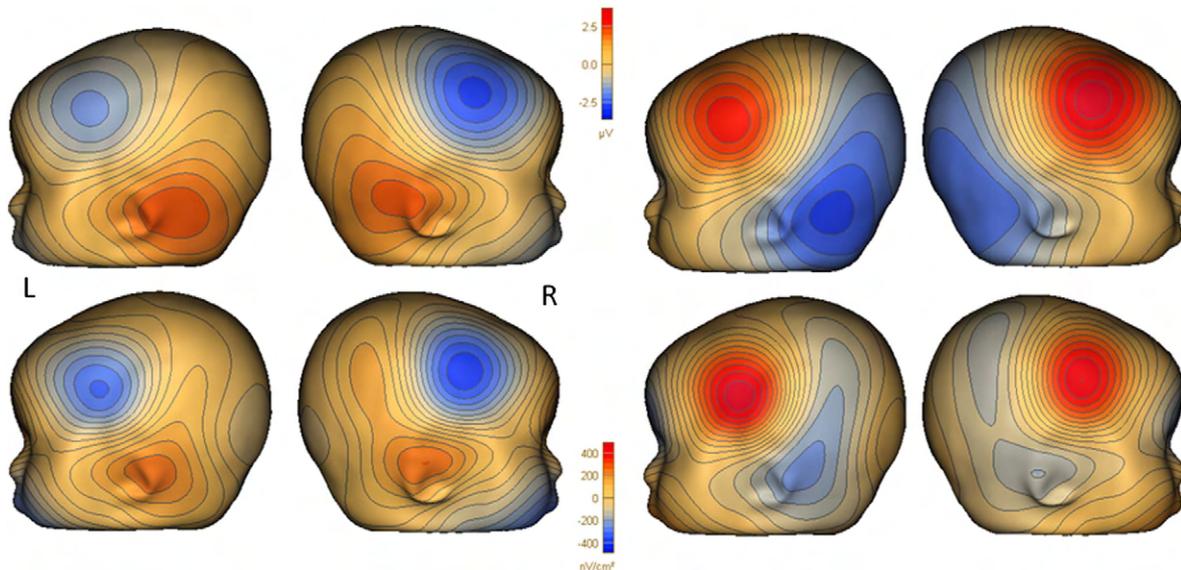


Fig. 8. Voltage (above) and current source density (below) maps at the peak of the negative (left) and positive (right) responses at 6 months of age plotted on the MRI reconstructed infant head.

a supratemporal source with negative voltages over frontal areas followed by an attention switching mechanism localized to the supratemporal and frontal cortices.

The largest response to the pitch change was a frontocentral positivity peaking at 268 ms. This response was preceded by a smaller frontocentral negative response at 164 ms that was clearly visible after applying a strict 3 Hz high-pass filter. The result is in line with He et al. (2007) that showed an increase in the negative component to a pitch change in piano tones at 180–210 ms in 2–4-month-old infants when a 3 Hz high-pass filter was used, as compared to a 0.5 Hz filter. Similarly, Weber et al. (2004) found an increase in the amplitude of the negative component in 5-month-old infants after changing the high-pass filter from 0.3 Hz to 1 Hz. Speech sounds with a stress pattern change were used to elicit the change detection response.

For the large positive response at 268 ms, both the dipole source model and the distributed source model (CLARA) showed activation in auditory areas, but the orientation of the electrical field was not consistent with the adult P3a, although the location was feasible for P3a (e.g. Alho et al., 1998; Opitz et al., 1999b). We found that in infants the orientation of the sources was more lateral compared to that found in adults (e.g. Huotilainen et al., 1998). In support of the source localization finding, the voltage and current source density maps also showed clearly bilateral distributions consistent with a more lateral source orientation. The more lateral orientation of the source in infants could be due to a different orientation of the gyri in the temporal areas of infants as compared to that in adults (see Pienaar et al., 2008, for an example of the changing gyral angles during development).

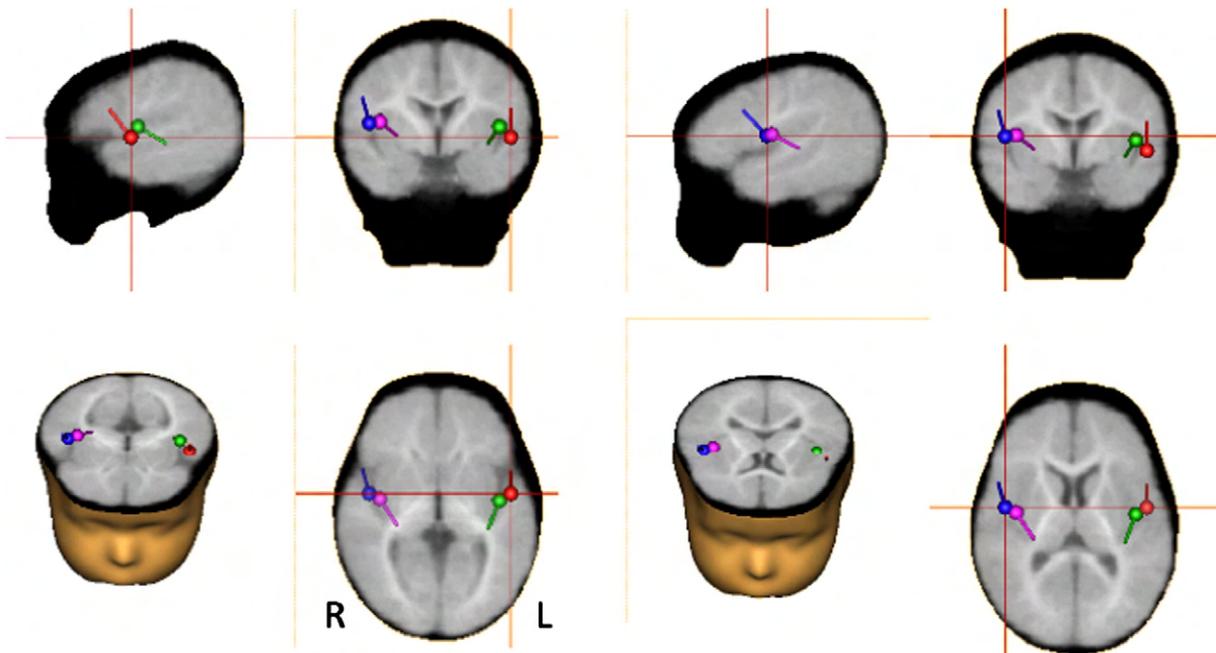


Fig. 9. Dipole source solutions are shown at 6 months of age based on the grand average with a 3 Hz high-pass filter. The crosshair is at the left and right dipole locations for the negative (red and blue) response in the average infant brain template. The positive response is represented by the pink and green dipoles.

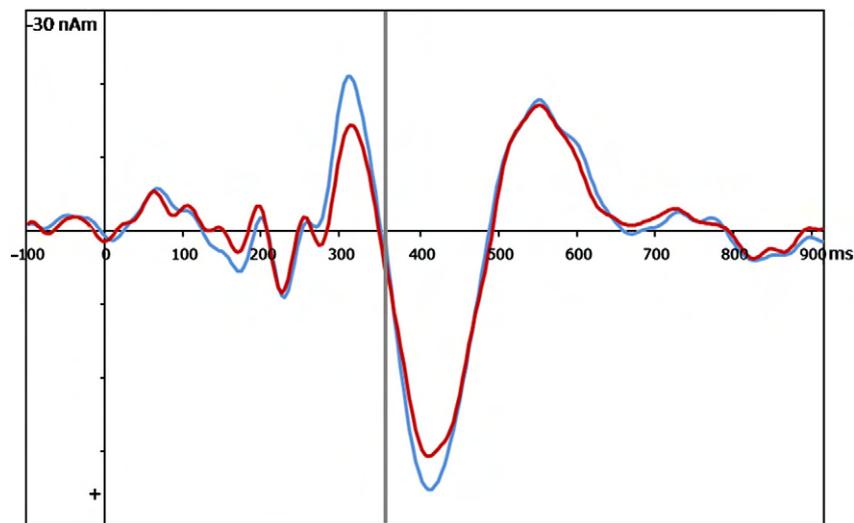


Fig. 10. Source waveforms for the left (blue) and right (red) dipoles adjacent to auditory cortex. The waveforms before the gray line are based on fitting at the negative peak ($N = 33$) and after the gray line at the positive peak ($N = 37$). Negative current is plotted up; vertical axis marks denoting 10 nAm.

The source activity of P3a in adults has been localized near the auditory areas in several previous studies using different imaging methods. One study examined the P3a using principal component analyses (PCA) and found sources in the temporo-parietal junction or in primary auditory cortex, depending on the rotation method used for the PCA (Dien et al., 2003). Another study using both ERPs and fMRI methods, showed fMRI activation in the middle part of the superior temporal gyrus for unattended novel sounds (Opitz et al., 1999b). Further, an MEG study in adults showed the generator locations for the P3a to be adjacent to auditory cortex (Alho et al., 1998). The activation near the superior temporal gyrus reported in these previous studies in adults would correspond to the infant source locations we identified for the positive response.

Interestingly a small frontal activity was found in the CLARA and dipole solutions for the positive response converging near the anterior cingulate cortex (ACC). This result is in line with the ACC activation for the P3a component found in adults engaged in active oddball ERP experiments (e.g. Crottaz-Herbette and Menon, 2006) and in intracranial recordings during active discrimination tasks (Baudena et al., 1995). The ACC activation seen has been suggested to reflect reallocation of attentional resources or monitoring of conflicts in the auditory (or other sensory) stream (Botvinick et al., 2004; Crottaz-Herbette and Menon, 2006). Thus it is possible that the positive response found in infants reflects attention switching mechanisms that are carried out by networks in the auditory and frontal cortices. Later in development other brain areas, such as the temporo-parietal junction and dorsolateral frontal cortex (Halgren et al., 1998; Polich, 2007), may become involved when denser cortico-cortical connections are more developed.

The sources of the negative change-detection response in infants were also located near auditory cortex with almost identical generator locations to the positive peak but with opposite polarity. The auditory cortex activation seen in infants is in line with adult studies on MMN source locations (for a review, see Näätänen et al., 2007). However, despite the close proximity of the generator locations, the source of the negative peak was about a half centimeter inferior (which was statistically significant) to the generators of the positive peak. Also, the source orientations for the negative response were closer to the tangential direction than those for the positive response, which showed a more oblique angle in relation to the supratemporal plane. The orientation for the negative response is similar to that found for the adult MMN, as it has the sink of the electrical field oriented tangentially producing maximal negative voltages at the midline frontocentral electrodes (e.g. Frodl-Bauch et al., 1997). The CLARA solution for the negative peak

showed activation in the ACC, similar to that found for the positive peak. However, the dipole could not be fitted for this frontal source, suggesting that the frontal source was not stable even in the grand averaged data.

The small difference in source location and orientation suggests that the two consecutive responses represent *separate* change detection-related processes that have been generated in adjacent cortical areas. Given the polarity, timing, source location and source orientation it is quite likely that the negative response in 6-month-old infants is a precursor of the adult MMN involved in the processing of feature-specific sensory information.

It should be noted that the exact source locations must be regarded cautiously given the relatively poor spatial resolution of EEG. An additional caveat is that the noise level in infant ERPs is higher than that typically observed in adult ERP recordings, thus introducing more error variance into the source localization results. Nonetheless, the temporal resolution of EEG is excellent, and in this case suggests temporally consecutive responses for the infant negative and positive activations. Further, even given these limitations, the source locations in the present study were surprisingly consistent with the expected auditory cortex activation and the dipole fit was relatively good even at the individual level (as seen in Fig. 6).

The present study supports the idea that the sound-feature-specific change detection response in infants at 6 months is an emerging negative deflection resembling the adult MMN component in latency, distribution, source location and source orientation. The following positive response, related to attention switching mechanisms, has very similar source locations, but the orientation of the sources suggests that it is generated in a cortical area adjacent to that of the negative response. These results represent a promising first step by demonstrating that the underlying source structures of the infant electrophysiological activity can be teased apart and used for inferring more information concerning infant cognitive processes and ongoing brain maturation.

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