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DEVELOPMENTAL NEUROSCIENCE

Cortical indices of sound localization mature monotonically in early infancy

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Abstract

In human neonates, orienting behavior in response to an off-midline sound source disappears around the first postnatal month, only to re-emerge at ~4 months. To date, it is unclear whether sound localization processes continue to operate between postnatal months 1 and 3. Here, we used an event-related potential, reflecting change detection in the auditory cortices, to measure the cortical responses elicited by large (± 90° relative to midline), infrequent changes in sound source location in 2-, 5-, 8- and 13-month-old infants. Both fast-negative mismatch negativity (MMN) Näätänen *et al.* (2007) and slow-positive mismatch response (MMR) Trainor *et al.* (2003) were elicited from all age groups. However, both components were smaller and the fast-negative component occurred later in the 2-month-old group than in older age groups. Additionally, the slow-positive component tended to diminish in amplitude with increasing age, whereas the fast-negative component grew larger and tended to occur earlier with increasing age. These results suggest that the cortical representation of sound location matures similarly to representations of pitch and duration. A subsequent investigation of 2-month-old infants confirmed that the observed MMR and MMN were elicited by changes in sound source location, and were not merely attributable to changes in loudness cues. The presence of both MMR and MMN in the 2-month-old group indicates that the cortex is able to detect changes in sound location despite the behavioral insensitivity observed around 1–3 months of age.

Introduction

Research suggests that the postnatal development of human spatial hearing is best approximated by a U-shaped function [reviewed by Muir *et al.* (1989)]. Neonatal orienting responses, as observed within the first postnatal month (Wertheimer, 1961; Crassini & Broerse, 1980), disappear between 1 and 3 months of age, only to re-emerge between 3 and 4 months of age, with decreased latency, greater sensitivity, and increasing absolute precision (Muir *et al.*, 1979, 1989; Clifton *et al.*, 1981; Muir & Hains, 2004). The dominant explanation for this dip in orienting behavior posits that neonatal localization is driven by a subcortically mediated reflex that becomes suppressed at ~1 month of age. Suppression is thought to have a facilitative role in the transition to a more volitional and cortically mediated sound localization mechanism (Muir & Clifton, 1985; Muir & Hains, 2004).

To date, it is not clear whether infants aged 1–3 months are actually able to localize sounds and, if they are, whether they are doing so at a cortical level. Here, we addressed this question by measuring electroencephalographic indices of pre-attentive change detection in the auditory cortices, known as mismatch response (MMR) and mismatch negativity (MMN), in a cross-sectional sample of 2–13-month-old infants. Developmental studies have consistently indicated a morphological transition in the mismatch component, with a slow-positive MMR being predominant in younger infants and diminishing in amplitude with age, and an adult-like fast-negative wave, resembling the MMN response of adults and older children, emerging in older infants and increasing with age [for reviews, see Trainor (2007, 2012a,b)]. In adults, the MMN originates primarily in the auditory cortex (for a review, see Näätänen *et al.*, 2007), and its morphological features, such as amplitude and latency, are highly correlated with behavioral measures of discrimination thresholds for many auditory features, including pitch (e.g. Novitski *et al.*, 2004), gap detection (Trainor *et al.*, 2001), and, of relevance to the current study, sound localization (Paavilainen *et al.*, 1989; Schröger, 1996; Schröger & Wolff, 1996; Kaiser *et al.*, 2000a,b; Altman *et al.*, 2005, 2009; Deouell *et al.*, 2006; Sonnadara *et al.*, 2006; Pakarinen *et al.*, 2007; Röttger *et al.*, 2007; Spierer *et al.*, 2007; Altmann *et al.*, 2009; Vasilenko & Shestopalova, 2010; Grimm *et al.*, 2012; Bennemann *et al.*, 2013).

The first experiment in the present study employed an oddball paradigm, such that, in 80% of trials, a sound was presented from directly in front of the infant at midline, and in the remaining trials from a location ± 90° relative to the midline. If infants are indeed localizing during the period of behavioral silence, we expect deviant trials to elicit one or both mismatch components from all age groups. Furthermore, if 2-month-old localization is driven primarily by subcortical processes, we expect the immature slow-positive MMR to dominate the 2-month-old response to deviant trials and an adult-like

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MMN response to emerge later. Alternatively, if neural localization processes, along with orienting behaviour, are suppressed between 1 and 3 months of age, we expect to observe both mismatch responses from 5-, 8-, and 13-month-olds, but neither from 2-month-olds. Finally, we expect the slow-positive response to diminish with age and the fast-negative response to increase in amplitude and decrease in latency with increasing age and cortical maturation.

A second experiment, conducted in a new group of 2-month-old infants, followed the procedures outlined for the first experiment, except that the amplitude of stimulus presentation was pseudo-randomly varied by ± 4 dB in order to control for those changes in stimulus loudness at higher frequencies that accompany ± 90° shifts in azimuthal sound source origin (Blauert, 1983).

Materials and methods

Experiment 1

Participants

We recruited a total of 73 healthy full-term infants, with no known hearing deficits, ranging in age from 2 to 13 months. Prior to the experiment, basic demographic information was obtained from each infant's care-giver. The final sample consisted of 16 infants aged 2 months (six females; mean age, 2.51 ± 0.20 months), 13 infants aged 5 months (five females; mean age, 5.49 ± 0.22 months), nine infants aged 8 months (six females; mean age, 8.46 ± 0.31 months), and 14 infants aged 13 months (five females; mean age, 13.05 ± 0.44 months). Nineteen infants (four aged 2 months, 13 aged 5 months, and two aged 8 months) were excluded from analysis because of excessive fussiness (e.g. crying, or not facing the center speaker) and/or too few artefact-free trials. Two additional infants (one aged 2 months and one aged 8 months) were eliminated from the final sample because they fell asleep during testing. All infants included in the final sample were awake during the course of the experiment. Written consent was obtained from all parents of the infants in compliance with a protocol approved by the McMaster Research Ethics Board. The study conformed to the Code of Ethics of the World Medical Association (Declaration of Helsinki), printed in the *British Medical Journal* (18 July 1964).

Stimulus

A burst of frozen white noise (duration, 300 ms) was generated with AUDACITY software (www.audacity.sourceforge.net). The stimulus was presented with a Tucker-Davis Technologies RP2 Real Time Processor, relayed through a Tucker-Davis Technologies PM2R Power Multiplexer, and amplified by a Hafler P1000 Trans.Ana 100-W amplifier. Stimulus presentation occurred in a sound-attenuated room through matching AudioVideo Methods speakers (P73) at an onset asynchrony of 500 ms and an average sound intensity of 76.5 dB(C) SPL.

Procedure

The infant was seated on the care-giver's lap. Both care-giver and infant faced the center speaker, which was positioned in front of the infant at a distance of 1 m. Additional loudspeakers were aligned at ± 90° relative to the center speaker, at a distance of 1 m from the infant and care-giver (Fig. 1). A silent video (Baby Einstein) and a live puppet show were used to keep the infant happy and to maintain the infant's attention in the direction of the center speaker. Stimulus presentation followed an oddball paradigm. Standard stimuli, defined as presentations through the center speaker, accounted for 80% of trials. Deviant stimuli, defined as presentations through one of the lateral speakers (± 90°), accounted for the remaining 20% of trials. Deviant stimulation was further divided such that trials occurred equally often between the left (10%) and right (10%) lateral speakers. The complete test session consisted of 2400 trials, although the experiment was stopped early if the infant became fussy or fell asleep. Of those infants included in the final sample, the number of accepted trials ranged from 868 to 2064, with a mean of 1815 (standard deviation of 207).

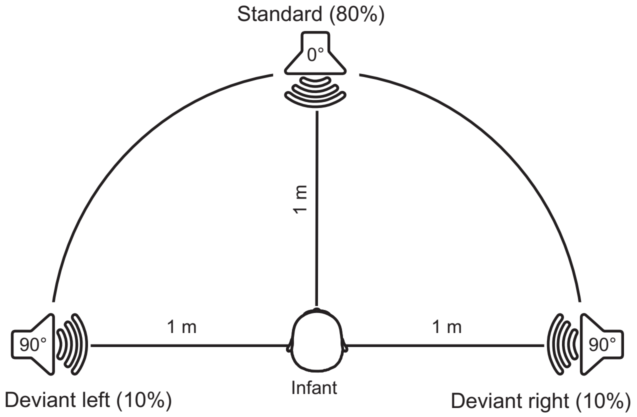

FIG. 1. Diagram of the experimental design. The infant was seated on the care-giver's lap in a sound-attenuating room. Both infant and care-giver were positioned at a distance of 1 m from three identical speakers. Stimulation was provided as bursts of frozen white noise emanating from one of the three speakers in a random order over 2400 trials (center, 80%; deviant left, 10%; and deviant right, 10%).

Data acquisition and analysis

During testing, we collected continuous electroencephalograms from 129 channels (referenced to vertex) with an Electrical Geodesics NetAmps 200 amplifier passing a digitized signal to Electrical Geodesics NETSTATION software (v.4.3.1). Signals were digitized at a rate of 1000 Hz and subjected to online filtering between 0.1 and 400 Hz. The electrical impedance of each electrode was maintained below 50 kΩ.

The continuous data were further filtered offline in EEPROBE software (Advanced Neuro Technologies) with two different bandpass filter settings: 0.5–20 Hz and 3–18 Hz. Filtering the data between 0.5 and 20 Hz is most effective at revealing the MMR, whereas filtering between 3 and 18 Hz effectively removes the slow-wave MMR and allows for visualization of the faster adult-like MMN. Thus, for each subject, the analysis technique generated two electroencephalographic traces, one in which the original data were filtered to visualize the MMR, and the other in which the data were filtered to visualize the MMN.

The filtered data were then resampled at 200 samples/s and epoched from −100 to 600 ms relative to stimulus onset. Artefact trials were defined, for each electrode, as those epochs where activity exceeded ± 100 μV. Trials containing artefact were corrected with an artefact-blocking algorithm applied in MATLAB (Mourad *et al.*, 2007; Fujioka *et al.*, 2011). Corrected data from each subject were re-referenced to the average reference before being averaged across epochs, separately for each filtered trace (MMR and MMN). Baseline activity, defined as the mean amplitude in the 100-ms window prior to stimulus onset, was subtracted from each epoch during averaging. For statistical analysis, 72 electrodes were selected and divided into four groups per hemisphere (Fig. 2). The waveforms for all electrodes in each group were averaged together to represent activity at the frontal (16 electrodes), central (20 electrodes), parietal (18 electrodes) and occipital (18 electrodes) scalp regions. Data representing each scalp region were also grand-averaged across subjects in each age group with respect to trial type. Finally, to visualize the MMR and MMN, difference waves for each deviant type (leftward or rightward) were constructed by subtracting the grand-averaged response to standard stimulation from the grand-averaged response to deviant stimulation.

MMRs, in the 0.5–20-Hz bandpass data, were characterized for each subject by measuring the area under the curve (AUC) of the difference wave in frontal and central scalp region waveforms from 100 to 500 ms after stimulus onset. The AUC was further divided into four 100-ms windows in order to examine the temporal morphology of the MMR. MMNs, in the 3–18-Hz bandpass data, were characterized for each subject by measuring the amplitude and latency of the largest negative deflection in the difference wave in frontal and central scalp regions between 100 and 300 ms after stimulus onset. Peak amplitudes of the MMN and the AUC of the MMR in frontal, central and occipital electrode groups were also tested against zero with a two-tailed one-sample *t*-test. All measures were extracted in MATLAB. Repeated-measures ANOVAS were used to test whether the MMRs and/or MMNs varied across the between-subjects factor Age Group (2, 5, 8 and 13 months), and the within-subject factors Deviant Side (left/right), Electrode Hemisphere (left/right), Electrode Group (frontal/central), and, only for AUC measures, Time Bin (100–200, 200–300, 300–400 and 400–500 ms after stimulus onset). Mauchly's test of sphericity was used to evaluate the assumption of equal variance for the differences between all combinations of related groups (levels). Huynh–Feldt correction was applied to critical *F*-values for levels found to violate assumptions of sphericity.

Experiment 2

Participants

We recruited a total of 15 healthy full-term 2-month-old infants (12 females; mean age, 2.61 ± 0.19 months) with no known hearing deficits. Prior to the experiment, basic demographic information was obtained from each infant's care-giver. The final sample consisted of 13 infants aged 2 months (10 females; mean age, 2.62 ± 0.21 months). Two infants were excluded from analysis because of too few artefact-free trials. All infants included in the final sample were awake during the course of the experiment. Written consent was obtained from all parents of the infants in compliance with a protocol approved by the McMaster Research Ethics Board. The study conformed to the Code of Ethics of the World Medical Association (Declaration of Helsinki), printed in the *British Medical Journal* (18 July 1964).

Stimulus and procedure

Frozen white noise bursts were presented in an oddball paradigm identical to that detailed for Experiment 1, except that stimulus

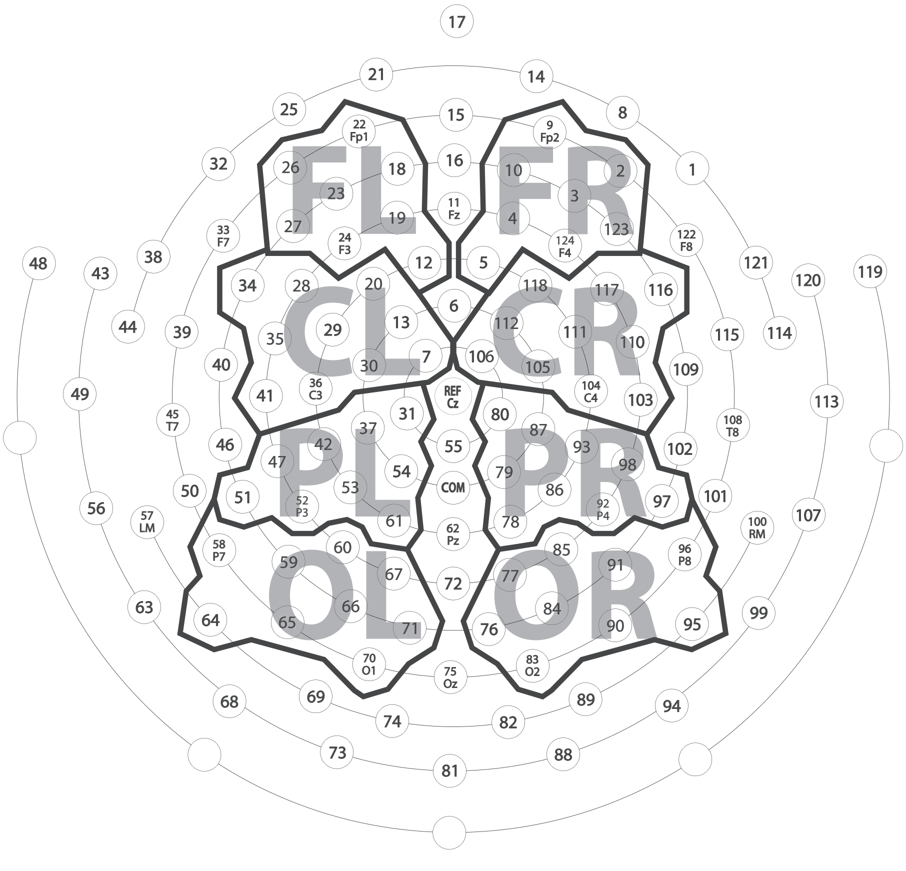

FIG. 2. A schematic of the 129-channel HyrdoCel Geodesic Sensor Net. Bordered regions denote electrode groupings used to represent frontal (FL/FR), central (CL/CR), parietal (PL/PR) and occipital (OL/OR) scalp-recorded activity. Each grouping contains between 8 and 10 electrodes per hemisphere. The remaining 57 electrodes were excluded from the analysis in order to reduce artefacts and allow for comparison between hemispheres. COM: Isolated Common; REF: Reference.

amplitude was pseudo-randomly varied around 76.5 dB(C) SPL by ± 4 dB in 1-dB increments. Amplitude assignment for each presentation also followed the restriction that no two subsequent presentations could be of equal amplitude, thereby ensuring that no sensory memory trace could be established for loudness cues associated with standard presentation from the center speaker. In this manner, the modified presentation paradigm controlled for the possibility that the MMN and MMR seen in Experiment 1 were evoked solely by the changes in loudness cues that accompany ± 90° shifts in azimuthal sound source origin, rather than the change in sound source location.

To address the added possibility that the care-givers were in some manner influencing the infants, all care-givers holding the infants wore sound-attenuating ear muffs during the experiment. Following the experimental session, researchers confirmed that care-givers could not identify the location of the sound source while wearing the ear muffs.

Data acquisition and analysis

The data were filtered and averaged with the same procedure outlined for Experiment 1. Peak amplitudes of the MMN and the AUC of the MMR in frontal, central and occipital electrode groups were tested against zero with a two-tailed one-sample *t*-test ($\alpha = 0.05$). To further examine whether loudness cues contributed significantly to the MMR and MMN recorded from 2-month-old infants, a two-tailed independent-samples *t*-test ($\alpha = 0.05$) was used to evaluate the null hypothesis of no difference in peak amplitude/latency (MMN) or AUC (MMR) between the groups of 2-month-olds tested in the roving and in the fixed-amplitude conditions. Repeated-measures ANOVAS, similar to those detailed for Experiment 1, were used to evaluate whether Deviant Side, Electrode Group or Electrode Hemisphere had any effect on MMN amplitude, MMN latency, and, with the inclusion of a Time Bin factor, MMR AUC.

Results

Experiment 1

The grand-averaged MMR (bandpass, 0.5–20 Hz) and MMN (bandpass, 3–18 Hz) of each age group are shown in Figs 3 and 6, respectively. Grand-averaged difference waves for each age group are shown for leftward and rightward deviants in Fig. 4 (MMR) and Fig. 7 (MMN).

MMRs

The slow-wave event-related potentials (ERPs) were dominated by broad positivity in the frontal and central electrode sites that spanned between 200 and 400 ms after stimulus onset. The fronto-central positivity was accompanied by reciprocal negativity in the occipital regions (Fig. 3). In each age group, except for 13 months, deviant trials elicited significantly more positive responses in frontal electrode groups than did standard trials. In all age groups, deviant trials elicited significantly more positive responses at central electrode groups, and more negative responses in occipital electrode groups, than did standard trials (Table 1; Fig. 4). The morphology and scalp topography of the deviant response was consistent with previous reports of infant ERPs elicited by other deviant classes, e.g. pure tones (Leppänen *et al.*, 1997), harmonic tones (Fellman *et al.*, 2004), piano tones (He *et al.*, 2007, 2009), and speech syllables (Friederici *et al.*, 2002; Friedrich *et al.*, 2004). The polarity inversion along the anterior–posterior axis further suggests bilateral generators around the temporal lobes, probably reflecting activity within the auditory cortices (Dehaene-Lambertz & Dehaene, 1994).

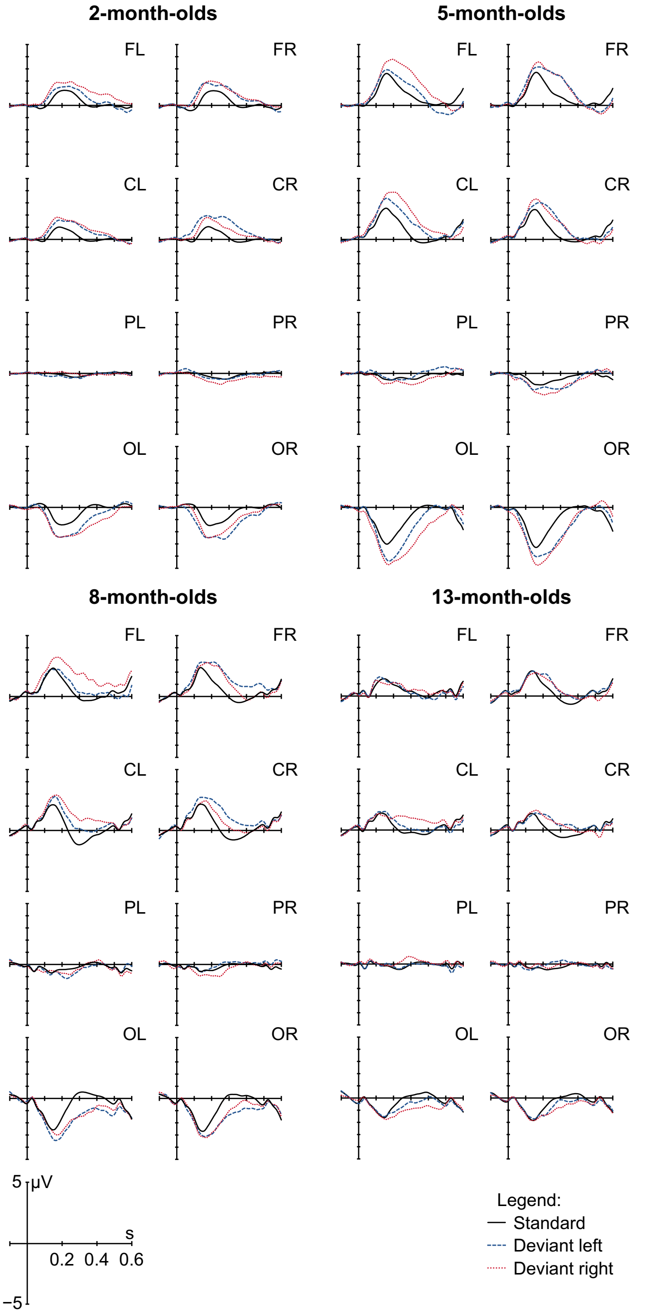

FIG. 3. Grand-averaged standard (solid), deviant left (dashed) and deviant right (dotted) responses recorded from four different age groups (2-, 5-, 8-, and 13-month-olds). The data shown here were bandpass-filtered between 0.5 and 20 Hz. Responses represent averaged activity in eight scalp regions: frontal (FL/FR), central (CL/CR), parietal (PL/PR), and occipital (OL/OR), as grouped in Fig. 2.

The omnibus ANOVA revealed a significant effect of Age Group on the AUC measured from the MMR ($F_{3,48} = 3.28$, $P < 0.05$) (Fig. 5A). Subsequent pairwise comparisons (Tukey HSD) found the AUC of the 13-month-old group to be significantly smaller than that of the 8-month-old group. No other age differences were significant. AUC measures were also significantly affected by Time Bin ($F_{2.74,131.67} = 55.78$, $P < 0.001$), and an interaction between Time

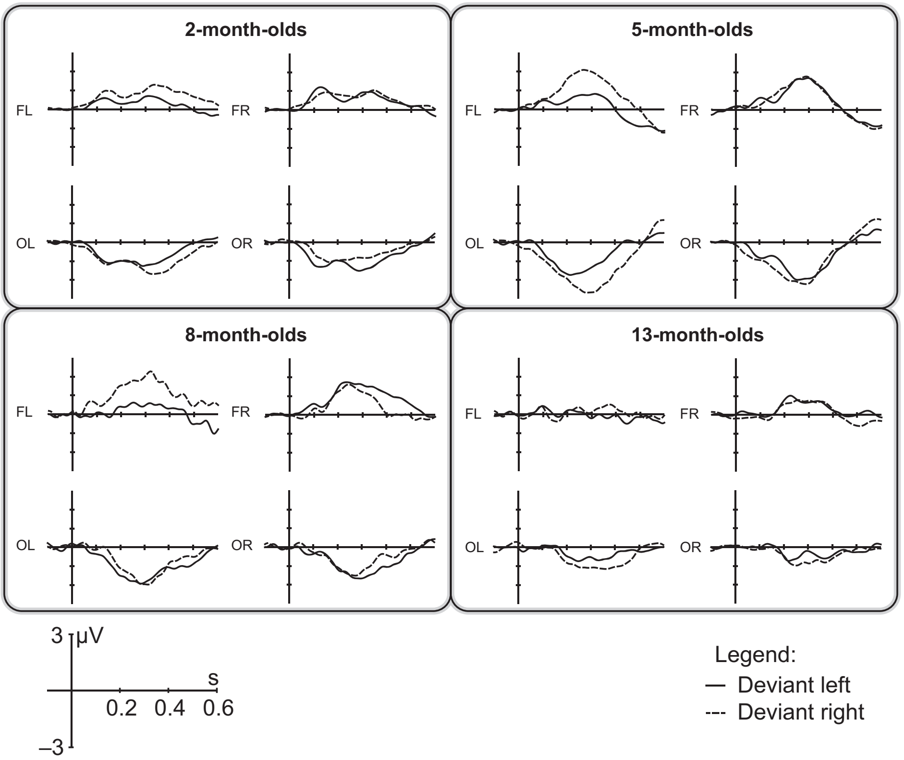

FIG. 4. Grand-averaged difference waves (deviant – standard; bandpass, 0.5–20 Hz) in frontal (FL/FR) and occipital (OL/OR) scalp regions as elicited in 2-, 5-, 8-, and 13-month-olds. Responses to leftward and rightward deviants are shown as solid and dashed traces, respectively.

TABLE 1. Average AUC of the MMR

	Electrode group		
Age (months)	Frontal	Central	Occipital
2	13.63 ± 10.81***	14.28 ± 6.40***	−19.43 ± 11.00***
2 – roving	12.56 ± 11.78**	11.87 ± 6.81***	−13.99 ± 11.22**
5	15.67 ± 15.49**	17.56 ± 9.86***	−25.21 ± 13.61***
8	19.02 ± 12.91**	17.51 ± 8.12***	−20.61 ± 7.91***
13	5.78 ± 14.17	10.15 ± 6.79***	−9.93 ± 7.11***

**$P < 0.01$, ***$P < 0.001$.

Bin and Age Group ($F_{8.23,131.67} = 4.82$, $P < 0.001$) (Fig. 5B). In the 5-, 8- and 13-month-old groups, the MMR appeared to be most positive between 200 and 400 ms after stimulus onset, with a peak at 200–300 ms, whereas the MMR of the 2-month-old group appeared to be more spread out over time. These data suggest that the neural processes responsible for generating the slow-positive MMR in response to acoustic spatial deviants undergo a transition between 8 and 13 months of age that is accompanied by diminution and/or suppression of the MMR.

The ANOVA revealed several additional effects that probably reflected the locations of the MMR generators. First, there was a significant effect of a Deviant Side by Electrode Hemisphere interaction ($F_{1,48} = 18.06$, $P < 0.001$) (Fig. 5C). Deviant trials elicited larger responses in the electrode hemisphere contralateral to the deviant sound's spatial position. Enhancement of the spatial MMN over the contralateral hemisphere has been observed in adult subjects (Kaiser & Lutzenberger, 2001; Sonnadara *et al.*, 2006), and is thought to reflect the contralateral predominance of cortical neurons in the auditory pathway (Phillips & Irvine, 1983). Second, the ANOVA revealed significant effects of a Time Bin by Electrode Hemisphere interaction ($F_{2.95,141.71} = 4.66$, $P < 0.01$) and a three-way interaction between Time Bin, Electrode Hemisphere, and Deviant Side ($F_{2.17,191.96} = 6.40$, $P < 0.01$). From 100 to 300 ms after stimulus onset, MMRs were larger over right hemisphere electrodes than over left hemisphere electrodes. This pattern was reversed from 300 to 500 ms after stimulus onset. When examined separately for each deviant stimulus, the AUC was larger over the hemisphere contralateral to the deviant source in every time bin. Third, there were also effects of a four-way interaction between Deviant Side, Time Bin, Electrode Group, and Electrode Hemisphere ($F_{2.33,112.04} = 8.49$, $P < 0.001$), and a five-way interaction between Deviant Side, Time Bin, Electrode Group, Electrode Hemisphere, and Age ($F_{7.00,112.04} = 2.26$, $P < 0.05$). AUC measured from central electrodes was always larger than that measured from frontal electrodes. However, the difference in AUC measured from the left and right hemisphere electrodes varied according to the location of the deviant source, time bin, electrode group, and age. These data indicate that the generators of the MMR signal do not respond identically to leftward and rightward deviants, and that this asymmetry is affected by development.

MMNs

Bandpass filtering of the data between 3 and 18 Hz was effective in removing the slow-wave MMR (Fig. 6). In all age groups, deviant trials elicited significantly more negative responses in the frontal and central electrode groups, and significantly more positive responses in the occipital electrode groups, than did standard trials (Table 2). Difference waves (Fig. 7) showd a negative

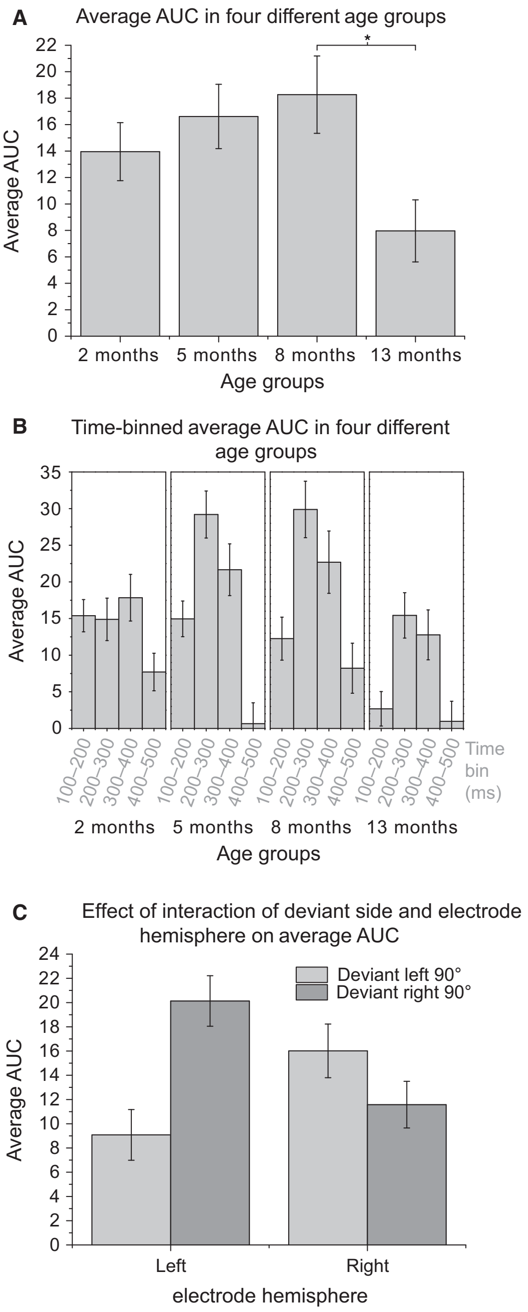

FIG. 5. (A) Average AUC, from 100 to 500 ms after stimulus onset, in each age group measured from the difference waves in the frontal (FL/FR) and central (CL/CR) scalp regions. Pairwise comparisons (Tukey HSD) revealed a significant difference between the AUCs of the 8- and 13-month-old groups ($P < 0.05$). No other significant differences were found. (B) Significant effect of an interaction between Age Group and Time Bin on average AUC measures taken from the slow-wave MMR data (bandpass, 0.5–20 Hz) in four different age groups ($P < 0.001$, Huynh–Feldt correction). (C) Significant effect of an interaction between electrode hemisphere and Deviant Side on the average AUC measured from 100 to 500 ms across all age groups ($P < 0.001$). In all figures, error bars represent standard errors.

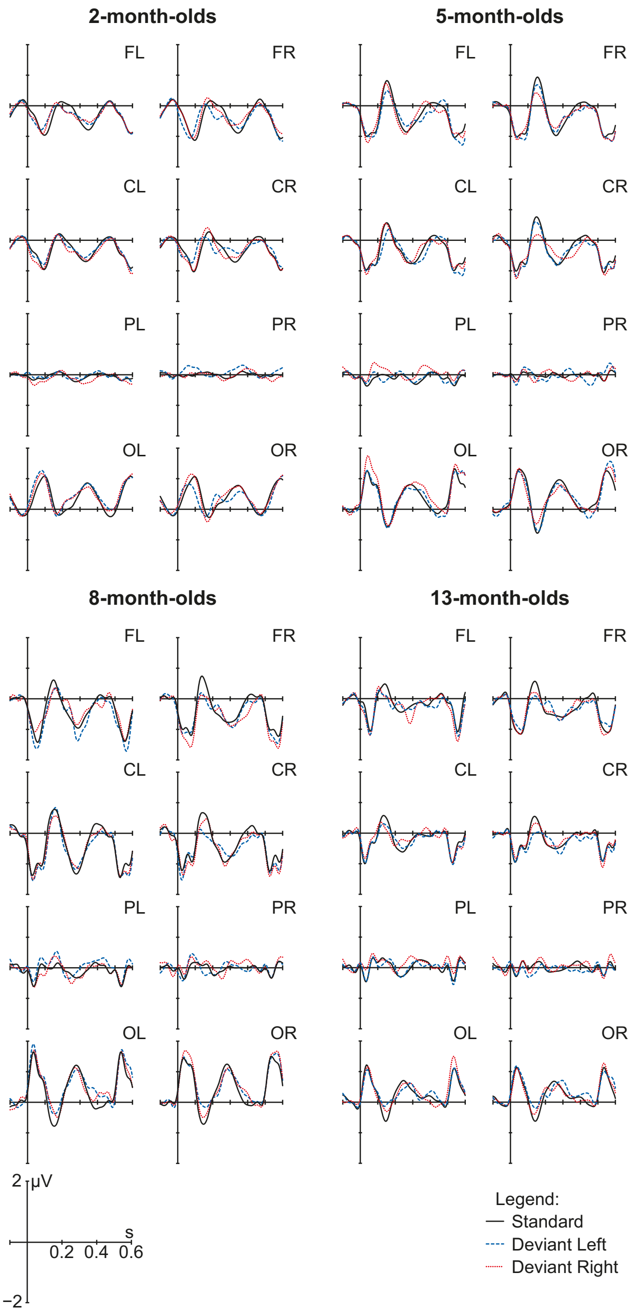

FIG. 6. Grand-averaged standard (solid), deviant left (dashed) and deviant right (dotted) responses recorded from four different age groups (2-, 5-, 8-, and 13-month-olds). The data shown here were bandpass-filtered between 3 and 18 Hz. Responses represent averaged activity in eight scalp regions: frontal (FL/FR), central (CL/CR), parietal (PL/PR), and occipital (OL/OR), as grouped in Fig. 2.

deflection peaking between 100 and 300 ms after stimulus onset accompanied by reciprocal positivity in the occipital electrode groups. Again, this topography is suggestive of generators around the auditory cortices.

Analysis of the MMN-like response revealed a significant effect of Age Group on the peak amplitude ($F_{3,48} = 4.49$, $P < 0.01$) (Fig. 8A) of the negative component. Pairwise comparisons (Tukey HSD) indicated that the effect of Age Group was driven primarily by smaller MMN amplitude in the 2-month-old group than in all other age groups. The omnibus ANOVA also revealed a significant effect of Electrode Group ($F_{1,48} = 8.28$, $P < 0.01$) on MMN amplitude, with peak amplitude larger in frontal than in central electrode groupings. As in the AUC data, there was also a significant effect of a Deviant Side by Electrode Hemisphere interaction on MMN amplitude ($F_{1,48} = 12.37$, $P < 0.01$) (Fig. 8C).

TABLE 2. Average peak amplitude (μV) of the MMN

	Electrode group		
Age (months)	Frontal	Central	Occipital
2	−0.58 ± 0.26***	−0.53 ± 0.34***	0.61 ± 0.31***
2 – roving	−0.56 ± 0.28***	−0.56 ± 0.23***	0.67 ± 0.20***
5	−0.85 ± 0.33***	−0.78 ± 0.23***	0.77 ± 0.24***
8	−0.88 ± 0.28***	−0.84 ± 0.22***	0.95 ± 0.25***
13	−0.86 ± 0.28***	−0.71 ± 0.28***	0.85 ± 0.25***

***$P < 0.001$.

Peak latency was significantly affected by Age Group ($F_{3,48} = 8.80$, $P < 0.001$) (Fig. 8B), with longer latency in the 2-month-old group than in all other age groups (pairwise comparisons, Tukey HSD). There were also significant effects of a Deviant Side by Electrode Hemisphere interaction ($F_{1,48} = 7.67$, $P < 0.01$) (Fig. 8C) and a three-way interaction between Deviant Side, Electrode Group and Electrode Hemisphere ($F_{1,48} = 12.39$, $P < 0.01$) on the peak latency of the MMN. Leftward deviants elicited shorter latency MMN-like negativities in frontal electrode groups, over both hemispheres, than rightward deviants. Conversely, a contralateral bias was observed in the latency measured from central electrode groups, where deviants elicited shorter latency MMN-like responses over the contralateral hemisphere.

Experiment 2

Grand-averaged difference waves for leftward and rightward deviants are shown in Fig. 9A (MMR) and Fig. 9B (MMN).

MMRs

The slow-wave ERPs showed a morphology consistent with the infant MMR as recorded in Experiment 1. The AUCs of responses elicited by deviant stimuli were significantly more positive at frontal and central electrode sites and significantly more negative at occipital electrode sites than those elicited by standard stimuli (Table 1). An independent-samples *t*-test failed to show any significant difference in the AUCs of the difference waves in any electrode group between data collected in Experiment 2 and those collected in Experiment 1 (Fig. 10).

The repeated-measures ANOVA revealed significant effects of Time Bin ($F_{2.292,27.504} = 7.483$, $P < 0.01$) and of an interaction between Time Bin and Electrode Group ($F_{1.982,23.783}) = 4.116$, $P < 0.01$) on the AUC of the MMR. Overall, the measured AUC was largest between 100 and 400 ms after stimulus onset, and was greatly diminished between 400 and 500 ms. The distribution of MMR signal strength across the electrode groups also varied over time. Between 100 and 200 ms after stimulus onset, the MMR signal was stronger at central electrode sites than at frontal electrode sites, after which this pattern was reversed.

MMNs

Filtering the data between 3 and 18 Hz revealed an MMN-like response, peaking at ~230 ms after stimulus onset, in the difference wave that was obtained by subtracting the averaged standard response from the averaged deviant response. One-sample *t*-tests conducted on the peak amplitude of the MMN confirmed that deviant responses were significantly more negative than standard responses at frontal and central electrode sites and significantly more

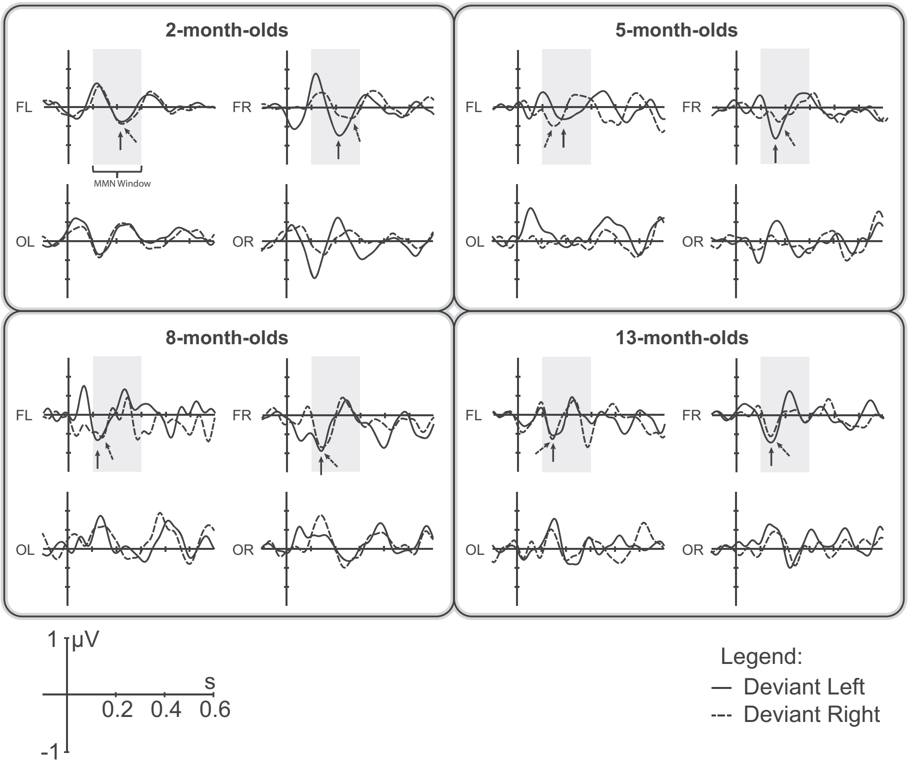

FIG. 7. Grand-averaged difference waves (deviant – standard; bandpass, 3–18 Hz) in frontal (FL/FR) and occipital (OL/OR) scalp regions as elicited in 2-, 5-, 8-, and 13-month-olds. Responses to leftward and rightward deviants are shown as solid and dashed traces, respectively. Gray windows denote the time after stimulus onset over which the MMN peak was extracted. Solid and dashed arrows denote grand-averaged MMN peaks in response to leftward and rightward deviants, respectively.

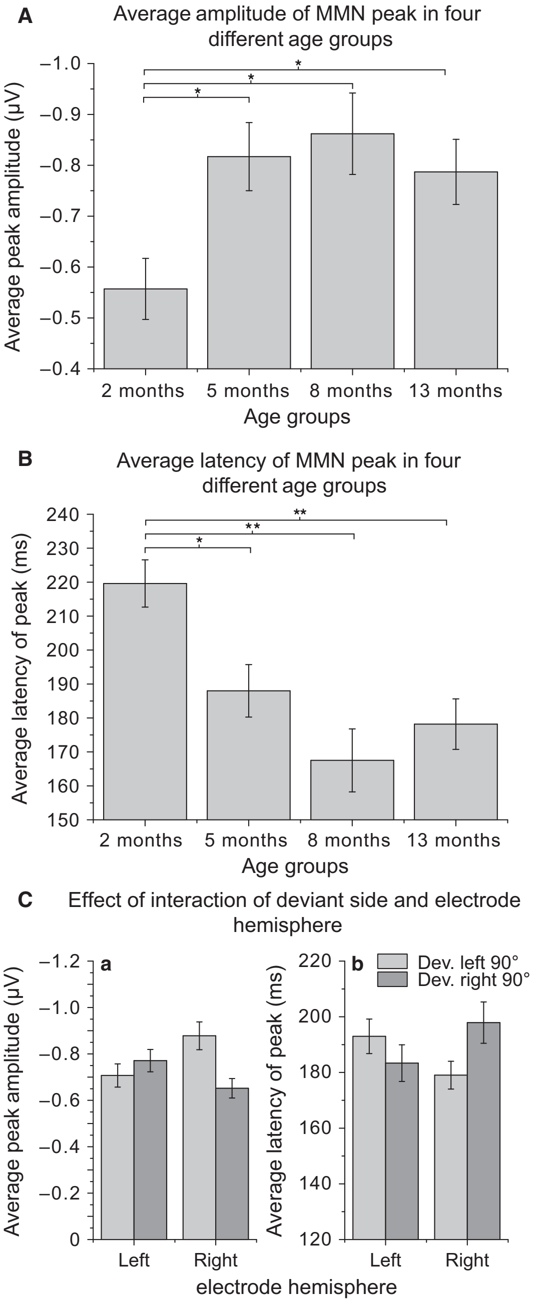

FIG. 8. Average peak MMN amplitude (A) (100–300 ms after stimulus onset) and latency (B) measured in the frontal (FL/FR) and central (CL/CR) scalp regions in each age group. Pairwise comparisons (Tukey HSD) revealed a significant difference between the peak MMN amplitude and latency of the 2-month-old group and those of all other age groups (*$P < 0.05$; **$P < 0.01$). No other significant differences were found. (C) Significant effect of an interaction between electrode hemisphere (*x*-axis) and Deviant Side (light gray, deviant left; dark gray, deviant right) on the average amplitude (left side) and latency (right side) of the MMN across all age groups ($P < 0.01$). In all figures, error bars represent standard errors.

positive at occipital electrode sites (Table 2). The repeated-measures ANOVA revealed no significant effects of Deviant Side, Electrode Group, or Hemisphere, or an interaction between them, on either the amplitude or latency of the MMN. As for the MMR, an independent-samples *t*-test failed to show any significant difference in the peak MMN amplitude or latency between data collected in Experiment 2 and those collected in Experiment 1 (Fig. 10).

Discussion

Experiment 1

The results provide evidence that infants of all ages perceived sound location changes, in that pre-attentive mismatch responses were evident in both the MMR and MMN in all age groups. However, changes in sound location produce interaural changes in loudness (which, of course, constitute one of the main cues regarding sound location), which necessarily means that there are also monaural changes in loudness (Blauert, 1983). Specifically, with respect to one ear, sounds in contralateral space will be slightly less intense than sounds in ipsilateral space. In order to rule out the possibility that the MMR and MMN responses that we observed here were attributable to monaural sound level differences, in Experiment 2 we repeated the experiment with the youngest age group, using a roving stimulus level.

Experiment 2

The results of Experiment 2 strongly suggest that the change-detection responses found in Experiment 1 were not elicited by monaural loudness cues, but rather primarily reflected responses to changes in sound location.

General

The pre-attentive mismatch response was present as both a slow-positive (MMR) and a fast-negative (MMN) component in 2-, 5-, 8-, and 13-month-olds. The effects of Deviant Side by Electrode Hemisphere interactions observed on the AUC measures of the MMR and peak amplitude/latency measures of the MMN are consistent with previous studies showing the adult MMN to be larger and to occur earlier in electrodes that are contralateral to the deviant sound source (e.g. Kaiser *et al.*, 2000a,b; Kaiser & Lutzenberger, 2001; Nager *et al.*, 2003; Sonnadara *et al.*, 2006; Richter *et al.*, 2009). Whole-cell recordings (*in vivo*) of pyramidal cells in superficial layers (II–IV) of the rat auditory cortex show a similar bias to contralateral sound presentation in free-field – faster-rising excitatory postsynaptic potentials, shorter spike latency, and greater likelihood of spike occurrence (Chadderton *et al.*, 2009). Along with the reversal in response polarity across frontal/central and occipital electrode groups (Figs 4 and 7), the observed contralateral response bias (Figs 5C and 8C) strongly implies generators situated in the auditory cortices. Moreover, the MMRs and MMNs recorded from 2-month-olds in Experiment 2 did not differ significantly from those recorded in Experiment 1, which rules out the possibility that these ERPs reflect primarily neural activity elicited by a change in stimulus loudness at each ear rather than the change in sound source spatial location. Thus, despite the well-documented behavioral insensitivity to sound location observed between 1 and 3 months of age (e.g. Muir *et al.*, 1979, 1989; Clifton *et al.*, 1981; Muir & Hains, 2004), our data indicate that infants in all age groups respond to changes in sound source location at a cortical level.

According to Muir and colleagues (Muir & Clifton, 1985; Muir & Hains, 2004), the subcortically generated reflex to off-midline sounds should undergo suppression between 1 and 4 months of age as the auditory system transitions to a cortical localization processor. We can look at this hypothesis by examining the MMR, because it reflects cortical activity directly driven by subcortical input. Positive obligatory evoked potentials, including the positive MMR, probably reflect a depolarization in layer IV of the auditory cortex (Eggermont & Moore, 2012). Layer IV receives activity from the ventral

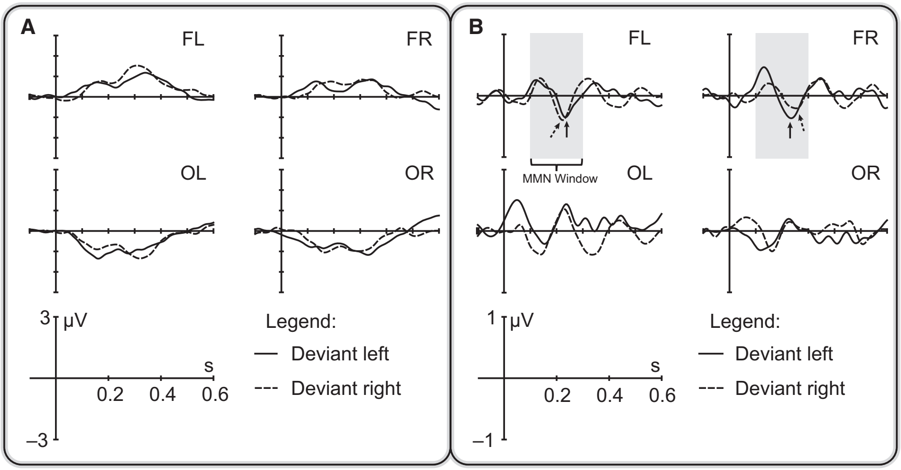

FIG. 9. Grand-averaged difference waves (deviant – standard) in frontal (FL/FR) and occipital (OL/OR) scalp regions elicited in 2-month-old infants in Experiment 2. Responses to leftward and rightward deviants are shown as solid and dashed traces, respectively. The MMR dominates the difference waves when the data are filtered between 0.5 and 20 Hz (A). Filtering the data between 3 and 18 Hz reveals an MMN-like response (B). Gray windows denote the time after stimulus onset over which the MMN peak was extracted. Solid and dashed arrows denote grand-averaged MMN peaks in response to leftward and rightward deviants, respectively.

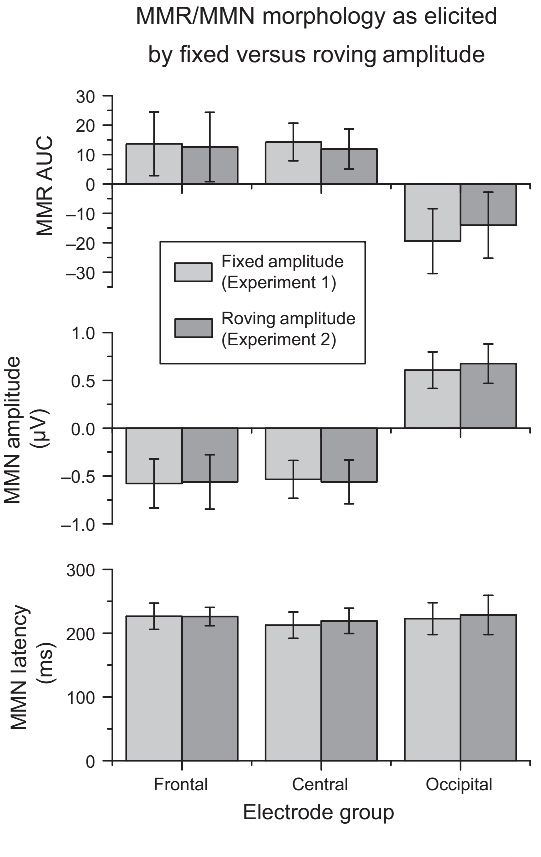

FIG. 10. Comparison of MMR and MMN morphology as elicited in two different groups of 2-month-old infants. Light gray bars represent data collected in Experiment 1, in which the amplitude of deviants and standards presentations was fixed. Dark gray bars represent data collected in Experiment 2, in which the amplitude of deviants and standards trials was pseudo-randomly roved by ± 4 dB. Independent-samples *t*-tests (two-tailed, $\alpha = 0.05$) revealed no significant differences between the fixed and roving amplitude experiments in the AUC of the MMR (top) or the peak amplitude (middle) and latency (bottom) of the MMN, as measured in frontal, central or occipital electrode groups.

medial geniculate nucleus via thalamocortical projections that do not undergo substantial myelination until 3 months of age. If suppression of a subcortically mediated localization process is taking place, our findings indicate that it does not affect input to the auditory cortex in a way that would significantly perturb the average amplitude of the MMR from 2 to 8 months of age. Although the AUC measured in 2-month-olds was more spread out in time than that of the 5- and 8-month-olds, this difference is not likely to be a reflection of a suppressed MMR generator(s), but rather reflects poor temporal synchrony in the population of cortical neurons stimulated by largely unmyelinated thalamocortical afferents (Eggermont & Moore, 2012). Furthermore, significant diminution of the MMR is not seen until between 8 and 13 months of age, which is at least 4 months later than the onset of the mature localization behavior thought to reflect engagement of cortical auditory spatial processing.

Interestingly, the lack of MMR amplitude diminution before 8–13 months of age highlights a protracted developmental trajectory as compared with that described for other acoustic deviants (e.g. Trainor *et al.*, 2003) [pitch deviants are reviewed in He *et al.*, 2007)]. It is difficult to ascertain whether the sustained presence of a slow-positive MMR is attributable to the nature of the experimental stimulation or to delayed development in auditory pathways conveying sound location information to the cortex. Kushnerenko *et al.* (2002) have suggested that the slow-positive component reflects a neural correlate of the infant orienting response, similarly to how the adult P3a response is thought to index an involuntary orienting of attention (Escera *et al.*, 2000). In this case, spatial deviants might have acted as maximally attention-grabbing stimuli, thus eliciting MMR in all age groups where neurophysiology still allowed for propagation of a slow-positive component from the cortex.

After the reported onset of thalamocortical myelination, a shorter-latency negative component is observed to precede the longer-latency positive MMR. The negativity is probably generated in layer I, which begins to receive excitatory projections from the medial division of the medial geniculate nucleus at ~4 months of age. According to Eggermont & Moore (2012), the persistence of a negative mismatch after 8 months of age requires a generator in layer I and/or layer II, and excitatory modulation from pyramidal cells with bodies in layers II, III, and V. In this neurophysiological framework, if the auditory cortex is at all sensitive to subcortically extracted spatial information, lemniscal (thalamocortical) projections should broadly activate layer IV and produce the dominant slow-positive MMR seen in all age groups. After sufficient thalamocortical myelination, cortical sensitivity to spatial information might additionally modulate non-lemniscal activity from afferents projecting from the medial division of the medial geniculate to layer I of the auditory cortex; however, this modulation does not necessarily preclude thalamocortical stimulation of layer IV from continuing to produce broad positive MMRs later in infancy, especially if the evoking stimulus is sufficiently salient to induce strong activation through the auditory pathway. In the case of our experiment, 90° spatial deviants in the azimuth represent maximally discrepant stimuli relative to the midline standards, and so might have continued to promote broad activation of layer IV in age groups in which positive MMR is rarely observed in response to other acoustic deviants. Of course, these proposed mechanisms are highly speculative, and the myriad of sources and sinks in various cortical layers that overlap in time and that give rise to surface-measured potentials is extremely complex (e.g. Steinschneider *et al.*, 2008). Nonetheless, it is useful to consider how differential patterns of MMR/MMN maturation, as elicited by different acoustic deviants, might inform us with respect to the general and/or specific development of early acoustic discriminative capabilities. This is especially relevant to the current experiment, in which the developmental course of the MMR is atypical as compared with that observed for other acoustic deviants, and therefore suggests a degree of within-domain specificity in the maturation of mismatch processes and/or generators.

As predicted, we did observe significant changes in the MMN between the 2- and 5-month-old groups that manifested as a larger average peak amplitude and shorter average latency. Enhancement of the MMN coincides with the reported onset of mature, probably cortically mediated, sound localization abilities. However, MMN emergence is also consistent with other infant studies of pitch discrimination (He *et al.*, 2007), gap detection (Trainor *et al.*, 2003), and resolution of the missing fundamental (He *et al.*, 2009). It is thus difficult to ascertain whether the age-related changes in the MMN elicited by our spatial deviants reflect something unique to the development of sound localization abilities or rather the general maturation of the auditory cortex. Follow-up studies could reveal the extent to which the adult-like MMN reflects behavioral sensitivity to spatial deviants presented within a hemifield. Insofar as such discriminations are thought to require an intact/functional auditory cortex, evidence that infant MMN indexes these changes after, but not before, 4 months of age would further imply that the MMN enhancement observed between 2 and 5 months of age is tied to the onset of cortically mediated localization processes.

After 2 months of age (i.e. in the 5-, 8- and 13-month-old groups), the amplitude and latency of the MMN-like fast negativity remain relatively stable. Behavioral studies do indicate substantial improvements in the minimum audible angle (MAA) between 5 and 13 months of age (Litovsky & Ashmead, 1997), with the MAA dropping from 19.8° at 5 months to 8.0° at 12 months. We did not record corresponding enhancements in MMN amplitude or latency over the same age range; however, assessment of the MAA was not performed in this study, and the MMN elicited by spatial deviants in free-field is known to saturate when the discrimination is greater than the MAA at the standard location (Paavilainen *et al.*, 1989). The large ± 90° shift used in the present study far exceeded the MAA in the 5-, 8- and 13-month-old age groups, probably causing saturation of the MMN generators. Subsequent studies might use smaller angular differences in azimuthal location to reveal potential differences in the MMN across age.

Given that 2-month-old infants are localizing sound sources at the cortical level, it is still unclear why reliable orienting behavior is absent between postnatal months 1 and 3. Furthermore, there is good evidence to suggest that the neonatal orienting to sound does not reflect the same sound localization mechanism observed in adults or older children (Litovsky & Ashmead, 1997; Muir & Hains, 2004; Litovsky, 2012). Neonatal localization abilities appear to be largely limited to left–right hemifield discriminations (Muir *et al.*, 1989), and require longer-duration transients than those necessary for localization in older infants and adults (Clarkson *et al.*, 1989). Neonates also lack sensitivity to the precedence effect – an auditory spatial illusion thought to be part of an echo suppression mechanism requiring neurons in the primary auditory cortex (Cranford *et al.*, 1971; Fitzpatrick *et al.*, 1999; Muir & Hains, 2004; Mickey & Middlebrooks, 2005). Sensitivity to precedence effect stimuli is not observed until between 4 and 5 months of age (Clifton *et al.*, 1984; Muir *et al.*, 1989), a window that tightly coincides with the reinstatement of orienting behavior (Clifton *et al.*, 1981). It is unlikely that the period of behavioral silence reflects heighted sensitivity to visual interference or habituation, as infants of this age continually fail to orient towards a sound source when tested in complete darkness (Muir *et al.*, 1979) or in response to a series of novel auditory tokens (Muir, 1985). Moreover, infants never lose the ability to turn their heads, and also continue to show robust orienting towards visual targets in both the temporal and nasal visual fields (Johnson, 1990). Therefore, the absence of an auditory orienting response cannot simply be attributed to physical limitations in the muscles of the neck or immaturities in the developing motor system.

One possibility concerns the sensitivity of head-turn or gaze-shift measures in assessing the auditory spatial abilities of infants. In a single-interval yes–no task, Morrongiello *et al.* (1990) asked observers to judge whether an infant showed any behavioral response (e.g. alerting, quieting, head turns towards or away from the sound source, or changes in pacifier-sucking behavior) to sound presentations that either did or did not include a shift in sound location [see the observer-based psychoacoustic procedure in Olsho *et al.* (1987)]. Under these test conditions, infants between 2 and 5 months of age show above-chance responses to sounds that shift laterally relative to a control sound source located at the midline. Moreover, the change in the MAA required to elicit some form of response decreases linearly from 2 to 5 months, and is accompanied by a complementary linear increase in the proportion of responses judged to be ‘yes’ coinciding with head turns towards the correct direction of the sound shift (Morrongiello *et al.*, 1990).

Another possibility is that, at this age, the developing motor system cannot make use of auditory spatial information in the same way that it can use visual information. Expanding on this idea, Muir & Hains (2004) propose that the neonatal auditory orienting response is suppressed to facilitate the integration of audio and visual spatial fields. As the visual field is very narrow at birth (Lewis & Maurer, 1992), the infant orienting response to sound sources might be delayed until the visual and auditory spatial fields become aligned at approximately 3–4 months of age. This age is coincident with the onset of reaching behavior in response to auditory targets presented in the dark (Clifton *et al.*, 1993). Behavioral sensitivity to the illusory percept known as the McGurk effect (requiring fusion of auditory speech stimuli and facial cues) also emerges after 4 months of age (Burnham & Dodd, 2004). Furthermore, adult data show a multisensory advantage in reaction time during localization of bimodal (auditory and visual) as compared with unimodal (auditory or visual) targets (Hughes *et al.*, 1994), and Neil *et al.* (2006) have found that a similar processing advantage is only observed after ~8 months of age. However, it is still unknown whether multisensory cues regarding spatial location elicit larger and/or earlier mismatch components in early infancy.

There is still much to be understood about how auditory space is represented in early infancy. Developing such an understanding is particularly important, given how sound localization processes are known to direct the infant's sensory and attentional systems towards potentially meaningful sound-producing objects in the environment (King, 2009), to integrate spatially congruent audio-visual cues (Lewkowicz, 2002; Neil *et al.*, 2006), and to facilitate auditory stream segregation (Hawley *et al.*, 2004; Hollich *et al.*, 2005), stimulus detection (Nozza, 1987; Nozza *et al.*, 1988), speech intelligibility in noise (Hirsh, 1950; Litovsky *et al.*, 2006), and language acquisition (Cho Lieu, 2004).

Conclusion

In this study, we tested the cortical responsiveness of 2-, 5-, 8- and 13-month-old infants to large spatial changes in the azimuthal position of a sound source by using the mismatch response. Despite the reported absence of overt behavioral orienting, it appears that 2-month-old infants detect large (± 90° relative to midline) changes in sound location at the cortical level. Moreover, the changes in MMR/MMN morphology for auditory spatial deviants generally follow the trajectory found for other auditory abilities, such as pitch discrimination and gap detection, over the first 13 postnatal months. One exception is that, relative to these other auditory discriminations, there is a protracted diminution of the slow-positive MMR. This may reflect enhanced salience of spatial deviants in all age groups. Future work should investigate whether and/or which of these mismatch components accurately reflects behavioral MAAs at different stages in early development and the early developmental trajectory for audio-visual spatial integration.

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Abbreviations

AUC, area under the curve; ERP, event-related potential; MAA, minimum auditory angle; MMN, mismatch negativity; MMR, mismatch response.

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