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Research report

Event-related potential features indexing central auditory discrimination by newborns

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Abstract

Behavioral research has produced little evidence on sound feature discrimination in neonates. Sensory processes underlying sound perception can be studied using the mismatch negativity (MMN) component of auditory event-related potentials (ERPs), which is not contingent on conscious perception and response. Thus, MMN is suitable for studying newborns, who are difficult to obtain behavioral responses from. The present study thus utilized spectrally rich sounds, known to elicit the most replicable MMN in adults, to investigate newborns' preattentive analysis of sound duration and frequency changes. An attempt was also made to control for the obligatory ERP effects on the MMN. Three-partial harmonic tones were presented in Duration and in Frequency oddball conditions to 55 newborns. In the other two, Equiprobable duration and Equiprobable frequency, conditions frequency and duration deviants of the oddball paradigms were presented with equal probabilities among sounds of other durations and frequencies. MMN was elicited in 81% of newborns in Frequency oddball condition and in 78% of newborns in Duration oddball condition. No significant amplitude differences between the duration and frequency MMNs were found, but MMN latency was delayed in Duration condition. The obligatory components seemed to contribute significantly to the deviant-standard difference in Duration but not in Frequency condition. The majority of neonates appear to possess effective sound frequency and duration discrimination mechanisms. Their preattentive sound discrimination is facilitated by spectrally rich sound content. The present findings support a change-detection nature of MMN in neonates; however, sound duration-related obligatory effects need to be taken into account in infant MMN studies.

Theme: Neural basis of behavior

Topic: Learning and memory: systems and functions

Keywords: Auditory event-related potentials; Auditory sensory discrimination; Mismatch negativity; Newborn

1. Introduction

Auditory sensory memory (ASM) is the earliest memory buffer where preconscious sound feature analysis, integration, and discrimination occur [45,52,53]. This memory module provides a database for an information read out to further, including conscious, information processing mechanisms [17,45]. Mismatch negativity (MMN) [47] is a component of brain event-related potentials (ERPs)[2] that can be used to investigate the afore-mentioned ASM functions [45,46,52]. An MMN is elicited when stream of identical, 'standard' sounds is violated by a different, 'deviant' sound. It was therefore suggested [52,56,60] that when sounds are repeated, a short-lived neural representation of the repeating (invariant) sound feature(s) is formed, and the real-time auditory input is compared to this representation. The deviant sound apparently triggers a

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[2]ERPs are induced by either environmental or endogenous events and appear as transient voltage changes in the ongoing electrical brain activity within a short time frame preceding or following the eliciting event.

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neural processing of change from this established short-term memory trace of invariance [56,60]. The output of this neuronal calculation is reflected in ERPs as a negative voltage difference (the MMN) between the deviant and standard stimulus responses. In adults, a change in acoustic, phonetic, or relational sound features commonly elicits the MMN if this change can also be perceptually discriminated [51,62,68]. The MMN can be elicited without attention to the stimuli, that is, preconsciously; nonetheless, MMN elicitation and amplitude have been shown to correlate with conscious sound discrimination performance in adults [35,48,62,68] and, at a group level, in children [4,29].

The MMN phenomenon is valuable when investigating subject populations whose behavioral responses are unavailable or unreliable, such as human infants. In newborns, an MMN peaking at 200–400 ms after sound change onset has been elicited by sinusoidal tone frequency change [1,12,32,38], phonemic vowel change [11], and duration change of fricative consonant in a pseudoword [34]. On the basis of the afore-mentioned studies and those performed on older infants [6,8,39] it has been concluded that the MMN is one of the ontogenetically earliest perception-related responses that can be recorded at the scalp (for a review, see Ref. [32]). However, elicitability of MMN in infants is somewhat lower than in adults. In studies that used sinusoidal tones the MMN was reported in six out of eight [1], 75% [32], and 50% [38] of newborns.

Lower MMN elicitation in neonates might be caused by several factors. First, it is possible that sensory auditory processing in newborns is less accurate, and discrimination poorer, than in older infants and children. This would be accounted for by the functional immaturity of the neonatal auditory system. Even though it has been shown that the newborn's cochlea matures structurally prior to birth [69], it continues to develop functionally until ca. 3 years of age [20]. Similarly, sound transmission in the brainstem, as indicated by evoked brainstem potentials, reaches mature parameters at 1–2 years of age [44,58]. No data is available on early neuro-functional development of the human auditory cortex, such as, e.g., synaptic efficacy or tonotopicity. Structural data indicate that synaptic density in the auditory cortex is maximal at 3 months post natum [23] and decreases thereafter. At birth, intracortical connectivity is deeply immature, especially in the superficial layers [59]. In these layers, adult-like connectivity develops only by 11 years of age, and fiber myelination progresses even longer [22].

Behavioral studies on newborns' sound feature discrimination partially support the notion that neonates have immature perceptual abilities. Leventhal and Lipsitt [40] and Trehub [67] found no evidence for newborns discriminating frequency contrasts of 100 vs. 200 Hz, 200 vs. 500 Hz, or even 1000 vs. 2000 Hz. However, in Leventhal and Lipsitt's study [40] the 200 vs.1000 Hz tone discrimination approached significance. Further, using a physiological method of fetal cardiac rate registration, Lecanuet et al. [36] found that 90% of 36–39-week-old fetuses detect pitch differences between two piano notes of fundamental frequencies 292 and 518 Hz. Just slightly older,1-month-old, infants were found to reliably increase their sucking rate when the 200-Hz test tone was replaced by a 500-Hz tone, and vice versa [71].

Studies of sound duration discrimination in newborns [14,15] have found that they require rather long sound duration (at least 1 s) to orient to the sound. No evidence for sound duration discrimination on a millisecond scale has been obtained. Infants aged 1 month and older were found to discriminate syllables and complex tones differing in voice-onset time (VOT) by 15–55 ms [21,26,27]. However, these findings were explained in terms of categorical perception of stimuli used in those studies. We are not aware of any comparable findings in newborns.

Behavioral responding, though, is contingent on many non-sensory factors such as the infant's state, motor abilities, and attention, which make it difficult to interpret the performance and to isolate sensory factors. Therefore direct measures of central sensory processing, such as obligatory ERPs and MMN, might be expected to be more accurate than the behavioral measures Still, the lower MMN elicitability in neonates indicates that sensory sound discrimination is poorer at birth than later in life. We wondered whether there were factors other than immaturity of the MMN generating system that might contribute to this result.

It has been demonstrated that obligatory components[3] of newborn ERPs are sensitive to sound intensity [54] as well as VOT and place of articulation cues in CV syllables [31,42]. They may even display changes consistent with categorical VOT boundaries [63]. Further, DeRegnier et al. [19] reported increased amplitude and shorter latency in the newborn ERP peak, called P2 in their study, in response to the voice of the mother (as compared to that of a stranger). Based on the aforementioned findings, it appears that newborns possess an ability to form sound feature representations at the level of neural processes that are indexed by obligatory responses. However, in adults obligatory responses either do not correlate with auditory perception or correlate only poorly. This might be expected to be the case in infants as well.

Even at birth, infant obligatory responses display robust refractoriness effects. Vaughan and Kurtzberg [70] reported a remarkable increase in the obligatory positivity in response to deviant sounds in both newborns and older infants. This might influence the deviant-standard ERP

[3] Exogenous, or obligatory, ERP components are those that are obligatorily elicited by the occurrence of stimulus, are determined by the physical stimulus characteristics, and change their properties only in relation to stimulus features. In contrast, endogenous components can be elicited without exogenous stimuli.

difference, and thus the researchers' interpretation of sound discrimination abilities. Some other studies also support this possibility. In the study by Leppänen et al. [38], the grand-mean response to an 1100-Hz deviant tone was more positive than to an 1000-Hz standard tone, even though deviance-related negativities were present in half of the 28 newborns studied. When the frequency difference between the deviant and the standard stimuli was increased by using 1300 Hz as the deviant tone, it was found that the ERP for the 1300-Hz deviant tone was negative relative to that elicited by 1100-Hz deviant tone. The authors of this study concluded that the deviant sounds evoke a positivity greater than the standard because they excite new afferent elements (which confirms earlier findings in Ref. [70]). They also suggested that in newborns the MMN might often appear as a reduction of the obligatory positivity in the deviant response. It can be further inferred that in order to appear as negativity in the deviant-standard difference, the newborn MMN has to be of a larger voltage than the increase in the positive obligatory response.

The exogenous components contribute to the deviant response also in adults [50,62]. However, it has been shown that in adults, even deviant sounds that are known to elicit a smaller obligatory N1 wave than the corresponding standards (e.g., lower intensity tones as compared to higher intensity tones) in an oddball paradigm evoke a negativity (the MMN) exceeding that in the standards [49,55]. It therefore appears that the obligatory effects differ significantly between infants and adults.

An alternative explanation for why the deviant sounds evoke positivities in infants would be that their discrimination response is positive in polarity. Two recent studies [37,57] have investigated sound duration discrimination, as indexed by MMN, in newborns. The authors presented the CV syllables /kaa/ (standard, duration 250 ms), and /ka/ (deviant, duration 110 ms) with a short stimulus onset asynchrony (SOA, onset-to-onset) of 425 ms to 32 newborns, and with a longer SOA of 855 ms to 11 newborns, all in quiet sleep state. In these studies, the ERPs to the deviant sounds were mostly positive in relation to those elicited by the standards. The authors [37,57] concluded that a positive difference obtained in response to the deviant syllable in infants could not be entirely accounted for by enhancement of the obligatory response, and thus might represent a genuine infantile discriminative response. However, before conforming to such a view one would need to systematically investigate whether, and how, sound features such as duration and frequency are reflected in obligatory positivity in newborns. Further, one would need to look for a way to eliminate such effects from the deviant-standard difference waveforms in order to be able to assess a genuine discriminative response.

The newborn MMN studies mentioned earlier in the paper have demonstrated that neonates are able to preattentively discriminate several acoustic contrasts. However, the characteristics of sensory processes underlying generation of MMN in newborns have been addressed by only a handful of studies [9,32,38].

In school-age children [5] and in adults [65], spectrally rich tones were found to elicit larger MMN responses and (in adults) to render the behavioral discrimination more accurate, compared with single-frequency sinusoidal tones. It was therefore inferred that spectrally rich sound content facilitates preattentive discrimination of pitch in both children and adults. Further, in adults it was shown that MMN replicability was better when deviant sounds were shorter in duration (by 66%), than when analogous frequency or intensity changes were used [66].

The present study therefore aimed to investigate preattentive (as reflected by MMN) sound frequency and duration discrimination in newborns, using harmonically rich, though acoustically not too complex stimuli (harmonic tones), with the purpose of clarifying whether similar facilitation of sensory auditory processing is already present at birth. An important parallel goal was to examine the reflectance of sound duration and frequency in obligatory ERPs in newborns, and to separate the discriminative responses from these obligatory effects.

2. Materials and methods

2.1. Experimental design and stimuli

Two main (oddball) and two control (equiprobable) experimental conditions were carried out in healthy full-term newborns.

2.1.1. Oddball conditions

In the Duration condition, the standard stimulus was a 200-ms harmonic tone consisting of three lowest partials of the 500-Hz fundamental frequency (i.e., 500, 1000, and 1500 Hz sinusoidals), the second and third components being lower in intensity than the first one by 3 and 6 dB, respectively. The deviant tone was otherwise identical but 100 ms in duration.

In the Frequency condition, the standard tone was 100 ms in duration and of the same spectral content as the standard tone in the Duration condition. The deviant tone in this condition was a 100-ms harmonic tone consisting of three lowest partials of the 750-Hz fundamental frequency (i.e., the 750, 1500, and 2250 Hz sinusoidals), the second and third components being lower in intensity by 3 and 6 dB, respectively.

In both conditions, the standard stimulus occurred with a probability of 85%, while the deviant stimulus occurred with a probability of 15%. The stimulus onset asynchrony (SOA, onset-to-onset) was set at 800 ms. Three to four stimulus blocks of 400 events each were presented to every newborn during the active sleep state. This resulted in 110–324 (mean 156) accepted deviant and 503–1847 (mean 900) accepted standard events.

2.1.2. Equiprobable conditions

Two control conditions with tones of three durations and three frequencies (in separate blocks, probability of each tone being 33%) were also carried out. The rationale behind the control conditions was to equalize, as much as possible, the contribution of the obligatory ERP components in the waveforms entering the subtraction procedure. The deviant-sound ERP may incorporate both the MMN and the enhancement of the obligatory ERP peaks, the latter resulting from the activity of neurons excited by the novel afferent input of the deviant sound. When the standard ERP is replaced in the subtraction by one obtained in the condition when the 'deviant' sound is presented with 100% probability and at the same rate as the standard, this does not eliminate the contribution of the obligatory enhancement to the difference wave, since the refractoriness level of such a 'deviant' response equals that of the standard-, not the deviant-stimulus ERP. Such a manipulation eliminates only those obligatory differences that are present in the refracted responses, and therefore are small in amplitude. One way to reduce the effects produced by new afferent elements is to present the 'deviant' sound with a probability close to that of an oddball paradigm but among several other sounds having the same probabilities and varying along the same feature as the deviant. In such a case, the ERP to the sound of interest (the 'deviant') will not contain the MMN but will contain a nearly full obligatory response of the 'new' afferent elements, since their refractoriness level will be low due to the infrequent repetition. Subsequently, when the standard ERP is replaced in the subtraction by such a 'deviant' ERP, it cancels out most of the obligatory effects contained in the oddball-deviant ERP.

Therefore, in the Equiprobable-duration condition, harmonic tones of duration 100-, 200-, and 300-ms (500-Hz fundamental frequency) were presented with an SOA of 800 ms and with probabilities of 33% each. In the Equiprobable-frequency condition, 100-ms three-partial harmonic tones of fundamental frequencies 500-, 625-, and 750-Hz were presented with the same 33% probabilities. Two to three blocks of 420 events each were delivered to every newborn that participated in these conditions.

The rise/fall time of all the stimuli used in the study was 10 ms. All sounds had intensity of 70 dB SPL (sound-pressure level) at the infant's head.

2.2. Subjects and selection criteria

Healthy full-term infants, delivered at the Department of Obstetrics and Gynecology, Helsinki University Central Hospital, were enrolled in the study with the written consent of their parents. The study was approved by the Ethics Committee of the hospital.

In total, 55 newborns aged 1–3 days (birth weight 3060–4280 g, gestational age 36–42 weeks) were enrolled in the study. Data of 12 infants who spent most of the experimental time in quiet sleep stage were not included in the present analyses. All newborns included in the present study passed a peripheral hearing screening by evoked otoacoustic emissions (EOAE).

Out of the remaining 43 newborns (17 males), negativity in response to the deviant stimuli was elicited in 33 (77%). We regarded the negativity as MMN when it exceeded -1.0 μV in at least two out of four fronto-central electrodes. Since the goals of this study were to compare MMNs elicited by changes in different sound features and to evaluate the obligatory-response influences on MMN, only those infants showing MMN were included in the comparisons between conditions.

Out of 41 newborns (20 males) participating in the Duration condition, 26 (79%) showed MMN in the active sleep state and thus were accepted for further analysis. Out of 26 newborns (seven males) participating in the Frequency condition, 17 (81%) showed an MMN in active sleep. Eleven of these newborns also participated in the Duration condition.

The Equiprobable-duration condition was presented to 16 newborns (7 males). Thirteen of these infants participated in the oddball Duration condition as well. The Equiprobable-frequency condition was presented to 13 newborns (4 males). All of these newborns also participated in the oddball Frequency condition. Eight infants participated in both Equiprobable-duration and Equiprobable-frequency conditions.

2.3. EEG recording and averaging

Experiments were conducted in a silent room at the Hospital for Children and Adolescents of the Helsinki University Central Hospital. Sounds were presented through two loudspeakers placed 20 cm from either side of the recumbent newborn's head.

Continuous EEG was recorded (bandpass 0.1–30 Hz, sampling rate 250 Hz) using NeuroScan 3.0 software. Single-use electrodes were attached to eight scalp sites: F3–F4, C3–C4, P3–P4, and T3–T4, according to the International 10–20 system. Off-line, the data was epoched into 900-ms stimulus-onset-locked intervals, including 100 ms pre-stimulus and 800 ms post-stimulus time. Epochs were filtered by a bandpass 1.0–15-Hz filter and baseline corrected with respect to the mean 100-ms pre-stimulus voltage. The first three epochs of each block and those with an absolute EEG voltage in any channel exceeding ± 150 μV were discarded from averaging. Eye movements were monitored with two electrodes, placed below and at the outer corner of the right eye. During recordings, all electrodes were referenced to the right mastoid. Offline the data were re-referenced to the average of left and right mastoid recordings. Epochs containing responses to the standard and deviant stimuli were averaged separately.

The recordings lasted 1–2 h, including electrode placement and necessary breaks. One or both parents were present during the recording if they so wished.

2.4. Sleep stage classification

Sleep was classified on the basis of infant's behavior, respiratory activity, eye and limb movements, and continuous EEG patterns. Active sleep was characterized by closed eyes, irregular respiration, rapid eye movements, and occasional body movements. The EEG showed mixed patterns (high voltage in θ–δ frequency ranges) or low-voltage irregular (θ–β ranges) continuous patterns [64]. Closed eyes, absence of rapid eye movements and presence of slow eye movements, regular, low-amplitude respiration, occasional startles, and chin clonuses characterized the quiet sleep. The EEG displayed discontinuous tracé-alternant (TA) and continuous high-voltage slow (HVS) patterns.

2.5. Data analysis

In this study, MMN was determined in two different ways, by applying two different types of subtraction to construct the difference waveforms. First, the ERP to the standard stimulus was subtracted from the ERP to the deviant stimulus. In an alternative procedure, the ERP elicited by the stimulus, identical to either duration or frequency deviant but obtained in the corresponding Equiprobable (duration or frequency) conditions (the 'deviant'), was used instead of the standard-stimulus ERP. That is, the ERP to the 100-ms 500-Hz fundamental-frequency harmonic tone from the Equiprobable-duration condition ($P=33\%$) was subtracted from the identical-tone ERP obtained when it was a deviant in the Duration oddball condition ($P=15\%$). Likewise, the ERP to the 750-Hz fundamental-frequency tone from the Equiprobable-frequency condition ($P=33\%$) was subtracted from the ERP elicited by the 750-Hz fundamental-frequency tone when it was a deviant in the Frequency oddball paradigm.

Similarly as in our previous studies [2,3,34], two peaks were seen in the deviant-minus-standard difference waves (Fig. 3). They were identified as MMN and LDN (the late discriminative negativity of childhood [2,34]). Hence, two corresponding latency windows were set for the latency and amplitude measurements of these components. The earlier component was measured from within 100–350 ms, and the latter from within 350–750 ms. These time windows were defined by the distribution of the MMN peak latencies in the individual infants' average waveforms across the conditions. Mean MMN amplitudes were then calculated as a mean voltage of 40-ms intervals, centered on each infant's MMN peak latency at the F3 (applied to the F3, C3, and P3 tracings), and the F4 (applied to the F4, C4, and P4 tracings) electrodes. The largest positive deflection of the standard-tone ERP was measured as described above, from within 100–400 ms after stimulus onset.

Two-tailed *t*-tests for dependent samples were used to test whether the mean MMN and LDN amplitudes significantly differed from 0 μV, for each condition and subtraction type. Unless mentioned otherwise, data from F3, F4, C3, C4, P3, and P4 recordings were used in ANOVA analyses. The electrode effects were tested by one-way ANOVA, and the amplitude and latency differences between the components, conditions, and subtraction types were tested with two-way ANOVAs (Component× Electrode, Condition×Electrode or Subtraction type× Electrode). The sources of significant main ANOVA effects were clarified using a LSD (least significant difference) post hoc test. Greenhouse–Geisser adjustments were performed when applicable.

3. Results

3.1. Standard-tone ERPs

In the Duration condition, the newborn ERP to the frequently repeated, 200-ms standard tone was polyphasic (Fig. 1, top, dashed lines). At short latencies (ca. 50 ms), a small but consistent negativity was elicited by both standard and deviant tones (Fig. 1). At longer latencies, the standard ERP was dominated by positivity, lasting from 200 to 500 ms. A small, negatively directed deflection overlapped this positivity at ca. 350 ms in the fronto-central tracings. The closing component of the standard ERP was a rather slow negativity with onset latency exceeding 500 ms.

The waveform structure of the standard-tone ERP in the Frequency condition (Fig. 1, bottom, dashed lines) did not differ from that obtained in the Duration condition. However, the obligatory positivity at 200–500 ms was larger in the Frequency than in the Duration condition ($F(1,125)=4.15$, $P<0.03$; Fig. 2).

3.2. Difference negativities

3.2.1. Duration condition

In the Duration condition, the deviant-minus-standard difference wave revealed two negative components peaking at 250 and 450 ms — the MMN and LDN, respectively (Fig. 3, dashed line). Their corresponding latencies were 150 and 350 ms, as calculated from stimulus-change onset. The MMN in this condition was significant at all recording sites, whereas the LDN was significant at all but the right temporal electrode (Table 1). One-way ANOVAs revealed significant Electrode effects for both peaks. For MMN, it was significant at $F(5,125)=2.41$, $P<0.04$, whereas for LDN at $F(5,125)=4.17$, $P<0.0015$. The post hoc test showed that these effects originated from both the MMN and LDN being larger at right and left frontal than at right

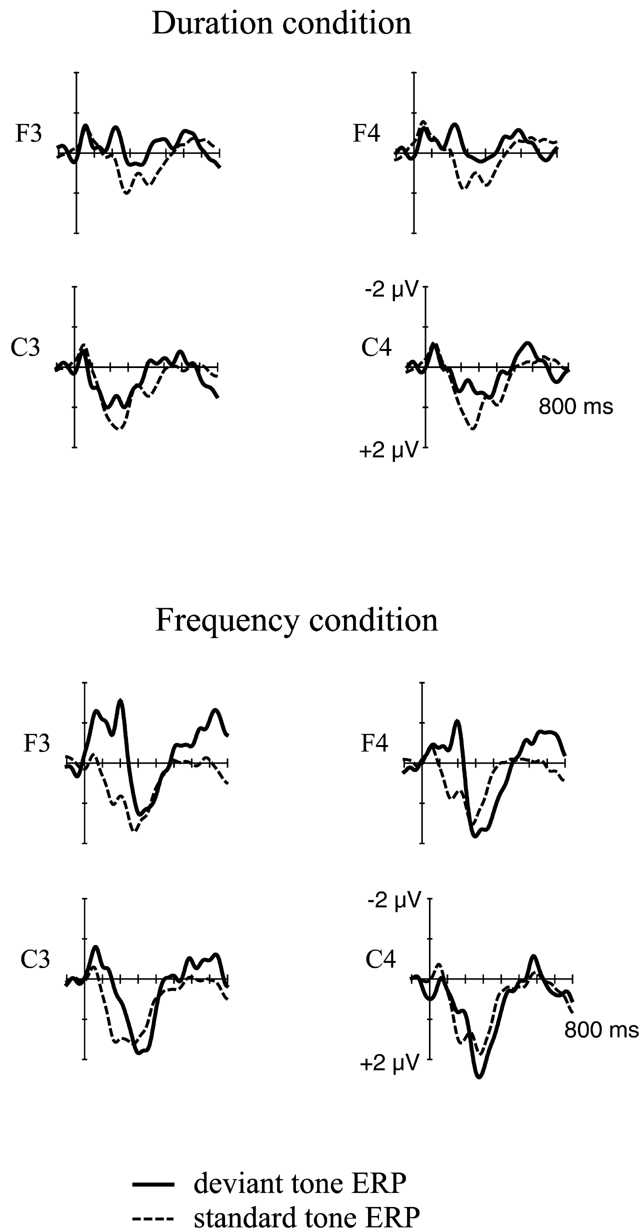

Fig. 1. Newborn ERPs to standard and deviant tones in the Duration (top) and Frequency (bottom) oddball conditions. In the Duration condition, both tones were three-partial harmonics of 500 Hz fundamental frequency. The standard tone was 200 ms long, and the deviant tone was 100 ms long. In the Frequency condition, both tones were 100 ms long. The standard tone was a three-partial harmonic of 500 Hz fundamental frequency, and the deviant tone was a three-partial harmonic of 750 Hz fundamental frequency. The F3–C4 refer to the electrode sites according to the International 10–20 system.

and left parietal electrodes ($P<0.005$–0.06 and $P<0.0003$–0.03, respectively).

A two-way ANOVA (Component×Electrode) revealed no significant Component or Component×Electrode interactions and only repeated the main Electrode effects found separately for the MMN and LDN, as described above.

The mean latency of the duration-decrement MMN, calculated across all the electrodes, was 257 ms, and that of LDN was 496 ms (see also Table 3).

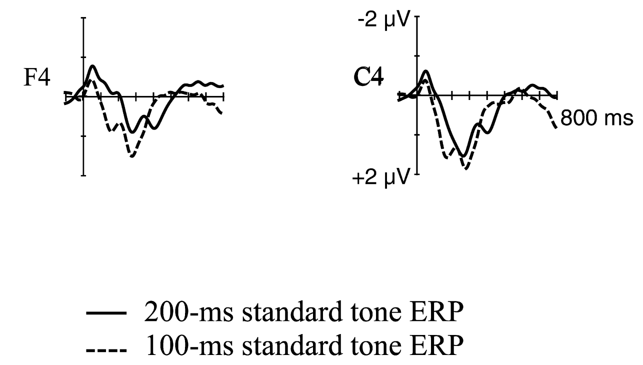

Fig. 2. Sound duration effects in the standard-tone ERPs. Overlaid are the 100-ms standard tone ERP obtained in the Frequency condition (dashed line) and the 200-ms standard tone ERP obtained in the Duration condition (solid line).

3.2.2. Frequency condition

In the Frequency condition the MMN, as determined from the deviant-minus-standard difference waves, was significant at the frontal and central electrodes (Table 2). The LDN, in addition, was significant at the left parietal electrode. The Electrode effect for the frequency-MMN was significant at $F(5,80)=4.32$, $P<0.0016$, again showing the largest MMN amplitudes at the frontal, as compared with the parietal and even the left central electrode ($P<0.0002$–0.02). For the LDN, the Electrode effect was also significant, $F(5,80)=5.86$, $P<0.0001$, originating from the LDN at both frontal electrodes being larger than that at both the parietal and right central electrode.

A two-way ANOVA (Component×Electrode) revealed no significant amplitude effects involving component.

The mean latency of the frequency-change MMN across the frontal electrodes was 171 ms, and that of the frequency-change LDN was 643 ms (see also Table 3).

Two-way (Gender×Electrode) ANOVAs were performed in order to test for possible gender effects on the MMN magnitude or latency. None of these analyses yielded significant results.

3.3. Between-condition comparisons

There were no significant amplitude differences between the Duration and Frequency conditions for either the MMN or LDN (Tables 1 and 2). However, latencies differed significantly between the conditions (Table 3). In the Duration condition, the MMN peaked on average 85 ms later than that in the Frequency condition ($F(1,9)=15.94$, $P<0.003$). In contrast, the mean latency of the LDN was longer in the Frequency than in the Duration condition ($F(1,10)=55.29$, $P<0.00002$).

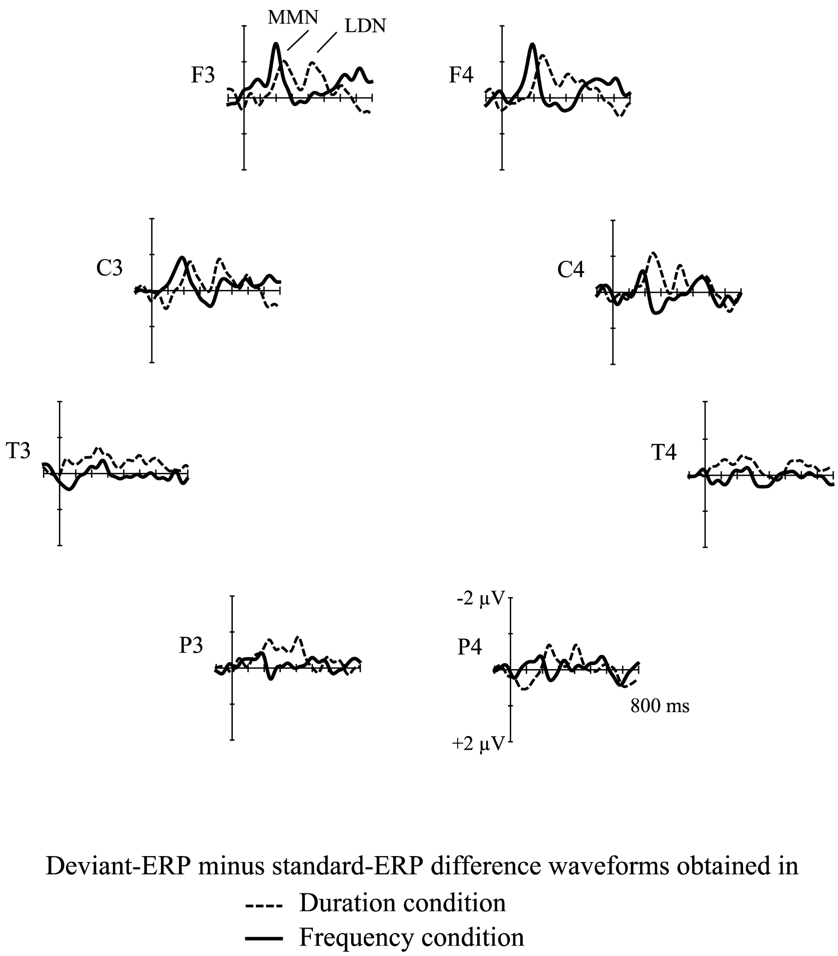

Fig. 3. Deviant-minus-standard ERP difference waves obtained in the Duration and Frequency oddball conditions. The MMN refers to the mismatch negativity; the LDN refers to the late discriminative negativity. The F3–P4 refer to the electrode sites according to the International 10–20 system.

Table 1
The MMN and LDN amplitudes (±S.D.) in the Duration condition

Electrode	MMN	LDN
F3	−1.57±1.79**	−2.18±1.40**
F4	−1.53±1.94**	−1.88±1.19***
C3	−1.16±2.28*	−1.66±1.81***
C4	−1.28±1.96**	−1.21±1.48**

*$P<0.05$, **$P<0.005$, ***$P<0.0001$.

Table 2
The MMN and LDN amplitudes (±S.D.) in the Frequency condition

Electrode	MMN	LDN
F3	−2.98±1.76***	−2.62±1.56***
F4	−2.37±1.25***	−2.35±1.31***
C3	−1.54±2.16*	−1.89±1.88**
C4	−1.48±1.68**	−1.45±1.54**

*$P<0.01$, **$P<0.005$, ***$P<0.0001$.

3.4. Effects of subtraction type

3.4.1. Duration condition

The difference waveform, obtained by subtracting the ‘deviant’-tone ERP, obtained in the Equiprobable-duration condition, from the deviant-tone ERP obtained in the oddball condition, differed significantly from that constructed using traditional, deviant-ERP minus standard-ERP, procedure (Fig. 4 and Table 4). The MMN, peaking at 250 ms, was enhanced ($F(1,12)=7.44$, $P<0.018$), while the LDN was reduced ($F(1,12)=8.83$, $P<0.01$) in the deviant-minus-equiprobable waveform as compared to the deviant-minus-standard waveform. (In this analysis, the components were measured as the mean amplitudes over 40 ms at 250 and 435 ms for each infant.) The Electrode effect in this analysis was significant for the MMN only, repeating the pattern described above. Interestingly, for the MMN the Electrode×Subtraction Type interaction also approached significance ($F(5,60)=2.12$, $P<0.07$). This tendency was produced by the MMN being larger over the frontal, as compared to the central, electrodes in the

Table 3
Mean latencies in ms (S.D.) of the MMN and the LDN peaks at F3 and F4 electrodes

Subtraction type	Frequency condition				Duration condition			
	MMN		LDN		MMN		LDN	
	F3	F4	F3	F4	F3	F4	F3	F4
Deviant-minus-standard	168 (49)	174 (60)	634 (105)	653 (103)	256 (48)	257 (49)	493 (102)	499 (101)
Deviant-minus-equiprobable	166 (50)	159 (44)	569 (37)	559 (32)	240 (67)	242 (66)	482 (81)	469 (79)

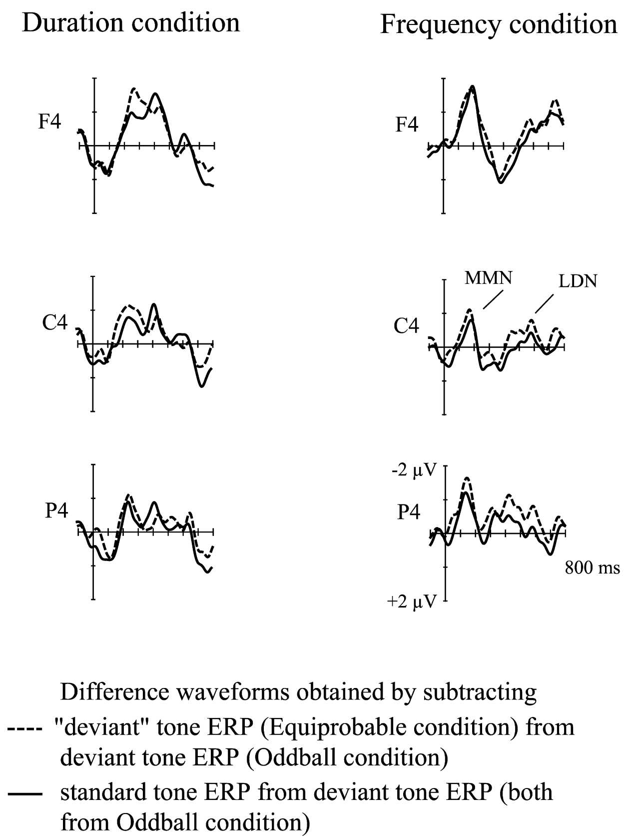

Fig. 4. Effects of the subtraction type. Deviant-minus-standard tone ERP difference waves are superimposed on the deviant-minus-equiprobable tone ERP difference waves. The MMN refers to the mismatch negativity; The LDN refers to the late discriminative negativity. The F4–P4 refer to the electrode sites according to the International 10–20 system.

deviant-minus-equiprobable difference wave, while in the deviant-minus-standard difference wave only the frontal and parietal electrode comparison yielded significant difference.

3.4.2. Frequency condition

The subtraction type did not significantly affect either frequency MMN or frequency LDN.

4. Discussion

This study investigated newborns' preattentive discrimination of the duration decrement and frequency increase in spectrally rich sounds, as reflected by the MMN. In addition, it examined obligatory tone frequency and duration effects on the deviant-standard difference.

Two discriminative negativities, MMN and LDN, were obtained in 77% of the 43 newborns studied in an active sleep state (Fig. 3). Both MMN and LDN were preponderant over the frontal scalp areas, as previously reported in children and adults [2,18,55]. The overall number of newborns (81%) who displayed an MMN-type response in the Frequency condition was larger than the highest (75%) reported so far [32] in a sufficiently large number of newborns. This was despite the fact that the criterion for 'MMN present' in the present study was somewhat higher, −1.0 μV, as compared with the −0.75 μV, applied [32]. The tighter filter settings of the present study in addition could have produced lower ERP amplitudes. However, this was not the case: the frequency-MMN amplitudes in the

Table 4
Subtraction type effects on the MMN and LDN amplitudes (±S.D.) in the Duration condition

Electrode	MMN		LDN	
	Deviant-minus-standard	Deviant-minus-equiprobable	Deviant-minus-standard	Deviant-minus-equiprobable
F3	−0.83±1.84	−1.91±2.59*	−1.59±1.99*	−0.82±2.26
F4	−1.29±2.26	−2.52±3.14*	−1.27±1.65*	−0.62±1.99
C3	−0.10±2.40	−0.97±2.75	−1.14±2.11	−0.43±2.23
C4	−1.00±2.36	−1.78±2.71*	−1.56±2.00*	−0.89±1.94

*$P<0.05$. The significance refers to the MMN and LDN amplitude differences between the subtraction types.

present study appeared to be larger, at the left frontal electrode approaching −3 μV (Table 2), than in the aforementioned study by Kurtzberg et. al [32] (−2 μV). (In both studies, the amplitudes refer only to those cases where the MMN was present.) In addition, the peak latency of the frequency-change elicited MMN was 171 ms in the present study, which is significantly earlier than 220–240 ms reported in studies in which simple tones were used [1,32,38]. Similar MMN amplitude and latency differences between harmonic and sinusoidal tones were reported in school-age children [5] and in adults [65]. Furthermore, in the present study responses to the standard stimuli were also robust (Fig. 1) despite the relatively fast stimulus pace. In previous newborn studies [1,7] using similar stimulus presentation rates, rather flat ERPs to standard stimuli were obtained. It therefore appears that spectrally rich sounds facilitate central sound encoding and preattentive sound discrimination in newborns, as they do in school-age children and in adults.

This is an important conclusion because it indicates that the negative behavioral results previously obtained in newborns [14,15,40,67] can be at least partially accounted for by the factors other than sensory. In accordance with this, the autonomic reactions which are automatic (such as cardiac pulse rate) were found to respond reliably in newborns to changes in synthetic vowels [13] or piano notes [36]. Furthermore, the magnitude of the cardiac response was larger for more complex sounds [13], which is in agreement with the present findings.

The duration-decrement condition also yielded significant MMN and LDN components. In this condition, responses were distributed more widely over the scalp than in the Frequency condition (Fig. 3, Tables 1 and 2). This pattern resembles that obtained in children [5] and in adults [24], where duration-MMN was found distributed posteriorly to the frequency-MMN. These findings might suggest differences in the configuration of frequency and duration MMN generators in newborns, and thus their functional specialization. Also the latency of the duration-MMN in the present study was significantly longer than that of the frequency-MMN, which indicates that the processes generating MMN cannot start until the offset of the duration deviant. To sum up, the findings of typical frontocentral MMN scalp distribution, together with typical duration-MMN latency delay, both resembling those in adults [24,25,66], support the change-detection nature of the MMN in newborns.

However, nearly 20% of newborns displayed no negativity in response to the deviant tones regardless of their intact peripheral hearing status, as indexed by the EOAE screening. We suggest that some of these newborns were indeed probably unable to accurately discriminate between the standard and deviant tones. This could be explained by the immaturity of the auditory system in some of them, since a developmental variation between individuals at this age is large [30]. Alternatively, in some of the newborns, the voltage relation between the positive-polarity obligatory ERP peaks and the negative-polarity MMN component possibly was in favour of the former, which did not permit detecting the MMN at the scalp surface. This would be in agreement with those ERP studies that found the deviant-standard ERP difference to be positive in polarity [37,38,57,70]. Accordingly, the deviant-tone ERP of the nine infants showing no MMN in the present study was positive relative to the standard-tone ERP (Fig. 5). The deviant-ERP waveform of these infants resembled that commonly recorded in response to the rare sounds [3,38,70], that is, as if the standard-sound context were not taken into account.

It is also possible that a small proportion of infants showing no MMN at birth are suffering from a central auditory disability. Molfese [41] and Molfese and Molfese [42,43] have found that the waveform morphology and amplitude of the cortical ERPs recorded at birth can be correlated with levels of language performance at 3 and even at 5 years of age. Therefore, one would need to re-test the newborns showing no MMN, and continue retesting those infants who did not develop a reliable response for an even longer period. This would allow determination of the normal age range for developmental sensory and ERP variability, during which the MMN should emerge in vast majority of healthy infants. It would also have practical consequences, namely in clarifying when absence of the MMN response should raise concerns about a possible central auditory dysfunction in an infant.

The present study found definite sound duration effects on obligatory (standard-tone) ERPs in neonates (Fig. 2). The 200-ms standard-ERP (Duration condition) was more negative during the 100–350 ms, but more positive during the 350–500 ms, than the standard-ERP elicited by an otherwise identical 100-ms duration tone (Frequency condition). This finding indicates that sound duration is represented in the central auditory system shortly after birth. When in subtraction the standard-tone ERP was replaced by the 'deviant'-tone ERP, obtained in the Equiprobable-duration condition, the duration-MMN significantly increased in amplitude, while the duration-LDN significantly decreased (Fig. 4 and Table 4). This effect apparently was caused by the fact that the 'deviant'-ERP contained obligatory sound duration effects similar in magnitude to the deviant-tone ERP obtained in the oddball paradigm (see also Section 2.1.2). Consequently, most of this obligatory effect was cancelled out during the subtraction. The differences in the standard-tone ERPs presented in Fig. 2 illustrate why the MMN was enhanced and the LDN was diminished in this alternative type of subtraction.

There are several lines of evidence that the subtraction type effects found in this study could not have been caused by the differences in the background EEG or by other general effects. First, there were two *opposite* effects, which were confined to rather short time intervals, that is 150–350 and 350–450 ms after stimulus onset (Fig. 4).

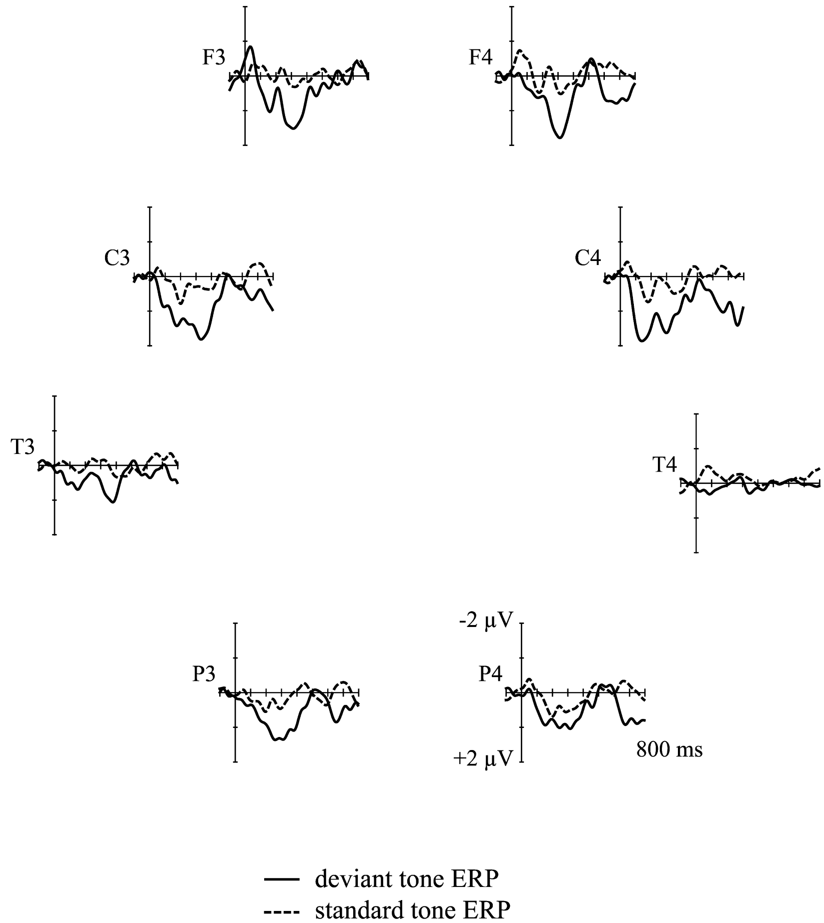

Fig. 5. Standard-tone and deviant-tone ERPs of the nine newborns showing no MMN in the present study. In this figure, responses to both types of the standard stimuli were averaged together, as well as the responses to both types of the deviant stimuli. The F3–P4 refer to the electrode sites according to the International 10–20 system.

These time intervals almost exactly matched those in which the duration-specific effects were evident in obligatory responses (Fig. 2). In addition, at the frontocentral electrodes the ERP waveform segments preceding and following these time windows nearly replicated each other across the two subtraction types. Such replicability eliminates the possibility of any significant bias in the data.

The present findings partially support the hypothesis advanced by Leppänen et al. [38] that considerable enhancement of obligatory responses inherent in the deviant-sound ERPs can significantly affect the deviant-standard ERP difference in infants. This is especially the case when duration contrasts are used to elicit MMN in newborns. Thus obligatory effects need to be controlled for, since at least in those cases where the deviant is shorter than the standard, the overall standard-deviant difference can apparently be significantly diminished.

However, our findings are at variance with the general notion that neonatal auditory discriminative response is positive in polarity, since as many as 81% newborns in the present study displayed the (negative) MMN.

It appears that that the 140-ms duration decrement in Leppänen et al. [37] and Pihko et al. [57] studies contributed to the difficulty of discerning the MMN in their experiments. However, as our anonymous referee pointed out, the difference between the duration contrasts in these and the present study (140 vs. 100 ms) might be considered too small to fully account for the discrepancy between the results. On one hand, there is behavioral evidence indicating that young infants (but not neonates) can discriminate VOT contrasts ranging from 15 to 55 ms [21,26,27]. Thus, the 40-ms difference between the duration contrasts might have influenced the ERP results as well. On the other hand, there were also other differences between the present study and those mentioned above, such as the nature of the stimuli (harmonic tones versus CV syllables), their absolute duration, recording and averaging parameters, and sleep states (active versus quiet), any of which might have contributed to the differences in results.

For the frequency MMN, the Subtraction type effect was much smaller (not significant, although in the same direction) as in the Duration condition. These cross-stimulus feature differences might imply that sound frequency and duration are encoded differently in the newborn auditory cortex and thus are reflected differently in their obligatory ERPs. One of the possible reasons for these different obligatory-effect magnitudes could be different orientations of the frequency-specific and duration-specific neuronal pools.

The LDN for the frequency change was rather small in the group grand mean waveform. However, it reached statistical significance when peaks were measured from a rather broad 350–750-ms latency window (Table 2). The amplitude of this response exhibited no Condition effect, but there was a significant latency difference, with the frequency-LDN peaking later than the duration-LDN. There is a possibility that the perceptually salient pitch change in the present study evoked also attentional effects, such as P3a component [61], indexing involuntary attention switch, and/or the Negative Component (Nc) [16] which is commonly elicited by novel, surprising stimuli. The P3a is known to peak at 300–400 ms after the deviant/novel stimulus onset, and the Nc at 700–800 ms [33]. Together with the fact that frequency changes are more attention catching than durational changes, this might explain the smaller amplitude of the LDN at its typical latency range, and its longer peak latency in the Frequency oddball condition.

The functional significance of LDN is unclear. Available evidence suggests that the LDN has a more protracted maturational course than the MMN [10] and may reflect processes other than preconscious sound discrimination, such as biological maturation of the central auditory systems [2], attention-related effects, or semantic aspects of sound processing [28]. In the present study, however, the LDN exhibited an amplitude and scalp distribution very similar to those of the MMN.

In conclusion, the majority of neonates appear to possess effective neural mechanisms for sound frequency and duration discrimination, as indexed by the MMN. Furthermore, their preattentive sound frequency and duration discrimination appear to be facilitated by acoustically rich sound content. Earlier behavioral findings on poor sound feature discrimination in newborns might thus be partially accounted for by extra-sensory factors. Obligatory feature-specific effects were found to contribute significantly to the deviant-standard difference for duration change but not for frequency change. These effects need to be taken into account in future infant MMN studies.

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References

[1] K. Alho, K. Sainio, N. Sajaniemi, K. Reinikainen, R. Näätänen, Event-related brain potential of human newborns to pitch change of an acoustic stimulus, Electroencephalogr. Clin. Neurophysiol. 77 (1990) 151–155, http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=1690117&dopt=Abstract.

[2] R. Čeponienė, M. Cheour, R. Näätänen, Interstimulus interval and auditory event-related potentials in children: evidence for multiple generators, Electroencephalogr. Clin. Neurophysiol. 108 (1998) 345–354, http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9714376&dopt=Abstract.

[3] R. Čeponienė, J. Hukki, M. Cheour, M.-L. Haapanen, M. Koskinen, K. Alho, R. Näätänen, Dysfunction of the auditory cortex persists in infants with certain cleft types, Dev. Med. Child Neurol. 42 (2000) 258–265, http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10795565&dopt=Abstract.

[4] R. Čeponienė, E. Service, S. Kurjenluoma, M. Cheour, R. Näätänen, Children's performance on pseudoword repetition depends on auditory trace quality: evidence from event-related potentials, Dev. Psychol. 35 (1999) 709–720, http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10380862&dopt=Abstract.

[5] R. Čeponienė, K. Yaguchi, A. Shestakova, P. Alku, M. Koskinen, K. Suominen, R. Näätänen, Sound complexity and speechness effects on preattentive auditory discrimination in children, Int. J. Psychopysiol., in press.

[6] M. Cheour, K. Alho, K. Sainio, K. Reinikainen, M. Renlund, O. Aaltonen, O. Eerola, R. Näätänen, The mismatch negativity to changes in speech sounds at the age of three months, Dev. Neuropsychol. 13 (1997) 167–174.

[7] M. Cheour, R. Čeponienė, J. Hukki, M.-L. Haapanen, R. Näätänen, K. Alho, Brain dysfunction in neonates with cleft palate revealed by the mismatch negativity (MMN), Clin. Neurophysiol. 110 (1999) 324–328, http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10210622&dopt=Abstract.

[8] M. Cheour, R. Čeponienė, A. Lehtokoski, A. Luuk, J. Allik, K. Alho, R. Näätänen, Development of language-specific phoneme representations in the infant brain, Nat. Neurosci. 1 (1998) 351–353, http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10196522&dopt=Abstract.

[9] M. Cheour, R. Čeponienė, P. Leppänen, K. Alho, T. Kujala, M. Renlund, V. Fellman, R. Näätänen, The auditory sensory memory trace decays rapidly in newborns, Scand. J. Psychol. (in press).

[10] M. Cheour, R. Čeponienė, T. Rinne, P.H.T. Leppänen, M. Tervaniemi, N. Kraus, R. Näätänen, Auditory event-related potentials in children and adults: MMN maturates early, LDN does not, in press.

[11] M. Cheour-Luhtanen, K. Alho, T. Kujala, K. Sainio, K. Reinikainen, M. Renlund, O. Aaltonen, O. Eerola, R. Näätänen, Mismatch negativity indicates vowel discrimination in newborns, Hear. Res. 82 (1995) 53–58, http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7744713&dopt=Abstract.

[12] M. Cheour-Luhtanen, K. Alho, K. Sainio, T. Rinne, K. Reinikainen, M. Pohjavuori, M. Renlund, O. Aaltonen, O. Eerola, R. Näätänen, The ontogenetically earliest discriminative response of the human brain, Psychophysiol. Special Report 33 (1996) 478–481, http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8753948&dopt=Abstract.

[13] M.G. Clarkson, W.K. Berg, Cardiac orienting and vowel discrimination in newborns: crucial stimulus parameters, Child Dev. 54 (1983) 162–171, http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=6831983&dopt=Abstract.

[14] M.G. Clarkson, R.K. Clifton, I.U. Swain, E.E. Perris, Stimulus duration and repetition rate influence newborns' head orientation toward sound, Dev. Psychobiol. 22 (1989) 683–705, http:/

/www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=2680684&dopt=Abstract.
[15] M.G. Clarkson, I.U. Swain, R.K. Clifton, K. Cohen, Newborns' head orientation toward trains of brief sounds, J. Acoust. Soc. Am. 89 (1991) 2411–2420, http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=1861001&dopt=Abstract.
[16] E. Courchesne, Chronology of postnatal human brain development: even-related potential, positron emission tomography, myelinogenesis, and synaptogenesis studies, in: R. Rohrbaugh, R. Parasuraman, R. Johnson (Eds.), Event-related Brain Potentials: Basic Issues and Applications, Oxford University Press, Oxford, 1990, pp. 210–241.
[17] N. Cowan, in: Attention and Memory. An Integrated Framework, Clarendon Press, Oxford, 1995.
[18] V. Csépe, On the origin and development of the mismatch negativity, Ear Hear. 16 (1995) 91–104, http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7774772&dopt=Abstract.
[19] R.A. DeRegnier, C.A. Nelson, K.M. Thomas, S. Wewerka, M.K. Georgieff, Neurophysiologic evaluation of auditory recognition memory in healthy newborn infants and infants of diabetic mothers, J. Pediatr. 137 (2000) 777–784, http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=11113833&dopt=Abstract.
[20] J. Eggermont, C. Ponton, S. Coupland, R. Winkelaar, Frequency dependent matureation of the cochlea and brainstem evoked potentials, Acta Oto-Laryngol. 111 (1991) 220–224, http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=1880297&dopt=Abstract.
[21] P. Eimas, E. Siqueland, P. Juscyz, J. Vigorito, Speech perception in infants, Science 171 (1971) 303–306.
[22] P. Huttenlocher, Synaptic density in human frontal cotex — developmental changes and effects of aging, Brain Res. 163 (1979) 195–205, http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=427544&dopt=Abstract.
[23] P. Huttenlocher, A. Dabholkar, Regional differences in synaptogenesis in human cerebral cortex, J. Comp. Neurol. 387 (1997) 167–178, http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9336221&dopt=Abstract.
[24] M. Jaramillo, P. Alku, P. Paavilainen, An event-related potential (ERP) study of duration changes in speech and non-speech sounds, NeuroReport 10 (1999) 3301–3305.
[25] S.L. Joutsiniemi, T. Ilvonen, J. Sinkkonen, M. Huotilainen, M. Tervaniemi, A. Lehtokoski, T. Rinne, R. Näätänen, The mismatch negativity for duration decrement of auditory stimuli in healthy subjects, Electroencephalogr. Clin. Neurophysiol. 108 (1998) 154–159, http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9566628&dopt=Abstract.
[26] P.W. Jusczyk, M.A. Reed, A. Fernald, M. Myers, Infant's discrimination of the duration of a rapid spectrum change in nonspeech signals, Science 222 (1983) 175–176.
[27] P.W. Jusczyk, D.B. Pisoni, A. Walley, J. Murray, Discrimination of relative onset time of two-component tones by infants, J. Acoust. Soc. Am. 67 (1980) 262–270, http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7354194&dopt=Abstract.
[28] P. Korpilahti, Electrophysiological Correlates of Auditory Perception in Normal and Language Impaired Children, Doctoral Dissertation, Painosalama OY, Turku, 1996.
[29] N. Kraus, T.J. McGee, T.D. Carrell, S.G. Zecker, T.G. Nicol, D.B. Koch, Auditory neurophysiologic responses and discrimination deficits in children with learning problems, Science 273 (1996) 971–973, http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8688085&dopt=Abstract.
[30] D. Kurtzberg, P.L. Hilpert, J.A. Kreuzer, H.G.J. Vaughan, Differential maturation of cortical auditory evoked potentials to speech sounds in normal fullterm and very low-birthweight infants, Dev. Med. Child Neurol. 26 (1984) 466–475, http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=6479466&dopt=Abstract.
[31] D. Kurtzberg, C.L.J. Stone, H.G.J. Vaughan, Cortical responses to speech sounds in the infant, in: R. Cracco, I. Bodis-Wollner (Eds.), Evoked Potentials, Frontiers of Clinical Neuroscience, Vol. 3, Alan R. Liss, New York, 1986, pp. 513–520.
[32] D. Kurtzberg, H.G.J. Vaughan, J.A. Kreuzer, K.Z. Fliegler, Developmental studies and clinical application of mismatch negativity: problems and prospects, Ear Hear. 16 (1995) 105–117, http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7774764&dopt=Abstract.
[33] D. Kurtzberg, H.G. Vaughan Jr., E. Courchesne, D. Friedman, M.R. Harter, L.E. Putnam, Developmental aspects of event-related potentials, Ann. NY Acad. Sci. 425 (1984) 300–318, http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=6588849&dopt=Abstract.
[34] E. Kushnerenko, M. Cheour, R. Čeponienė, V. Fellman, M. Renlund, K. Soininen, P. Alku, M. Koskinen, K. Sainio, R. Näätänen, Central auditory processing of durational changes in complex speech patterns by newborns: an event-related brain potential study, Dev. Neuropsychol. 19 (2001) 85–99.
[35] H. Lang, T. Nyrke, M. Ek, O. Aaltonen, I. Raimo, R. Näätänen, Pitch discrimination performance and auditory event-related potentials, in: C.H.M. Brunia, A.W.K. Gaillard, A. Kok, G. Mulder, M.N. Verbaten (Eds.), Psychophysiological Brain Research, Vol. 1, Tilburg University Press, Tilburg, 1990, pp. 294–298.
[36] J. Lecanuet, C. Graniere-Deferre, A. Jacquet, A. DeCasper, Fetal discrimination of low-pitched musical notes, Dev. Psychobiol. 36 (2000) 29–31, http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10607359&dopt=Abstract.
[37] P.H. Leppänen, E. Pihko, K.M. Eklund, H. Lyytinen, Cortical responses of infants with and without a genetic risk for dyslexia: II. Group effects, NeuroReport 10 (1999) 969–973, http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10321469&dopt=Abstract.
[38] P.H.T. Leppänen, K.M. Eklund, H. Lyytinen, Event-related brain potentials to change in rapidly presented acoustic stimuli in newborns, Dev. Neuropsychol. 13 (1997) 175–204.
[39] P.H.T. Leppänen, H. Lyytinen, Auditory event-related potentials in the study of developmental language-related disorders, Audiol. Neuro-Otol. 2 (1997) 308–340, http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9390838&dopt=Abstract.
[40] A.S. Leventhal, L.P. Lipsitt, Adaptation, pitch discrimination, and sound localization in the neonate, Child Dev. 35 (1964) 759–767.
[41] D. Molfese, The use of auditory evoked responses recorded from newborn infants to predict later language skills, Birth Defects Orig. Artic. Ser. 25 (1989) 47–62, http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=2690964&dopt=Abstract.
[42] D. Molfese, V. Molfese, Electrophysiological indices of auditory discrimination in newborn infants: the basis for predicting later language performance?, Infant Behav. Dev. 8 (1985) 197–311, http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8909889&dopt=Abstract.
[43] D. Molfese, V. Molfese, Discrimination of language skills at five years of age using event-related potentials recorded at birth, Dev. Neuropsychol. 13 (1997) 135–156.
[44] J. Moore, C.W. Ponton, J.J. Eggermont, B. Wu, J. Huang, Perinatal maturation of the auditory brainstem response: changes in path length and conduction velocity, Ear Hear. 17 (1996) 411–418.
[45] R. Näätänen, Attention and Brain Function, Lawrence Erlbaum, Hillsdale, NJ, 1992.
[46] R. Näätänen, K. Alho, Mismatch negativity — a unique measure of

sensory processing in audition, Int. J. Neurosci. 80 (1995) 317–337, http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7775056&dopt=Abstract.

[47] R. Näätänen, A.W.K. Gaillard, S. Mäntysalo, Early selective attention effect on evoked potential reinterpreted, Acta Psychol. 42 (1978) 313–329, http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=685709&dopt=Abstract.

[48] R. Näätänen, A. Lehtokoski, M. Lennes, M. Cheour, M. Huotilainen, A. Iivonen, M. Vainio, P. Alku, R. Ilmoniemi, A. Luuk, J. Allik, J. Sinkkonen, K. Alho, Language-specific phoneme representations revealed by electric and magnetic brain responses, Nature 385 (1997) 432–434, http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9009189&dopt=Abstract.

[49] R. Näätänen, P. Paavilainen, K. Alho, K. Reinikainen, M. Sams, The mismatch negativity to intensity changes in an auditory stimulus sequence, in: R. Johnson, J.W. Rohrbaugh, R. Parasuraman (Eds.), Current Trends in Event-Related Brain Potential Research, Electroencephalogr. Clin. Neurophysiol. Suppl, Vol. 40, 1987, pp. 125–131, http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=3480111&dopt=Abstract.

[50] R. Näätänen, T. Picton, The N1 wave of the human electric and magnetic response to sound: a review and an analysis of the component structure, Psychophysiology 24 (1987) 375–425, http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=3615753&dopt=Abstract.

[51] R. Näätänen, E. Schröger, S. Karakas, M. Tervaniemi, P. Paavilainen, Development of a memory trace for a complex sound in the human brain, NeuroReport 4 (1993) 503–506, http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8513127&dopt=Abstract.

[52] R. Näätänen, I. Winkler, The concept of auditory stimulus representation in cognitive neuroscience, Psychol. Bull. 125 (1999) 826–859, http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10589304&dopt=Abstract.

[53] U. Neisser, Cognitive Psychology, Appleton-Century-Crofts, New York, 1967.

[54] G.P. Novak, D. Kurzberg, J.A. Kreuzer, H.G.J. Vaughan, Cortical responses to speech sounds and their formants in normal infants: maturational sequence and spatiotemporal analysis, J. Electroencephalogr. Clin. Neurophysiol. 73 (1989) 295–305, http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=2477216&dopt=Abstract.

[55] P. Paavilainen, K. Alho, K. Reinikainen, M. Sams, R. Näätänen, Right hemisphere dominance of different mismatch negativities, Electroencephalogr. Clin. Neurophysiol. 78 (1991) 129–141, http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=1712282&dopt=Abstract.

[56] T.W. Picton, C. Alain, L. Otten, W. Ritter, A. Achim, Mismatch negativity: different water in the same river, Audiol. Neuro-Otol. 5 (2000) 111–139, http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10859408&dopt=Abstract.

[57] E. Pihko, P.H. Leppanen, K.M. Eklund, M. Cheour, T.K. Guttorm, H. Lyytinen, Cortical responses of infants with and without a genetic risk for dyslexia: I. Age effects, Neuroreport 10 (1999) 901–905, http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10321457&dopt=Abstract.

[58] C.W. Ponton, J.K. Moore, J.J. Eggermont, Auditory brain stem response generation by parallel pathways: differential maturation of axonal conduction time and synaptic transmission, Ear Hear. 5 (1996) 402–410, http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8909888&dopt=Abstract.

[59] C.W. Ponton, J.K. Moore, J.J. Eggermont, Prolonged deafness limits auditory system developmental plasticity: evidence from an evoked potentials study in children with cochlear implants, Scand. Audiol. Suppl. 51 (1999) 13–22, http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10803910&dopt=Abstract.

[60] W. Ritter, D. Deacon, H. Gomes, D.C. Javitt, H.G.J. Vaughan, The mismatch negativity of event-related potentials as a probe of transient auditory memory: a review, Ear Hear. 16 (1995) 52–67, http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=7774769&dopt=Abstract.

[61] W. Ritter, P. Paavilainen, J. Lavikainen, K. Reinikainen, K. Alho, M. Sams, R. Näätänen, Event-related potentials to repetition and change of auditory stimuli, Electroencephalogr. Clin. Neurophysiol. 83 (1992) 306–370, http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=1385087&dopt=Abstract.

[62] M. Sams, P. Paavilainen, K. Alho, R. Näätänen, Auditory frequency discrimination and event-related potentials, Electroencephalogr. Clin. Neurophysiol. 62 (1985) 437–448, http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=2415340&dopt=Abstract.

[63] P. Simos, D. Molfese, Electrophysiological responses from a temporal order continuum in the newborn infant, Neuropsychologia 35 (1997) 89–98, http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=8981381&dopt=Abstract.

[64] J.E. Stockard-Pope, S.S. Werner, R.G. Bickford, Development of sleep-wake states, in: Atlas of Neonatal Electroencephalography, Raven Press, New York, 1992, pp. 93–104.

[65] M. Tervaniemi, T. Ilvonen, J. Sinkkonen, A. Kujala, K. Alho, M. Huotilainen, R. Näätänen, Harmonic partials facilitate pitch discrimination in humans: electrophysiological and behavioral evidence, Neurosci. Lett. 279 (2000) 29–32, http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10670780&dopt=Abstract.

[66] M. Tervaniemi, A. Lehtokoski, J. Sinkkonen, J. Virtanen, R.J. Ilmoniemi, R. Näätänen, Test-retest reliability of mismatch negativity (MMN) for duration, frequency, and intensity changes, Clin. Neurophysiol. 110 (1999) 1388–1393, http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=10454274&dopt=Abstract.

[67] S.E. Trehub, Infants' sensitivity to vowel and tonal contrasts, Dev. Psychol. 9 (1973) 91–96.

[68] K. Tremblay, N. Kraus, T. McGee, The time course of auditory perceptual learning: neurophysiological changes during speech-sound training, NeuroReport 9 (1998) 3557–3560, http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=PubMed&list_uids=9858359&dopt=Abstract.

[69] D. Tucci, Deafness and disorders of central auditory processing, in: B.O. Berg (Ed.), Principles of Child Neurology, McGraw-Hill, New York, 1996, pp. 155–188.

[70] H.G.J. Vaughan, D. Kurtzberg, Electrophysiologic indices of human brain maturation and cognitive development, in: M.R. Guunar, C.A. Nelson (Eds.), Minnesota Symposia on Child Psychology, Vol. 24, Lawrence Erlbaum, Hillsdale, NJ, 1991, pp. 1–36.

[71] S.J. Wormith, D. Pankhurst, A.R. Moffit, Frequency discrimination by young infants, Child Dev. 46 (1975) 272–275.