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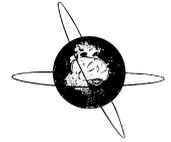
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Change detection in newborns using a multiple deviant paradigm: A study using magnetoencephalography

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ABSTRACT

Objective: Mismatch responses are elicited to changes in sound streams in healthy newborns. In the ideal case, these responses can predict cognitive problems later in life. We employed a multiple deviant paradigm for a fast assessment of the ability of the newborn brain to respond to various types of acoustic changes.

Methods: In 12 healthy newborns, we recorded an electroencephalogram (EEG) and magnetoencephalogram while presenting auditory stimuli. Between repeated stimuli, four types of acoustic changes (frequency, intensity, duration, and a gap) were presented, varying in deviance magnitude.

Results: One major response was present in the neonatal evoked potentials and fields at 250–260 ms. Magnetic mismatch responses were elicited to all change types except for the duration deviant and they were positive in polarity. The frequency deviant elicited more positive EEG amplitudes than the standard, whereas the response to the duration deviant was more negative.

Conclusions: These results show that newborns can detect changes to at least four types of deviances within a sound stream. Furthermore, the use of magneto- and electroencephalography is complementary in newborns, since the methods may reveal different outcomes.

Significance: Further studies are warranted to determine whether the present study design can play a role in testing auditory function in clinical infant populations.

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1. Introduction

The most prominent deflection in the auditory event-related potential (ERP) and field (ERF) of a healthy sleeping newborn is a positive deflection around 200–300 ms after stimulus presentation (Ohlrich and Barnet, 1972; Ellingson et al., 1974; Pihko et al., 2004; Sambeth et al., 2006). Another deflection at similar latencies is found in neonates in response to infrequent deviant sounds presented amongst repeated standard sounds in an oddball paradigm (Huutilainen et al., 2003; Leppänen et al., 2004; Sambeth et al., 2006). This deflection is suggested to be related to the mismatch negativity (MMN) found in adults and older children.

The MMN (Näätänen et al., 1978) is a sensory memory based change detection response that originates from the auditory cortex and correlates with behavioral sound discrimination accuracy. It is elicited by any discriminable change in repetitive auditory stimulation, such as a change in frequency or duration of a stimulus (for a review, see Kujala et al., 2007). The MMN is called pre-attentive because it is irrespective of attention or task manipulations, which makes it a useful tool for clinical populations and infant studies. In newborns, the deflection can even be recorded during sleep. This is important because newborns sleep most of the day and EEG and especially MEG recordings greatly benefit from recording during sleep, because the newborns move much less, making the signal-to-noise ratio better. Change-detection responses in newborns have been measured using pure (Cheour et al., 2002a; Leppänen et al., 2004; Carral et al., 2005) or complex tones (Kushnerenko et al., 2002; Huutilainen et al., 2003; Sambeth et al., 2006), but also using speech stimuli (Cheour et al., 2002c; Kujala et al., 2004) and to novel

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sounds, e.g., dog barks and braking glass (Sambeth et al., 2006; Kushnerenko et al., 2007).

It has been shown that the responses recorded with speech stimuli in neonates correlate well above chance level with language development 2.5 (Guttorm et al., 2005) and 8 (Molfese, 2000) years later in the same children. For instance, children who had an elevated genetic risk for developmental dyslexia and who revealed large positive activity in the right hemisphere at birth, had poorer than normal receptive language skills at 2.5 years of age (Guttorm et al., 2005). This suggests that results from speech studies might be used to predict future language development.

Dysfunctions in change detection have not only been found in infants at risk for dyslexia (Leppänen et al., 1999; Pihko et al., 1999), but for example also in infants with cleft palate (Cheour et al., 1999; Čeponienė et al., 2000) and infants born pre-maturely (Cheour et al., 1998; Fellman et al., 2004), both of which also show problems in sound perception and language development later in life. Furthermore, children that were originally born with scaphocephaly, but later received corrective surgery, also reveal deficiencies in auditory change detection and language development (Virtanen et al., 1999). The above studies used one deviant type only, but different auditory impairments may have different selective responses to different types of deviations and it is therefore important to have a test that screens for different deficiencies. For example, the MMN in children with specific language impairments is only smaller to speech stimuli, but not to pure tones (Uwer et al., 2002). If we could detect a specific auditory impairment in infants, they could receive additional training in order to reduce problems later in life.

A new paradigm was recently developed to present multiple deviants in one oddball paradigm in adults (Näätänen et al., 2004; Pakarinen et al., 2007). In the first paradigm by Näätänen and colleagues, responses to five types of acoustic changes, namely frequency, intensity, duration, perceived sound-source location, and a gap in the middle of the tone, were examined. They showed that the MMNs to the five deviant types were not different from those elicited in traditional, much more time-consuming, oddball paradigms (Näätänen et al., 2004). In the second study by Pakarinen and her co-workers (2007), MMN responses to changes in frequency, intensity, duration, and sound-source location were measured in the same block at six different magnitudes of deviation. In this way, deviant specific differences in the sensitivity to the magnitude of stimulus deviance could be detected. The amplitude of the MMN responses increases and the latency decreases as a function of the magnitude of deviance. Furthermore, the hit rate of deviance detection correlated with the MMN amplitude (see also Sams et al., 1985; Tiitinen et al., 1994). These types of correlations between behavioral and brain response are not very feasible in infants, but we can interpret larger MMN amplitudes and shorter MMN latencies as a sign that infants can discriminate the deviant from the standard.

The amplitude of the P200–300 in newborns depends on the sleep stage of the neonate; in quiet sleep (QS) the response amplitude is typically larger than in active sleep (AS) (Pihko et al., 2004; Sambeth et al., 2008). The effects of sleep stage on change detection responses in the newborns are, however, unclear (Cheour et al., 2002a; Martynova et al., 2003). Cheour and her co-workers found larger responses in the AS than in the QS, but Martynova and her colleagues found that the MMN responses did not significantly differ between sleep stages.

In the present experiment, we used an adapted version of the paradigm developed by Pakarinen and her colleagues to assess how well the human brain can discriminate between various types of auditory stimuli at birth. We examined evoked fields and potentials in healthy sleeping newborns, while presenting a total of 25 different stimuli (one standard and four deviant types with six levels of change magnitude each). We also analyzed the effects of sleep stage in the present study.

2. Methods

2.1. Subjects

Auditory magnetic fields were recorded from 13 healthy term newborns (gestational age 37–42 weeks, 3 female) at the age of 1–8 days after birth. In one infant, the recording was not long enough to obtain enough responses. Therefore, this infant was excluded from analysis. The infants had a normal Apgar score (8–10 at 1 min) and birth weight (2900–4720 g), indicating good health (maximum possible Apgar = 10). They were recruited to the study from the maternity ward of the Women's Hospital at Helsinki University Central Hospital. Parental written informed consent was obtained before the enrolment. The Ethics Committee of the Hospital District of Helsinki and Uusimaa approved the study plan.

2.2. Data acquisition

The MEG was recorded using a helmet-shaped Vectorview MEG instrument (Elekta Neuromag, Oy, Helsinki) of the BioMag Laboratory, Helsinki University Central Hospital, with 306 channels, in an electromagnetically shielded environment. The channels of the MEG instrument are located at 102 positions uniformly distributed over the adult head with two orthogonal planar gradiometers and one magnetometer at each location. The measuring helmet was used in its supine position and the newborn was lying with the right hemisphere over the 'occipital' part of the helmet, enabling the recording of responses of the right hemisphere of the neonates.

The head position inside the MEG helmet was verified at the beginning of the recording and again later, in case the recording had to be temporarily paused. An additional new recording session was always started when the newborn moved notably, as indicated by the behavioral scoring of the experimenter. If the head position of various files was close enough, in the end an average of both files was used. However, if the head position was too far apart (more than 1 cm in either direction), only the file that contained the largest number of trials was used for analysis. Four indicator coils were attached to the neonates' head at locations known in an anatomical coordinate system defined by the nasion and the preauricular points. The signals from the indicator coils were used in determining the precise position of the neonate's head inside the helmet.

Simultaneously with the MEG, EEG and electro-oculographic (EOG) recordings were made with silver–silver chloride disk electrodes. The EEG was recorded at F4, Cz, and P4 locations. The EOG was recorded from the upper left and lower right corners of the eyes. The reference electrode was placed on the right mastoid and the ground electrode on the forehead.

Both MEG and EEG were continuously recorded with a band-pass filter of 0.03–200 Hz and sampled at 600 Hz.

2.3. Stimuli and procedure

The sound stimuli were presented in the multi-feature oddball paradigm (Pakarinen et al., 2007). All together, the infants were presented with one standard and 24 deviant tones. The standard (Sta) was a 494 Hz tone with two upper harmonics (988 and 1482 Hz) and a duration of 100 ms (including 10 ms rise and fall times). The intensity of the first and second harmonic components was decreased relative to the fundamental by 3 and 6 dB, respectively. The stimulus onset asynchrony (SOA) was 800 ms.

The deviant stimuli differed from the standard stimuli by only one acoustic feature, namely in frequency (Fre), intensity (Int), duration (Dur), or by placing a silent gap in the middle of the tone (Gap). For each deviant type, six levels of change size (e.g., Fre1, Fre2, etc.) were constructed that varied from difficult to easily

detectable. Half of the six frequency deviants were higher and the other half were lower than the standard. Each level was increased/decreased by one semitone (i.e., the fundamental frequencies of the increments were 523, 554, 587, 622, 659, and 698, from levels Fre1 to Fre6, respectively). The intensity deviants were either increments or decrements in intensity by steps of 3 dB, with the extreme deviants being 18 dB louder or softer than the standard. The six duration levels were all decrements in duration by steps of 12 ms. Thus, the shortest deviant had a duration of 28 ms. A silence period was placed in the middle of the tone with increasing steps of 6 ms for the gap stimulus, with the largest gap comprising a silence of 36 ms in the middle of the 100 ms period.

All tones were presented within the same multi-feature paradigm sequence, the standard being presented every other stimulus presentation (=50% probability) and one of the 24 different deviants being presented in the remaining positions (probability of $50/24 = 2.1\%$ for every single deviant). Each deviant type (Fre, Int, Dur, and Gap) was presented once in a sequence of four successive deviants. Furthermore, two successive deviants were always of different types, although two equal levels of a different change type were allowed to follow each other. The different levels of deviation appeared in a pseudo-randomized order and the 24 deviants were equiprobable. An example of a sequence is as follows: Sta – Dur1 – Sta – Fre1 – Sta – Int3 – Sta – Gap6 – Sta – Int2 – Sta – Fre2 – Sta – Gap1 – Sta – Dur5, etc.

The stimuli were presented to the left, contralateral to the recording site, ear of the newborns through a plastic tube with a soft earpiece. The infant was placed in a crib and the EEG and EOG electrodes were attached to the skin. A cloth cap was placed over the EEG and EOG electrodes and four marker coils were attached to the cap for determining the position of the head. The positions of the coils in the head coordinate system were determined with an Isotrak 3D digitizer (Polhemus). Thereafter, the infant was placed on a bed next to the MEG helmet in a magnetically shielded room (ETS; Lindgren Euroshield Oy, Eura, Finland). If necessary, the baby was fed before the recording started. The behavior of the infant (eyes open/closed, eye and muscle movements and breathing pattern) was continuously monitored and registered by one of the researchers sitting inside the recording room with a direct eye-contact to the infants. The recording was started when the newborn was sleeping and the total measurement time (preparation and recording) never exceeded 3 h.

2.4. Sleep stage determination

We determined the sleep stages in the neonates according to the classes of awake, AS and QS typically used for neonates. During the recording, one researcher was seated next to the newborn to determine the sleep stages behaviorally. If the neonate showed closed eyes, an irregular respiration pattern, saccadic eye movements, and occasional facial twitches, AS was scored. When the eyes were closed, the respiration pattern was regular, and the muscle tension low, QS was scored.

Offline, the final sleep stage was determined using the MEG, EEG, EOG, and behavioral measures of the newborns. The EEG and MEG signals showed low-voltage high-frequency activity during AS, whereas they showed either high-voltage low frequency activity or tracé alternants (high and low-voltage slow waves alternating) during QS. Responses were averaged separately according to those sleep stages.

2.5. Analysis

Averages for each of the 25 stimulus types separately were made offline, according to the sleep stages, for both MEG and EEG activity. Furthermore, additional averages were made according to the

deviant type, thus including responses to all six levels within one average.

The averaging epochs were taken from –100 ms to trigger onset to 800 ms. The first 100 ms were baseline corrected. Trials during which the neonate moved were rejected. Furthermore, trials at which the sleep stage could not be determined or during which an intermediate sleep stage seemed to be present, were also excluded. Next, the Signal Space Separation method (Taulu et al., 2004) was performed in 2 out of 13 newborns to remove artifacts that were coming from outside the helmet, but were recorded by the MEG instrument (e.g., heart beats and line frequency noise).

Subsequently, vector sums were calculated from the orthogonal gradiometer channel pairs. Note that vector sums are a measure of the combined amplitude of the signal from two gradiometer channels. This measure always results in positive amplitude, but says nothing about the real polarity of the deflection. The vector sums were 40 Hz low-pass filtered. Next, mean amplitude was calculated of three close gradiometer pairs for each infant, in order to increase the signal-to-noise ratio. The gradiometer pairs were chosen individually for each infant so that they were those neighboring pairs that showed the largest responses. The averages of the vector sums were used to compare the amplitudes of the 25 stimulus type averages and the two sleep stages with each other.

One major deflection was found in the magnetic responses of the newborns, generally around 250 ms. For each individual neonate, the actual maximum latency was determined and a mean of 100 ms around the maximum (50 ms before and 50 ms after the latency with the maximum deflection) was used for statistical analysis. In other words, for each neonate, the mean amplitude over a 100 ms interval close to the actual peak was calculated. The corresponding deflection was also found in the EEG, at latencies of 260 ms after stimulus onset.

Before performing statistics, field distributions were calculated to determine the polarity of the components, since it cannot be deducted from the evoked fields themselves which polarities the deflections have. In most infants, the deflections revealed a positive polarity, but in two newborns, the polarity was negative. Therefore, the results of these newborns were excluded from analysis (see also Section 3).

Since the data were normally distributed, the parametric analysis of variance (ANOVA) was used to statistically test the results. With regard to the averages over six levels within a stimulus type, at least 140 acceptable trials were recorded in each newborn during the QS. A Univariate repeated-measures ANOVA with Stimulus type (Sta, Fre, Int, Dur, and Gap) as within-subject factor was performed on these data. Since this revealed a significant effect, each of the deviant types was compared with the standard in separate ANOVAs.

In six of the newborns, enough trials when averaging over levels were recorded during both QS and AS. An additional ANOVA was performed on these data with Stimulus type (Sta, Fre, Int, Dur, and Gap) and Sleep stage (QS vs. AS) as within subject factors.

Unfortunately, not enough trials were recorded in most of the neonates to all six levels of deviation (around 40 trials per level when averaged across all neonates). Therefore, we could not perform a repeated measure ANOVA including all six levels. However, we did perform a linear regression analysis on the P250m for each deviant type separately.

The level of significance was set at 0.05 throughout.

3. Results

Fig. 1 shows a group of gradiometer channels for one newborn (Infant 3) recorded over the right hemisphere of the infant. The responses during QS to the standard and all four deviant types (average over the 6 magnitudes of deviation) are presented. A P250m can be detected around 250 ms after stimulus onset. Most of the

Magnetic responses of Infant 3

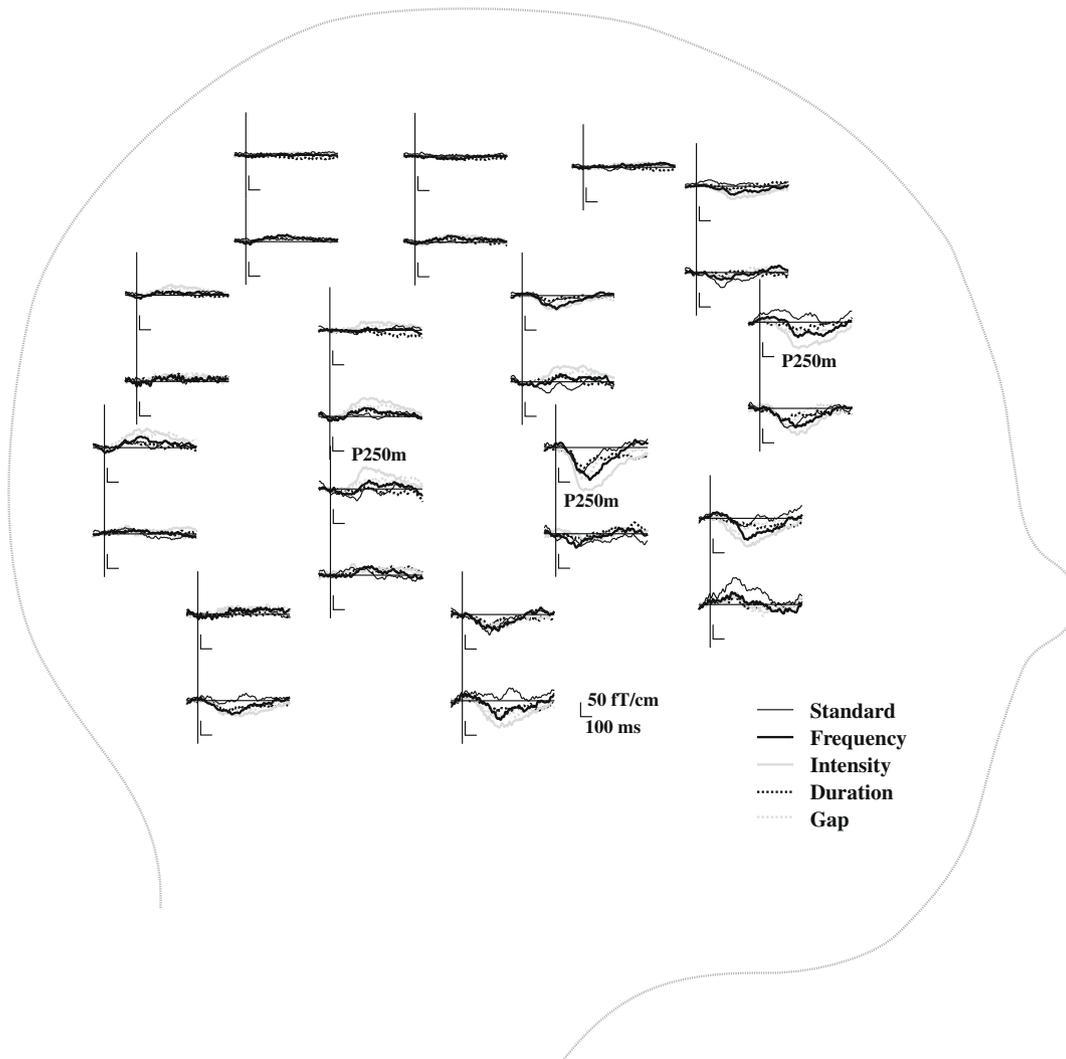


Fig. 1. A subset of gradiometer channels of one representative newborn during QS from the 'occipital' part of the helmet, on which the right hemisphere of this neonate was lying. Evoked magnetic responses to an average over all levels of magnitude of each of the four deviant types are presented: frequency, intensity, duration, and gap. The responses to the standard are also shown. One clear peak can be determined at latencies of 250 ms after stimulus onset, pointed out as P250m.

neonates showed this slow, very large deflection during QS, as can be seen in Fig. 2. In some newborns, however, no clear response could be found (e.g., Infant 11), or the polarity was opposite (Infants 2 and 5).

3.1. Field distributions

Fig. 3 shows field distributions at P250m for the five different stimulus types in one representative newborn (Infant 13). It can be seen from the course of the arrow that depicts the direction of the neural currents, that the responses recorded with evoked potentials would appear positive in polarity at the frontal and central electrodes (see also Fig. 4 for EEG data showing the same polarity). It can be seen by the size of the arrow that the strength of the field was larger to frequency, intensity, and gap deviants than that to standards and duration deviants. Generally, the distributions were similar in the infants, except for Infants 2 and 5, who revealed the opposite polarity (see also Fig. 2). Therefore, the results of these newborns were excluded from statistical analysis.

3.2. MEG effects during QS

Since, in most of the infants, not enough trials were recorded for the six different levels of magnitude of deviation, here we present an average over all deviation magnitudes. Responses obtained from the MEG are shown in Fig. 2 for each newborn separately. Furthermore, the mean amplitudes to the five stimulus types are presented in Table 1.

Separate ANOVA comparisons between the deviant and standard stimuli were performed for each of the four deviant types, because an analysis over all stimulus types was significant ($F(4,36) = 5.850, p = .001$). The frequency deviants elicited larger amplitudes than did the standard ($F(1,9) = 18.547, p = .002$). Responses to the intensity deviants were larger in amplitude than those to the standard stimulus for the P250m response ($F(1,9) = 15.148, p = .004$). The ANOVA for the duration deviants did not reveal significant effect at P250m ($p = .756$). The gap deviant elicited larger amplitudes than did the standard ($F(1,9) = 17.830, p = .002$).

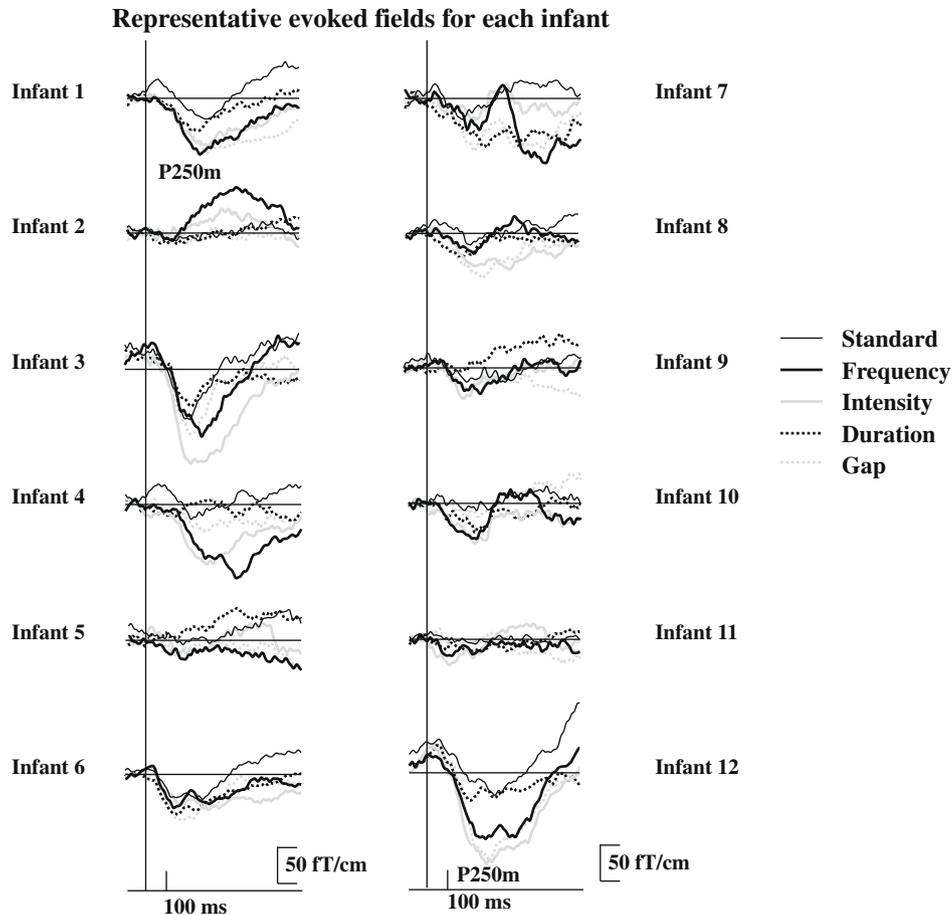


Fig. 2. Evoked magnetic fields of 13 newborns to an average over all levels of each of the four deviant types, frequency, intensity, duration, and gap, as well as responses to the standard are shown. For each infant, the gradiometer channel with the largest response is presented. Note that Infants 2 and 5 display an opposite polarity compared with those of the others. Therefore, the results of these neonates were not included in the statistical analysis. Furthermore, the statistics were performed on vector sums that were calculated on average amplitudes obtained from the gradiometer channel shown and the other channel that corresponds to this one (e.g., shows activity from the same brain area).

3.3. EEG effect during QS

As was the case for the MEG data, only averages over all six levels of deviation were used for statistical analysis. Responses to the EEG from electrode F4 can be seen in Fig. 4 and Table 1. Note that the responses look relatively similar to those obtained from the MEG with regard to the standard, frequency, and intensity stimuli. The responses to the duration and gap deviants, on the other hand, are smaller (more negative going) than those in the MEG. Fig. 4 also shows difference signals (deviant minus standard) for each of the deviant types. It can be seen that small positive responses are present for the frequency and intensity deviant, whereas negative responses are seen for the duration and gap stimuli. EEG results are missing for Infant 7, because the quality of the EEG signal was low at the F4 electrode. Therefore, statistics were performed on only nine newborns. In the statistical comparisons, only data from the F4 electrode was included, since this was the electrode that showed the clearest responses.

An ANOVA with frequency and standard as within-subject variables revealed a significant effect for the P260 ($F(1,8) = 8.55$, $p = .019$). Responses were more positive in amplitude to the frequency than to the standard stimuli.

The ANOVA for the intensity deviants did not reveal any significant effects. With regard to the duration deviant, the following effect was found. The duration deviant elicited less positive (=more negative) amplitudes than did the standard stimulus

($F(1,8) = 6.37$, $p = .036$). None of the comparisons between the gap and standard stimuli reached significance.

3.4. Sleep stage comparison

In 6 of the 10 newborns who were used for statistical analysis, enough trials were recorded during both AS and QS. An ANOVA was performed in those infants with sleep stage (AS and QS) and stimulus type (standard, frequency, intensity, duration, and gap) as within-subject factors (for amplitudes see Table 2). A main effect of sleep stage was found for P250m ($F(1,5) = 9.620$, $p = .027$), indicating that amplitudes were generally larger during QS than during AS. There was neither a main effect of stimulus, nor an interaction between sleep stage and stimulus at P250m.

When examining the effect of sleep stage for each deviant type vs. the standard separately, no significant interactions were found for any of the deviant types when compared to the standard.

3.5. Regression analysis on MEG responses

Since not enough trials were recorded in most neonates for all six different levels of deviation magnitude, there was a lot of noise in the responses. Therefore, we could not perform repeated measures ANOVA. However, to get a general impression of the effect of the magnitude of deviation, we performed a regression analysis on the P250m responses during QS for each of the four deviant

Magnetic responses to all stimulus types

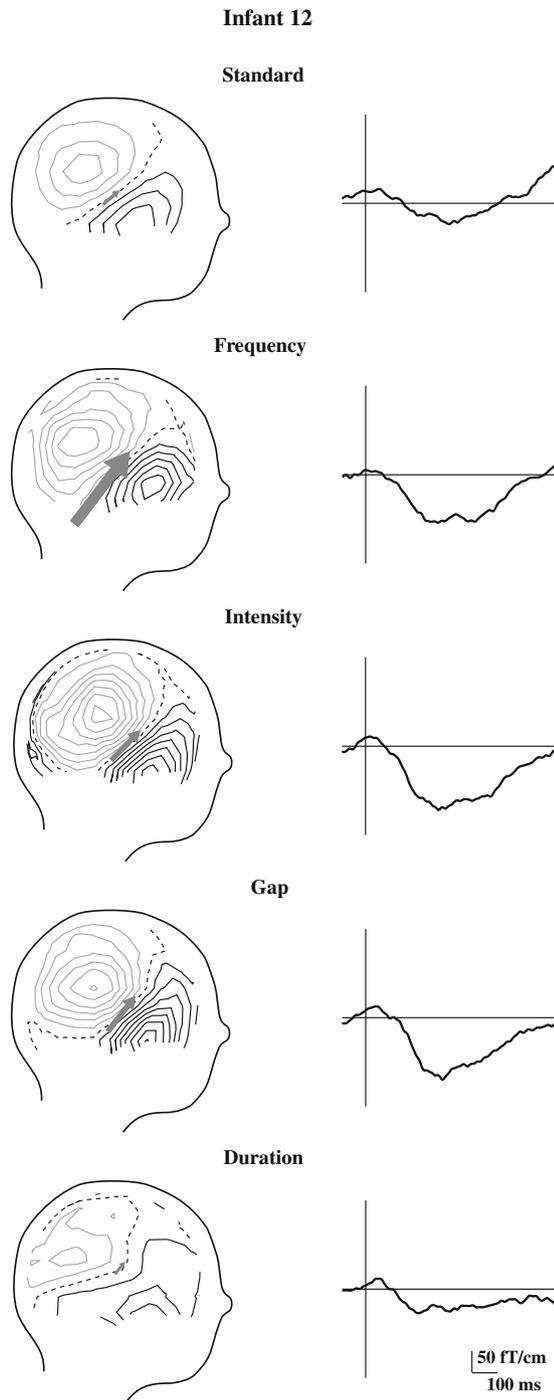


Fig. 3. Field distributions for the first deflection to each deviant type and the standard for Infant 12, with a contour step of 100 fT. It can be deduced from the direction of the arrow, depicting the direction of the neural currents, that the responses recorded as evoked potentials should appear positive in polarity at the frontal and central electrodes. Note that the frequency, intensity, and gap deviants elicited a stronger response than those elicited by the duration deviant and standard stimuli.

types. The results can be seen in Fig. 5. Note that the amplitude increased with increasing deviation for the frequency, intensity, and gap deviants. The response to the duration deviant, however, decreased with increasing deviation. Statistical analysis did not reveal any significant effects.

4. Discussion

The results of this study showed that the newborn brain is able to detect various deviances presented within one and the same paradigm, albeit with different responses to different stimulus types. The amplitudes were more positive for the frequency, intensity, and gap deviants than for standard stimuli, whereas the duration deviants elicited more negative responses.

The prominent deflection found in the present study peaked around 250 ms after stimulus onset. The deflection was generated in the temporal cortex, as can be seen in Fig. 3. This is in accordance with previous research in neonates (Huotilainen et al., 2003; Kujala et al., 2004) that revealed sources in or near the auditory cortices of the temporal lobe. Furthermore, as in one of our previous studies (Sambeth et al., 2006), we found the responses to be mainly vertex-positive rather than negative.

In the present study, the amplitude of the P250m response was larger to deviant than to standard stimuli. It is this difference between the P250m responses to the deviant and standard that is usually interpreted to correspond to the adult MMN component. In previous research in newborns, mismatch responses were found to frequency (e.g., Leppänen et al., 1997; Huotilainen et al., 2003; Sambeth et al., 2006; Kushnerenko et al., 2007) and duration (e.g., Kushnerenko et al., 2001a,b; Cheour et al., 2002b) deviants, and to changes in speech sounds (e.g., Cheour et al., 2002c; Kujala et al., 2004). Our results are in accordance with the previous work in the sense that the frequency deviants elicited larger amplitudes than did the standard stimuli. Furthermore, we found significant change detection responses for the duration deviants, in the EEG (negative).

To our knowledge, no previous infant studies have examined effects of intensity on the change detection response. Generally, the MMN in adults appears negative to intensity, irrespective of whether the intensity was increased or decreased when compared to the standard (Jacobsen et al., 2003; Rosburg, 2003; Pakarinen et al., 2007), at least when quite small intensity increments and decrements are used. In the present study, we used both increments and decrements in intensity and pooled the data in the average. We found a significant change detection response to intensity changes in the MEG, but not in the EEG. Newborn infants, thus, do process changes in intensity. The question then remains as to why these effects were only found in the MEG, but not the EEG responses. First, we recorded EEG activity from F4, Cz, and P4 electrodes, of which only the F4 showed clear responses also seen with MEG. If we had measured the EEG from other leads too, we might have found a significant change detection response for the intensity deviant. Secondly, the signal-to-noise ratio of MEG is higher than that of EEG (de Jongh et al., 2005), which might especially be the case in infants since, in contrast to the EEG, the MEG is not affected by the fontanelles and sutures of the skull (Flemming et al., 2005).

In the present study, we also presented deviants with a gap in the middle of the tone. To newborns, such stimuli have never been presented. However, Trainor and her colleagues (2003) recorded ERPs in 2-month-old infants in a similar gap condition as in the present study. They found no MMN component, although it is typically present at the age of 6 months (Trainor et al., 2003). However, a positive deflection was present to the deviants in the 2-month-old infants, which significantly differed from the standard stimuli. In the present study, we also found change detection response to the gap stimulus, at least in the MEG. This suggests that neonates already possess the ability to perceive gaps within tones, at least when the gaps are large enough.

Next to changes in amplitude over six pooled levels of magnitude, we also assessed the changes per level using a regression

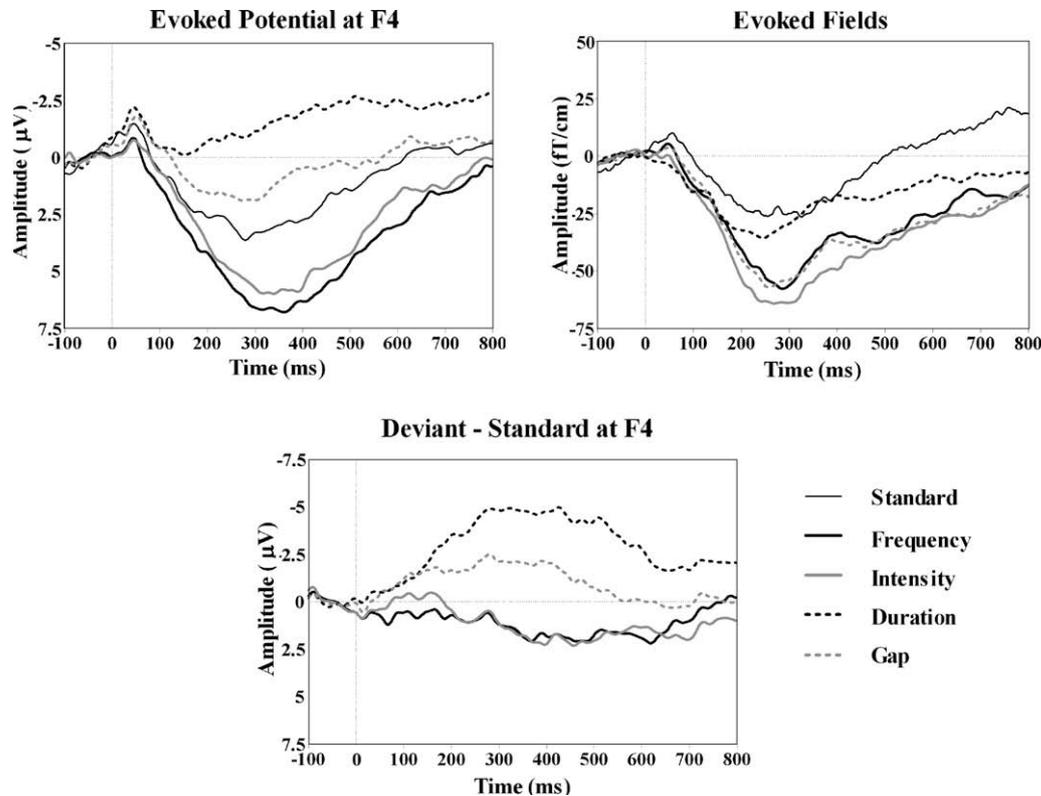


Fig. 4. Grand average evoked potentials, evoked fields, and difference waves of the 10 newborns whose data were included in the statistical analysis. On top, evoked potentials and evoked fields to an average over all levels of each of the four deviant types, as well as the responses to the standard are shown. The evoked potentials are taken from F4, whereas an average over all representative MEG channels is depicted for the evoked fields. The lower figure shows the difference waves for the F4 electrode site, which showed the largest responses in the neonates. Note that, whereas a positive mismatch response was present to the frequency and intensity deviants, the duration and to a lesser extent gap deviant elicited a negative mismatch response.

analysis. In case of the duration and gap deviants, there was only one type of change, namely the shortening of the sounds. With regard to the frequency and intensity changes, we presented increments and decrements. Considering that the magnitude of change is what determines the response rather than an increment or decrement in frequency or intensity (Jacobsen et al., 2003; Pakarinen et al., 2007), we pooled those changes for each level (e.g., +3 and –3 dB changes were averaged). None of the four deviant types showed a statistically significant increase or decrease in amplitude with increasing change magnitude, possibly due to a large variability between infants. However, as can be seen in Fig. 5, the amplitude in response to intensity changes was considerably increased from level 1 to level 6, whereas the amplitude to duration deviants decreased. This suggests that infants do process various levels of changes and that this paradigm could be a good tool to examine deficiencies in this type of auditory processing.

Prior studies have shown that the evoked responses in newborns are larger during the QS than during the AS (Pihko et al.,

2004; Sambeth et al., 2008). Results are, however, unclear with regard to the change detection response. In this study, we showed that the amplitudes to both the deviants and standard stimuli decreased from QS to AS. However, there was no significant interaction between sleep stage and stimulus type, which indicates that the difference between a deviant and the standard is not larger during QS than during AS. In other words, the change-detection response was not affected by sleep stage. Considering that we could only record sufficient trials for this analysis in six of the newborns, it may be too premature to draw any conclusions. Therefore, even though it seems very appropriate to separate between sleep stages in infant studies, more research is needed to clarify whether the mismatch response is sensitive to changes in sleep stages.

One issue that is still debated is the question why some researchers find a negative change detection response in neonates, whereas others show positive responses. Recently, Leppänen and co-workers (2004) gave a very nice and complete overview of possible factors that affect the polarity of ERP components in neonates.

Table 1

Mean amplitudes with standard error (in parentheses) of the P250m and P260 responses to auditory stimulation for the standard, frequency, intensity, duration, and gap stimuli during QS. Note that the deviants are averages over all six levels of deviation.

| | MEG data, vector sum of maximum channels (in fT/cm), P250m | EEG data, F4 electrode (in µV), P260 |
|-----------|--|--------------------------------------|
| Standard | 35.96 (8.51) | 3.55 (1.36) |
| Frequency | 52.65 (10.88) | 6.36 (1.56) |
| Intensity | 61.25 (13.83) | 5.71 (1.78) |
| Duration | 33.74 (5.17) | –.66 (1.42) |
| Gap | 54.49 (11.78) | 2.51 (1.81) |

Table 2

Mean amplitudes with standard error (in parentheses) of the P250m responses to auditory stimulation for the standard and for the frequency, intensity, duration, and gap stimuli in the quiet (QS) and active (AS) sleep stages.

| | MEG data, vector sums of maximum channels (in fT/cm) | |
|-----------|--|---------------|
| | QS | AS |
| Standard | 35.59 (13.76) | 26.42 (8.36) |
| Frequency | 49.16 (14.56) | 46.29 (20.23) |
| Intensity | 56.71 (19.71) | 43.11 (15.56) |
| Duration | 32.37 (5.44) | 33.79 (8.96) |
| Gap | 51.36 (18.29) | 43.87 (17.62) |

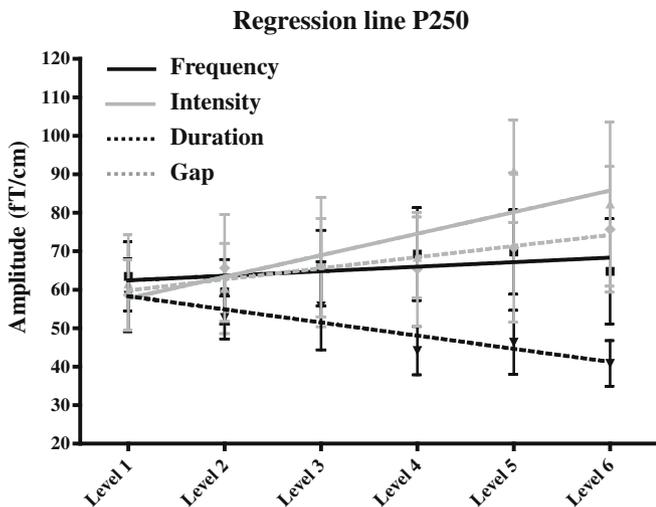


Fig. 5. Regression lines for each of the four deviant types. The average evoked fields, as calculated from the vector sums, for each of the six levels of magnitude are shown with error bars. Note that the amplitudes for the frequency, intensity and gap deviants tend to become larger with an increasing magnitude of deviation. The response to the duration deviant, however, seems to decrease with increasing magnitude of deviation.

They concluded that maturity is a very, if not the most, important factor. The more mature a newborn is the more positive the responses become. Other reasons mentioned were stimulus presentation rate, placement of the reference electrode, and digital filtering.

In the present study, we may possibly have found another factor that plays a role in the polarity of responses. With regard to the EEG results, we found that, the shorter the stimuli were, the smaller the responses became (see also Paavilainen et al., 1993). In Fig. 4, it is shown that the frequency deviant elicited a positive mismatch response, whereas the duration deviant revealed a negative mismatch response. It may be obvious that all the factors discussed previously (Leppänen et al., 2004) are constant in this study and cannot account for the differences found. It is possible that the neonates have a long auditory integration window for intensity, that is, very short sounds are interpreted as being very soft, which reduces the obligatory responses in general. And if a positive response is found to standards, then the absence of a clear response to a duration deviant may result in a negative change detection response in the difference signal. Further research, in which short standard stimuli are compared to longer deviant stimuli, thus opposite to what we examined in the present study, is necessary to support this claim.

One final point that we want to make is that we did not find exactly the same results for the EEG and the MEG. The question is why. As already mentioned, the signal-to-noise ratio may be better with regard to the MEG than to the EEG. This is likely due to the fact that magnetic waves are not disturbed by the fontanel, skull, and hair. This does not mean that either one is not a good tool, or that our EEG data are incorrect. In our opinion, this shows how important it is to assess brain activity in different ways in the infants, because it may provide more information than just one procedure.

In conclusion, we showed that the neonatal brain not only detects changes in frequency and duration, but also changes in intensity and of the continuity of a tone. We found that the multiple-deviant paradigm is a promising tool for investigating auditory discrimination abilities in newborn clinical populations, such as infants at risk for dyslexia or those with other developmental disorders already known at birth. Furthermore, this study has

shown that MEG and EEG are complementary in newborns, because they may reveal different results.

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