

COGNITIVE NEUROSCIENCE

Development of infant mismatch responses to auditory pattern changes between 2 and 4 months old

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Abstract

In order to process speech and music, the auditory cortex must learn to process patterns of sounds. Our previous studies showed that with a stream consisting of a repeating (standard) sound, younger infants show an increase in the amplitude of a positive slow wave in response to occasional changes (deviants) in pitch or duration, whereas older infants show a faster negative response that resembles mismatch negativity (MMN) in adults (Trainor *et al.*, 2001, 2003; He *et al.*, 2007). MMN reflects an automatic change-detection process that does not require attention, conscious awareness or behavioural response for its elicitation (Picton *et al.*, 2000; Näätänen *et al.*, 2007). It is an important tool for understanding auditory perception because MMN reflects a change-detection mechanism, and not simply that repetition of a stimulus results in a refractory state of sensory neural circuits while occasional changes to a new sound activate new non-refractory neural circuits (Näätänen *et al.*, 2005). For example, MMN is elicited by a change in the pattern of a repeating note sequence, even when no new notes are introduced that could activate new sensory circuits (Alain *et al.*, 1994, 1999; Schröger *et al.*, 1996). In the present study, we show that in response to a change in the pattern of two repeating tones, MMN in 4-month-olds remains robust whereas the 2-month-old response does not. This indicates that the MMN response to a change in pattern at 4 months reflects the activation of a change-detection mechanism similarly as in adults.

Introduction

Extracting patterns among successive auditory stimuli is an essential part of identifying auditory objects, and a vital basis for processing the complex communication signals comprising speech and music. Animal studies indicate that single neurons in primary and secondary auditory cortex can be activated by changes in auditory patterns (e.g. cats: McKenna *et al.*, 1989; Robin *et al.*, 1990; marmosets: Wang & Sachs, 1994). In humans, event-related potential (ERP) studies have shown that the brain automatically tracks patterns in incoming auditory stimuli and, on the basis of this information, makes predictions about future events (Näätänen *et al.*, 2007; Trainor & Zatorre, 2009). If such predictions fail to match the incoming stimuli, a frontally negative ERP deflection called mismatch negativity (MMN) is seen, with the main generators located in the secondary auditory cortex (for reviews, see Näätänen & Winkler, 1999; Picton *et al.*, 2000; Näätänen *et al.*, 2007). A few behavioural studies suggest that infants as young as 2 months old process sound patterns in that they discriminate languages on the basis of prosodic features (Nazzi *et al.*, 1998). In the present study, we investigated cortical responses to changes in pattern in infants at 2 and 4 months old.

Previous ERP studies of sound discrimination in young infants have involved the occasional presentation of a deviant sound that differs

from the repeating standard sound in pitch (e.g. Alho *et al.*, 1990; Leppänen *et al.*, 1997, 2004; Čeponienė *et al.*, 2000; Fellman *et al.*, 2004), duration (e.g. Trainor *et al.*, 2001, 2003; Friederici *et al.*, 2002; Hirasawa *et al.*, 2003), speech sound category (e.g. Cheour-Luhtanen *et al.*, 1996; Cheour *et al.*, 1998; Pang *et al.*, 1998) or conjunctions of more than one feature (Pihko *et al.*, 1999; Dehaene-Lambertz & Pena, 2001; Čeponienė *et al.*, 2002; Ruusuvirta *et al.*, 2003, 2004; Winkler *et al.*, 2003). In response to such changes, younger infants typically show a slow frontally positive response (e.g. Trainor *et al.*, 2001; Friederici *et al.*, 2002; Morr *et al.*, 2002; Winkler *et al.*, 2003; Friedrich *et al.*, 2004; Leppänen *et al.*, 2004; Ruusuvirta *et al.*, 2004; Novitski *et al.*, 2007) and older infants an MMN-like frontally negative response (e.g. Alho *et al.*, 1990; Cheour *et al.*, 1998; Čeponienė *et al.*, 2000, 2002; Trainor *et al.*, 2001, 2003; Kushnerenko *et al.*, 2002; Hirasawa *et al.*, 2003; He *et al.*, 2007, 2009). In previous work (He *et al.*, in press), we found that the slow positive difference to a simple pitch change in young infants decreases with increases in rate of presentation, whereas the MMN-like negativity to pitch change seen in 4-month-olds remains robust with increases in tempo, suggesting that the two responses might be functionally distinct.

In these previous studies, the deviant and standard sounds activate different neurons in the auditory cortex. However, in adults such sensory-based responses to sound change have been distinguished from higher-order change-detection mechanisms. Notably, sensory responses such as N1 decrease in amplitude as sounds are presented at faster rates, whereas MMN remains robust at fast tempi

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(Mäntysalo & Näätänen, 1987; Czigler *et al.*, 1992). Alain *et al.* (1994) presented adults with a repeating two-tone sequence composed of one high and one low tone. They found that MMN responses were reliably elicited by a change in the order of the tones, even though no new tones were introduced, indicating that MMN can be elicited when incoming sounds violate only the pattern of the previous input. Furthermore, MMN can be observed when standard trials are randomly drawn from a set of tone sequences whose members contain no pitches in common, but have a common pattern, such as a rising pitch contour or a particular sequence of melodic intervals (e.g. Saarinen *et al.*, 1992; Paavilainen *et al.*, 1995; Trainor *et al.*, 2002; Fujioka *et al.*, 2004, 2005). Such automatic extraction of sound pattern properties has been termed 'primitive intelligence' (Näätänen *et al.*, 2001).

Few studies have examined the development of mismatch responses in infants to changes in the pattern of auditory input. However, Carral *et al.* (2005) presented newborns with standard trials consisting of pairs of sine wave tones where the second note was higher in frequency than the first. They found a slow positive response to occasional deviants in which the second tone was lower than the first. Here we use stimuli similar to those of Alain *et al.* (1994) to examine responses to a pattern change in older infants, with a particular interest in the emergence of the adult-like MMN. Specifically, we presented 2- and 4-month-old infants with two tones of different pitch in an alternating sequence, and examined slow wave and MMN responses to a change in the alternating pattern.

Materials and methods

Participants

Eleven (seven female) healthy university students (aged 18–25 years, mean age 19.2 years) with no hearing deficits participated in the present study. Informed written consent was obtained from all participants prior to the experiment and course credits were assigned to compensate their participation.

A total of 29 healthy, full-term infants, either 2 months (16, nine female) or 4 months old (13, six female), with no known hearing deficits were included in the final sample. All infants were between 38 and 42 weeks gestation, and were over 2500 g at birth. All infants were awake during testing. An additional 25 infants (14 2-month-olds and 11 4-month-olds) were excluded from the final sample either because they fell asleep during testing (six 2-month-olds and four 4-month-olds), or because they became fussy during testing and failed to produce the minimum of 100 artefact-free deviant trials for averaging (eight 2-month-olds and seven 4-month-olds). Informed written consent was obtained from all parents prior to the experiment. After the experiment, a certificate and a bath toy were provided as thanks for their participation.

Stimuli

Standard trials consisted of piano notes C₅ and F#₅, with fundamental frequencies of 523 and 740 Hz, respectively, played in ascending pitch (C₅ followed by F#₅). Deviant trials consisted of the same two notes, but played in descending pitch (F#₅ followed by C₅). All notes were 400 ms in duration, and the onset asynchrony between adjacent notes, whether within or between trials, was 450 ms so that a continuous alternating sequence was formed (Fig. 1).

Apparatus

All of the piano tones were monaural and synthesized with REASON 2.0 software (Propellerhead Software), and recorded with ADOBE AUDITION 1.0 software (Adobe Software). Stimuli were played using E-prime 1.1 software (Psychology Software Tools) on a Dell OptiPlex280 computer with an Audigy 2 platinum sound card (Creative Labs) through a WestSun loudspeaker (WestSun Jason Sound, JSIP63) located 1 m directly in front of the participant. The stimuli were presented at 70 dB SPL (A) in a room with a background noise level of 29 dB SPL (A).

Procedure

Participants sat on a comfortable chair (infants sat on their parents' laps) in a sound-treated room containing surround floor-to-ceiling double velour curtains and acoustic ceiling panels. Participants watched either a silent movie (adult participants) or an animated video (infants) in a passive protocol while the piano tone stimuli were played. An oddball paradigm was used with 85% standard trials and 15% deviant trials. Stimulus order was randomized with the constraint that at least two standards trials occurred between successive deviants. The complete experiment consisted of 1500 trials (225 deviant trials) but testing was stopped early if infants became fussy. All study procedures were approved by the McMaster University Research Ethics Board. The McMaster Ethics Research Council follows the Canadian Tri Council Policy Statement: Ethical Conduct for Research Involving Humans.

Recording and analysis

Electroencephalogram (EEG) was recorded from 124 locations on the scalp for infants, and 128 locations for adults, with a Geodesic Sensor net (Electrical Geodesics). All electrode impedances were maintained below 50 kΩ. The electrical potential was digitized at 1000 Hz. The online recording was referenced to the vertex and a band-pass filter of 0.1–400 Hz was used.

Continuous EEG responses were off-line filtered between 0.5 and 20 Hz with filter roll-off of 24 dB/oct. The filtered continuous data were then segmented into 950-ms epochs, which covered the duration

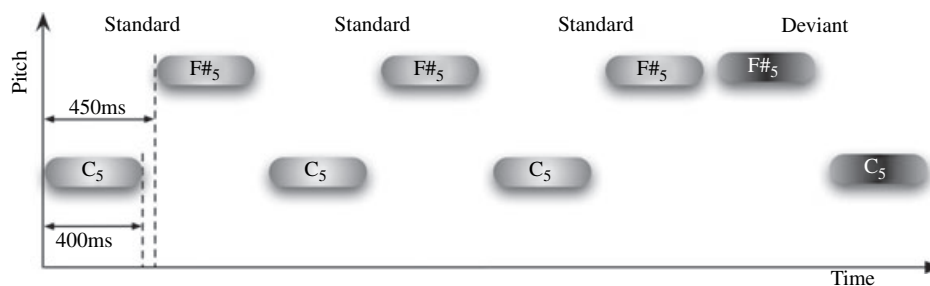


FIG. 1. Illustration of the stimuli. On occasional deviant trials the order of the two tones was reversed.

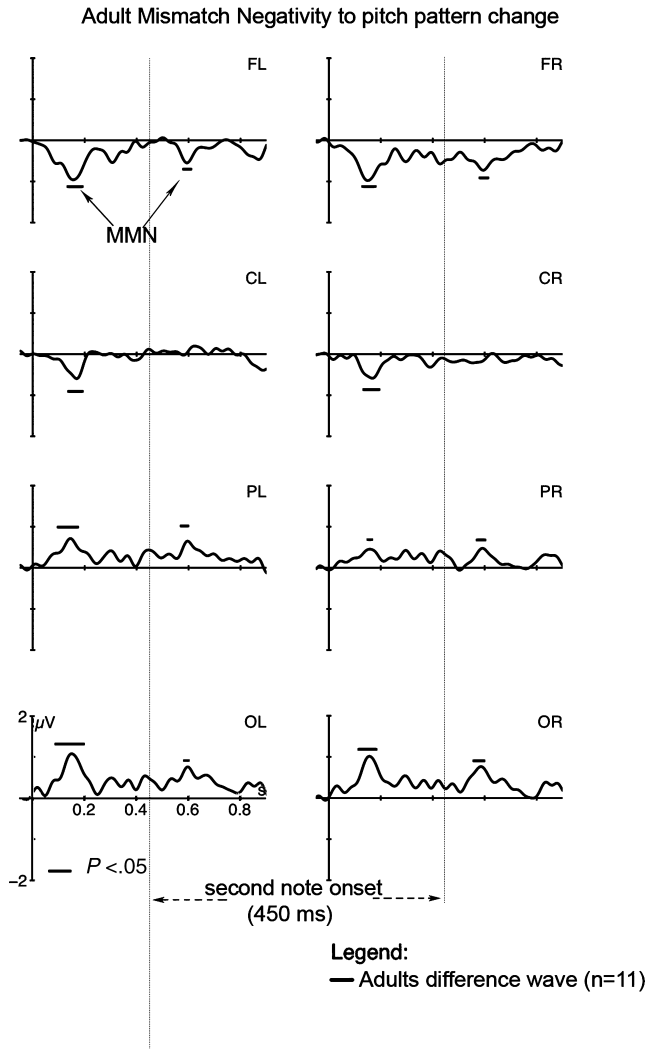


FIG. 2. Adult mismatch negativity (MMN) response to a change in pitch pattern. Difference waves (deviant – standard) show an MMN about 150 ms after onset of both tones in the pair. The amplitude of the MMN is larger for the first than for the second tone. Portions of the waveforms where MMN is significantly different from zero are shown in the bars above and below the waveforms. F, frontal; C, central; P, parietal; O, occipital sites. L, left hemisphere; R, right hemisphere.

of both tones within one trial and included a 50-ms baseline before the onset of the first note. EEG epochs from adult participants were then subject to fixed threshold ($\pm 120 \mu\text{V}$) epoch rejection to omit the artefact due to eye blinks. The averaged number of accepted deviant epochs across all 11 adult participants ranged from 127 to 219 ($M = 166$). For infants, channel-independent epoch rejection with a threshold of $\pm 120 \mu\text{V}$ was conducted to remove the epochs contaminated by blinks, eye, head or body movement (see He *et al.*, 2007). The number of accepted deviant epochs across the 29 infants ranged between 103 and 183 ($M = 136$). Standard epochs immediately following deviant epochs were excluded. The accepted standard and deviant epochs were averaged separately, baseline corrected, and referenced to an average reference. Difference waves were obtained by subtracting the standard from the deviant waveforms.

For statistical analysis, 76 channels were selected and divided into four groups for each hemisphere to represent the average response from frontal (20 channels), central (20 channels), parietal (20 channels) and occipital (16 channels) scalp regions. Midline electrodes

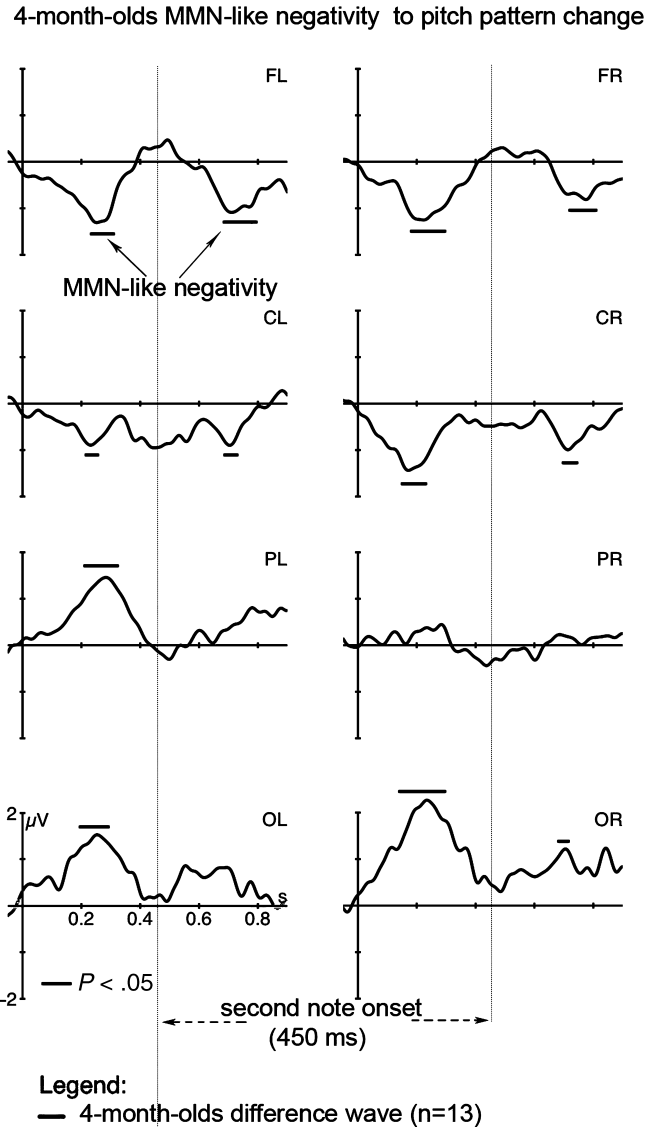


FIG. 3. Four-month-old infants' response to a change in pitch pattern. Difference waves (deviant – standard) show a mismatch negativity (MMN)-like negativity about 250 ms after the onset of both tones in the pair. The amplitude of the MMN-like negativity is larger for the first than for the second tone. Portions of the waveforms where MMN is significantly different from zero are shown in the bars above and below the waveforms. F, frontal; C, central; P, parietal; O, occipital sites. L, left hemisphere; R, right hemisphere.

were excluded in order to examine hemispheric differences; extreme frontal and peripheral electrodes were eliminated in order to reduce contamination from eye movement and other muscle movement (see He *et al.*, 2007 for details of the grouping scheme). Two-tailed paired *t*-tests were calculated at each time point between standard and deviant waveforms to reveal the time window of significant difference separately at each of the eight scalp regions for adults, 4- and 2-month-olds.

In 4-month-olds and adults, the peak latency and peak amplitude of the MMN or MMN-like negativity after the first and second note of each trial were measured in the difference waveforms of each participant. The MMN was defined as the largest negative peak

between 100 and 300 ms in the frontal regions. Separate ANOVAs were calculated on peak latencies and amplitudes for the MMN-like negativity to examine whether it varied significantly between adults and 4-month-olds, between first and second notes in deviant tone pairs, and across hemispheres and scalp regions. Because 2-month-olds exhibited only broad discriminative slow wave deflections that rendered peak picking difficult (consistent with He *et al.*, 2007), the average standard and deviant amplitudes in successive 50-ms time bins between 100–450 and 550–900 ms after stimulus onset were measured for each scalp region and subjected to repeated-measures ANOVAs to test whether the waveforms varied significantly between standard and deviant conditions and/or across time bin, hemisphere and scalp region.

In all of the above ANOVAs, the Greenhouse–Geisser correction was applied to all within-subjects measures with more than two levels. The Tukey HSD test was used for *post hoc* comparisons. The Bonferroni correction was applied to multiple within-subject comparisons.

Results

MMN in adults and MMN-like negativity in 4-month-olds

Group difference waves (deviant – standard) for adults and 4-month-olds are shown in Figs 2 and 3, respectively. Adults showed typical MMN responses peaking about 150 ms after both tones of deviant trials (Fig. 2). The polarity of the MMN peak reversed at the back of the head, consistent with generators in the auditory cortex. For 4-month-olds, a MMN-like negative response was clear in response to both deviant tones, but the latency of this negativity was much later (about 250 ms) than for adults. This negativity is similar to that found for a change in a single pitch in infants of a similar age (e.g. Kushnerenko *et al.*, 2002; Morr *et al.*, 2002; Fellman *et al.*, 2004; He *et al.*, 2007; under review) as well as for changes in duration (Trainor *et al.*, 2001, 2003). In order to compare the MMN response in adults and the MMN-like negativity in 4-month-olds, peak latencies and absolute amplitudes were subject to separate ANOVAs

with age as a between-subjects factor, and note (first or second note within tone pairs), hemisphere and scalp brain region as within-subject factors.

For amplitude, the main effect of age was significant ($F_{1,22} = 17.0$, $P < 0.001$), reflecting larger peak amplitudes in 4-month-olds (mean \pm SEM = $1.28 \pm 0.066 \mu\text{V}$) than in adults ($0.88 \pm 0.071 \mu\text{V}$). The main effect of note was also significant ($F_{1,22} = 8.55$, $P = 0.008$), with a larger peak amplitude in response to the first note within the tone pair ($1.19 \pm 0.068 \mu\text{V}$) than the second note ($0.97 \pm 0.055 \mu\text{V}$). Region was also significant ($F_{3,66} = 3.01$, $P = 0.04$), reflecting different peak amplitudes in different regions. The largest peak amplitude was in the occipital region ($1.26 \pm 0.091 \mu\text{V}$) and the smallest in the central region ($0.94 \pm 0.08 \mu\text{V}$), but no two regions differed significantly by *post hoc* tests. The age by hemisphere interaction approached significance ($F_{1,22} = 3.48$, $P = 0.081$), reflecting a trend for a larger peak amplitude in the right hemisphere ($1.37 \pm 0.077 \mu\text{V}$) than in the left hemisphere ($1.19 \pm 0.075 \mu\text{V}$) among 4-month-olds but not adults. The whole head topographic voltage map of 4-month-olds and adults at the peak latency of the mismatch responses are shown in Fig. 4.

The ANOVA on the latencies of the MMN/MMN-like negativity revealed an extremely robust main effect of age ($F_{1,22} = 5394$, $P < 0.001$) due to much longer latencies in 4-month-olds (mean = 252 ± 0.95 ms) than in adults (mean = 149 ± 1.03 ms). The main effect of note was also significant ($F_{1,22} = 53.1$, $P < 0.001$), with shorter peak latencies for the second (206 ± 1.25 ms) than the first MMN peak (195 ± 0.75 ms). The main effect of hemisphere was also significant ($F_{1,22} = 8.18$, $P = 0.009$), with later peak latencies in the left hemisphere (202 ± 0.68 ms) than in the right hemisphere (199 ± 1.05 ms). The interaction between hemisphere and age ($F_{1,22} = 5.38$, $P = 0.03$) further showed that the hemisphere difference was only significant in 4-month-olds, with significantly shorter ($P = 0.001$) latencies (250 ± 0.92 ms) in the right hemisphere than in the left hemisphere (255 ± 1.42 ms).

To summarize, both adults and 4-month-olds showed mismatch in response to changes in the pitch pattern. However, the MMN in adults

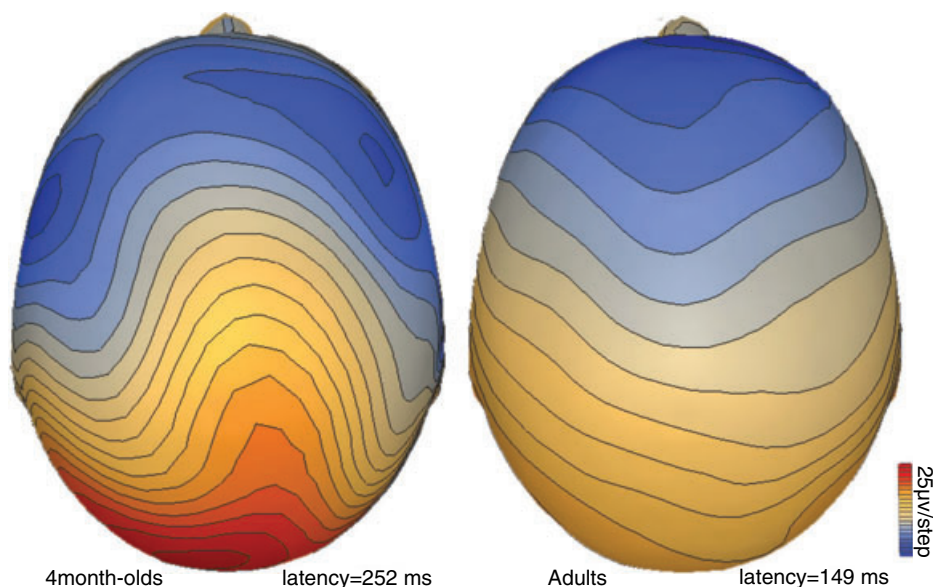


FIG. 4. Whole-head voltage map of MMN in adults and 4-month-olds. The MMN was maximal at frontal-central locations in adults. As seen in the left panel, the negativity of 4-month-olds was frontal and bilaterally distributed, while having a more frontal focus in the right than in the left hemisphere, which is consistent with the trend of statistical test results (see Results).

and MMN-like negativity in 4-month-olds differed substantially in both latency range and peak amplitude. For 4-month-olds, a trend for right hemisphere dominance of MMN-like negativity was also found, which is similar to the results of He *et al.* (2007) for simple pitch changes in infants of the same age. Interestingly, both MMN and MMN-like negativity were smaller in amplitude and shorter in latency in response to the second note in the pair compared with the first note.

Responses in 2-month-olds

Unlike 4-month-olds and adults, the standard and deviant waves (Fig. 5) of the 2-month-olds were significantly different in amplitude at only a few regions in the paired *t*-test result (see significance bars in Fig. 5). Neither a negative mismatch response, like that of 4-month-olds and adults, nor a positive mismatch response, like that found in He *et al.* (2007) for 2-month-olds for simple pitch changes, is very clear. However, both notes in both standard and deviant tone pairs elicited a slow positive wave, which is similar to the positivity that has been reported in previous studies (e.g. Leppänen *et al.*, 1997, 2004; Friederici *et al.*, 2002; Trainor *et al.*, 2003; Friedrich *et al.*, 2004; He *et al.*, 2007).

Because peak picking is difficult for slow wave activity, we calculated the average amplitude of standard and deviant waveforms in each successive 50-ms time bin from 100 to 450 ms and 550 to 900 ms, then conducted a four-way repeated-measures ANOVA to further investigate the difference between the standard and deviant waves in 2-month-olds, with stimulus type (deviant, standard), time bin (14 bins in total), brain region (frontal, central, parietal, occipital) and hemisphere (left, right) as within-subject factors. The results indicated a significant main effect of region ($F_{13,195} = 484.45, P < 0.0001$), and an interaction between region and time bin ($F_{39,585} = 4.52, P < 0.001$). The large effect of region and its interaction with time bin are due to the reversal in the polarity of the slow waves in both standards and deviants from anterior to posterior sites. Neither the main effect of stimulus type nor the stimulus type by time bin interaction was significant, which indicates that, by this analysis, the deviant and standard waves were not significantly different.

However, as shown in Fig. 5, by multiple *t*-tests comparing standards and deviants, four of the eight brain regions showed periods of significant difference. It can be seen that the significant regions at right frontal (FR) and left and right parietal (PL, PR) regions are quite late, occurring only after the second note, but that the significant region at the left occipital (OL) site occurs after the first note and its time course corresponds to that of previously reported discriminative slow wave activity in young infants (e.g. He *et al.*, 2007). An ANOVA at this site with stimulus type (deviant, standard) and time bin (14 bins in total) as within-subject factors revealed significant effects of time bin ($F_{13,195} = 3.94, P = 0.002$), and an interaction between time bin and stimulus type ($F_{13,195} = 2.29, P = 0.04$). *Post hoc* pairwise comparisons further indicated that the amplitudes of deviant waves were significantly larger than the amplitudes of standards between 250–300 ms ($P = 0.003$), 300–350 ms ($P = 0.009$), 350–400 ms ($P = 0.02$), 700–750 ms (250–300 ms after second note, $P = 0.002$) and 750–800 ms (300–350 ms after second note, $P = 0.03$). Thus, this analysis shows a significant discriminative slow wave response to both tones at the left occipital region, and suggests that there is at least some cortical response to the pattern change in 2-month-old infants as a group. There was considerable variance across infants, which may have obscured the effects at other regions, but the data of many infants were too noisy to analyse on an individual basis. However, two of the

2-month-olds response to standard and deviant tone pairs

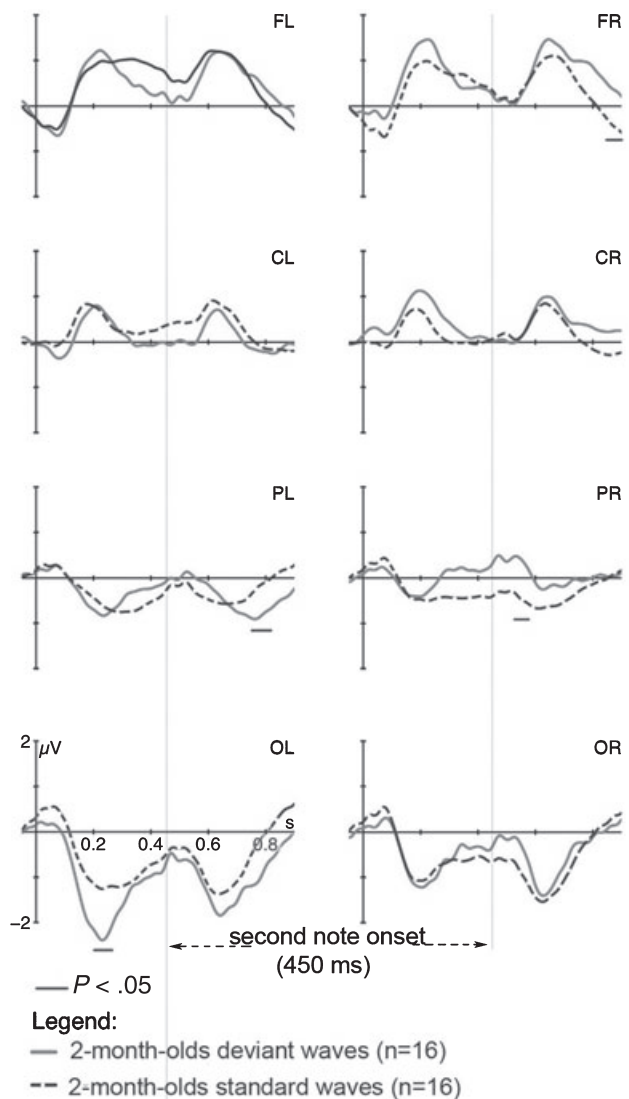


FIG. 5. Standard and deviant waves of 2-month-olds to a change in pitch pattern. Portions of the waveforms where standards and deviants were significantly different are shown in the bars above and below the waveforms. The standard and deviant waves were largely similar. Both tones elicited a positive response about 250 ms after tone onset. A few sites showed a trend for larger amplitude in deviant than in standard waveforms about 200–300 ms after the onset of each tone. F, frontal; C, central; P, parietal; O, occipital sites. L, left hemisphere; R, right hemisphere.

2-month-olds demonstrated very clear positive mismatch responses in their waveforms, as can be seen in Fig. 6.

Discussion

The present study demonstrates that infrequent changes in the order of a sequence of alternating piano tones elicit an MMN-like response in 4-month-old infants that is similar to that of adults, although with a longer latency and a trend for right-hemisphere dominance. The latter is consistent with previous infant studies (e.g. He *et al.*, 2007) and with the possible contribution of a frontal generator to the MMN (Näätänen & Winkler, 1999; Näätänen *et al.*, 2007). The MMN

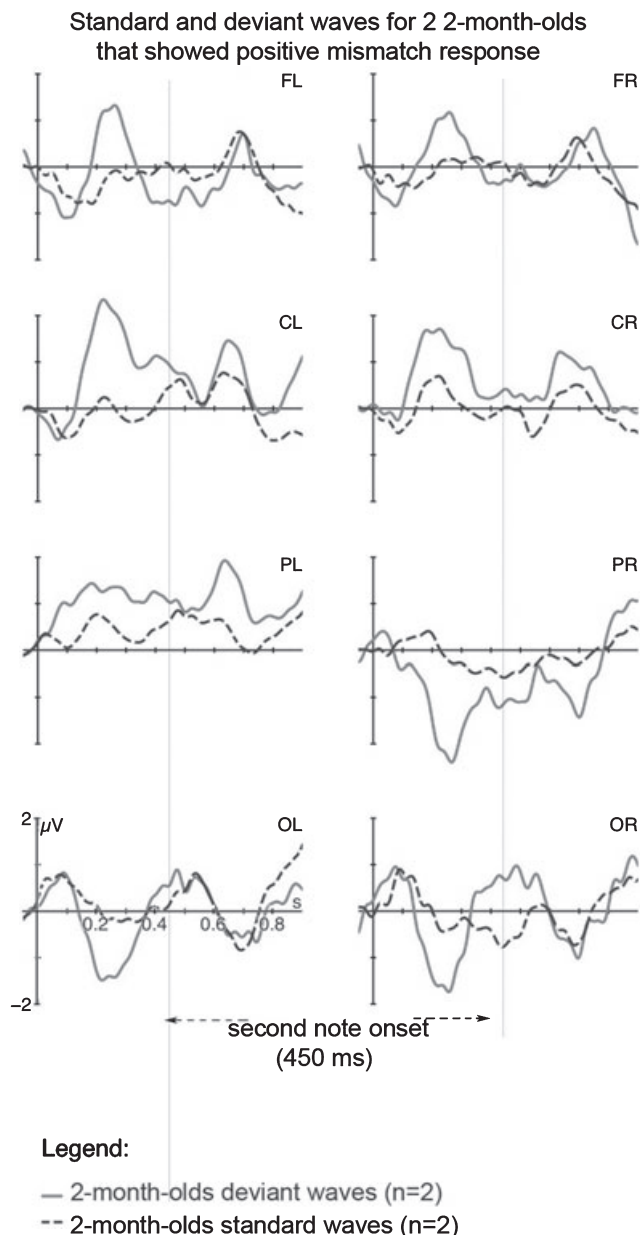


FIG. 6. Standard and deviant waves of two 2-month-olds showing a positive mismatch response to a change in pitch pattern. The deviant waves were larger in amplitude than the standard waves about 250 ms after the onset of each tone in the pair. F, frontal; C, central; P, parietal; O, occipital sites. L, left hemisphere; R, right hemisphere.

response to the change in pattern in 4-month-olds appears to be similar to that previously reported for simple changes in pitch, duration and speech sounds (e.g. Alho *et al.*, 1990; Cheour *et al.*, 1998; Čeponiene *et al.*, 2000, 2002; Trainor *et al.*, 2001, 2003; Kushnerenko *et al.*, 2002; Hirasawa *et al.*, 2003; He *et al.*, 2007), suggesting that all of these MMN responses at 4 months may represent the operation of a true change-detection mechanism.

The 2-month-olds in our previous study (He *et al.*, 2007) showed no adult-like MMN response to a simple change in pitch but, rather, a frontally positive slow wave response. The present study is consistent with this in that the 2-month-olds showed no adult-like MMN response to a change in pitch pattern, but evidence of a slow wave

response. However, the slow wave response was not particularly robust or consistent across infants. An overall ANOVA did not reveal significant differences between standard and deviant responses, but multiple *t*-tests showed significance in a few regions. An ANOVA on the left occipital region and follow up *post hoc* tests revealed significant slow wave responses to a change in pattern on both the first and second tones of the pattern between about 250 and 400 ms after the onset of each tone.

Carral *et al.* (2005) reported a slow positive response to a change in pitch pattern in newborn infants. The question becomes, then, why the positive response to change was more robust in the newborn infants in the Carral *et al.* (2005) study than in the 2-month-olds of the present study. The most intriguing possibility is that the slow wave response diminishes with increasing age, as has been found for the response to simple changes in pitch (He *et al.*, 2007) and duration (Trainor *et al.*, 2003).

However, there are at least three other possibilities. First, the infants in the Carral *et al.* (2005) study were asleep whereas our 2-month-olds were awake. The slow wave activity might well decrease when infants are more alert. The other two possibilities have to do with differences in the stimuli used. A recent study by Kushnerenko *et al.* (2007) found that the newborn, but not adult, response to an occasional change in an auditory stimulus was driven largely by the spectral bandwidth of the deviant stimulus. In particular, when presented with a stream of tones, occasional white noises, whose sensory representations would span large areas of auditory cortex, elicited large responses in newborns. We used harmonically rich piano tones whereas Carral *et al.* used pure tones, so it is possible that this may have led to the difference across studies, although the exact mechanism remains unclear. The third possibility has to do with the nature of the pattern used in the two studies. Carral *et al.* presented tone pairs at a different pitch level on each presentation of a standard stimulus whereas we used only two alternating pitches and occasionally changed their order. In our case, when the order was changed the same note was repeated (see Fig. 1). Thus, when the deviant note was presented, the neural circuits encoding that note had very recently been activated and therefore might have been in a somewhat refractory neural state, making them less able to respond. This suggests one of two possibilities. The slow positive response to change might be sensitive to refractory processes as suggested by He *et al.* (2007) and unlike adult MMN, or a sensory refractory process is occurring at the same time as the response to change, and masking it. In sum, more research is needed in order to know whether the very small positive response to the pattern change seen at 2 months reflects refractory processes or a developmental decrease in the amplitude of this component with increasing age.

There are still questions remaining as to the nature of the response to pattern changes in 2-month-old infants, but there is clearly no evidence for an adult-like MMN response at this age. On the other hand, a clear adult-like MMN response is seen at 4 months, likely reflecting the operation of a change-detection mechanism similar to that of adults.

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Abbreviations

EEG, electroencephalogram; ERP, event-related potential; MMN, mismatch negativity.

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