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Serial magnetoencephalographic study of fetal and newborn auditory discriminative evoked responses

Rossitza Draganova [a,c], **Hari Eswaran** [a,*], **Pamela Murphy** [a], **Curtis Lowery** [a], **Hubert Preissl** [a,b]

[a] *SARA Research Center, Department of Ob/Gyn, University of Arkansas for Medical Sciences, 4301 West Markham Street, #518, Little Rock, Arkansas 72205-7199, United States*
[b] *MEG Center, University of Tübingen, Tübingen, Germany*
[c] *Institute of Biomagnetism and Biosignalanalysis, University of Münster, Münster, Germany*

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Abstract The mismatch negativity (MMN) response elicited to auditory stimuli is an indicator for cognitive function of sound discrimination in humans. MMN was successfully recorded in previous studies in newborns and fetuses (33—40 weeks of gestation) with magnetoencephalography (MEG). The aim of our study was to perform systematic serial MMN recordings on fetuses starting at 28 weeks of gestation with a follow up recording within 2 weeks after birth. The recording of weak magnetic fields from the fetal brain were performed with the 151 channel MEG system called SARA (SQUID Array for Reproductive Assessment). Two tone bursts were presented in a sequence of a standard complex tone of 500 Hz intermixed with a deviant complex tone of 750 Hz in 12% of the stimuli, inter-stimulus interval 800 ± 100 ms. Eighteen pregnant women between 28th and 39th gestational weeks participated in the study. Measurements were performed every two weeks and once after delivery. The averaged evoked responses to standard and deviant tones were obtained and subtraction between them was calculated.

A successful detection of response to the frequency change was found in 66% of the fetal data and 89% of the neonatal data. Responses to the standard tone were detected in 56% of all records. In the 28—39 week gestational age group, the discriminative brain responses to tone frequency change could be detected as early as 28 weeks. Although not statistically significant, a decrease in latency was observed with increase in gestational age. The ability of the fetus to detect changes in sounds is a prerequisite to normal development for cognitive function; related to language learning and clinical aspects of auditory disorders.

* Corresponding author. Tel.: +1 501 526 4334; fax: +1 501 603 1544.
E-mail address: eswaranhari@uams.edu (H. Eswaran).

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1. Introduction

Investigation of functional brain development in the fetus can be approached indirectly by behavioral studies or directly by brain imaging techniques. Behavioral studies are usually performed by observation of fetal behavior changes in response to auditory or visual stimulation. The technique of magnetoencephalography (MEG) is described as a noninvasive direct method to investigate fetal brain activity by Preissl et al. [1].

Several studies have addressed functional development of the human auditory system. Morphological structures of the peripheral auditory system essential for hearing develop by 20 weeks of gestational age (GA) [2,3]. Animal studies on auditory competencies at the onset of the cochlea functioning suggest lack of frequency discrimination, which improve rapidly in later GA [4]. Behavioral studies in human fetuses detected a pure tone stimulus response at 19 weeks [5] and to vibroacoustic stimulation at 24—25 weeks [6]. Fetal MEG responses to auditory stimuli between 28 and 34 weeks were shown in several studies [7—15].

Although studies have confirmed the fetal auditory system is functional at 20 weeks GA, the fundamental question of when sound discrimination occurs has remained unanswered. A sequence of standard (frequent) sounds intermixed with deviant (infrequent) sounds is a classical oddball paradigm used to elicit specific endogenous brain response corresponding to sound discrimination. The difference waveform obtained by subtracting the evoked response to the standard from the deviant tone exhibits a specific component, Mismatch Negativity (MMN), [16—18].

The discriminative capability reflected by MMN was demonstrated in healthy premature infants born 30—35 GA [19]. Previous newborn electroencephalographic studies showed neonatal brain responses to stimulus frequency changes [20—22] and vowels [23—26]. Late discriminative negativity (LDN) occurs 300 ms to 600 ms after stimulus onset and is an additional endogenous response which was demonstrated in newborn studies by Huotilainen et al. [27] (MEG) and Martinova et al. [26] (EEG). Kushnerenko et al. [22] recorded LDN responses in longitudinal EEG studies of infants starting soon after birth. The occurrence of LDN was also observed in children between three and nine years of age [28—30]. Fetal brain response to tone frequency change was first demonstrated using MEG by Huotilainen et al. [31] and Draganova et al. [32]. Using two-tone oddball stimulation paradigm, they found existence of auditory brain discriminative response staring at 33 and 35 weeks GA.

Our goal was to explore the presence of fetal discriminative response to tone frequency starting at 28 weeks of gestational age and to perform systematic serial studies to investigate if any trend exists across gestation.

2. Methods

2.1. Subjects

Eighteen pregnant women between 28th and 39th gestational weeks participated in the study. Measurements were performed every two weeks and once after delivery. All the patients were recorded at least twice at different gestational ages. A total of 76 fetal measurements were recorded. Nine of the women returned within two weeks after delivery for neonatal studies. The stimulation paradigm was equivalent for fetuses and newborns. The study was approved by the local Institutional Review Board and each mother signed an informed consent.

2.2. Stimulation

A sequence of two complex sounds was presented to the subjects in an oddball protocol. The "standard" frequent stimulus (probability of 88%) consisted of a 500 Hz tone with additional harmonics at 1000 Hz and 1500 Hz, attenuated in amplitude by 3 and 6 dB, respectively. The "deviant" infrequent stimuli (probability of 12%) consisted of a 750 Hz tone with harmonics at 1500 Hz and 2250 Hz with the same amplitude attenuation as in the standard tone. The stimuli were generated as tone bursts with duration of 100 ms (including 10 ms rise and fall times). The inter stimulus interval (ISI) was set to 800 ms and randomized with 100 ms (ISI = 800 $\pm$ 100 ms). The data of each session were collected in a 12 minute continuous recording.

Stimulus delivery was controlled by the STIM software (Neurosoft, El Paso, TX). The sound was generated by a speaker located outside the room and delivered to the maternal abdomen through plastic tubing. The distal end of the tubing was attached to an inflated bag that was placed over the maternal abdomen. The sound measured at the end of the bag was 120 dB SPL (re 20 μPa, "C" frequency weighted). Taking into account the reported attenuation of sound through the maternal abdomen [33,34] it was expected that an intensity of approximately 80 dB SPL reached the fetus. In the newborn study, the baby was positioned in a cradle with the sound delivery bag located above the cradle. An equivalent sound intensity of 80 dB SPL was applied for the auditory stimulation of the newborns.

2.3. Data acquisition and recording

The SARA system consists of 151 primary magnetic sensors (first order gradiometers) spaced approximately 3 cm apart covering an area of 850 cm^2. The noise level of primary sensors is below 4 $fT/\sqrt{Hz}$. The sensors are arranged in a concave array covering the maternal abdomen from the pubic symphysis to the uterine fundus, and laterally over a similar span. This array is curved to match the shape of the gravid abdomen. The mother sits and leans forward against the smooth surface of the array (see [35]). Our past experience has shown that the mother can tolerate up to 12 min of continuous studies beyond which they may get restless thus contributing to motion artifacts in the signals. In this study we tried to optimize the recording time based on maternal comfort and maximize the number of deviant stimuli in the given period.

To attenuate the influence of external magnetic fields, SARA is installed in a magnetically shielded room (Vakuumschmelze, Germany). In order to determine the position of the fetal head in relation to the observed MEG signal we utilized a fiduciary marking system which consisted of four coils. Three coils were attached to the mother with one each on her back, left and right sides. The fourth coil was positioned over the fetal head whose location was confirmed using a portable ultrasound device in the shielded room prior to the study. Before each recording, the location of the coils was determined by activating them at a certain frequency to compute their coordinates in relation to the SQUID sensors.

2.4. Data analysis

2.4.1. Magnetic field analysis criteria for response validity

The magnetic field signals were recorded with a sampling rate of 312.5 Hz and low-pass filtered at 100 Hz. A marker trigger was set to each standard and deviant stimulus. The artifacts from maternal and fetal magnetocardiogram signals were attenuated by using an orthogonal projection algorithm, described in Eswaran et al. [14]. Amplitude sensitive threshold detection was applied to the data and all trials with amplitude higher than 2 pT were rejected. Separate averages were computed for responses to the standard and deviant tones. Only those deviant trials were included in the averages for which the deviant stimuli followed at least two standards. Auditory evoked response was determined by averaging approximately 600 trials of standard tones and 70 trials of deviant tones. The responses were averaged with 100 ms pre-stimulus and 600 ms post stimulus interval and filtered between 0.5 Hz and 10 Hz in order to further attenuate any residual artifacts related to maternal and fetal cardiac activity. The responses were validated to following criteria. (i) A response to the standard and deviant tones with similar latency was obtained after averaging the even and odd trials. The similarity of the odd—even response was based on existence of a latency peak in the same latency range (+/−25 ms) and similarity in morphology. (ii) The differences detected between no response and discernible response was determined based on a method called plus—minus averaging. It calculates the difference between the averages of the odd and even numbered trials. The mathematical comparison between the conventional averaging and the plus—minus averaging gives a measure of signal to noise ratio, the amount of noise present and thus the reliability of the signals. A criterion of signal to noise ratio of at least 2:1 was applied. (iii) The magnetic field distribution showed activity in the area around the head coil location. The criteria was to choose as many channels that showed a response around the location of the head coil which was placed on the mother's abdomen by ultrasound determination.

The MMN response was then calculated by subtracting the response to the standard tone from the response to the deviant tone. If a maximum peak in the subtracted response occurred between 250 and 350 ms, this was regarded as an MMN response. In addition, if a second response was visible with the same polarity at latency above 400 ms it was classified as LDN response. This was based on the values that were obtained in our earlier study and from the literature of previous fetal and premature neonatal studies. The fetal recordings were split in three groups based on the GA, group (1): 28 to 31 weeks, group (2): 32 to 35 weeks and group (3): 36 to 39 weeks. The averaged response latencies and their standard deviation were calculated for each gestational group across all measurements.

2.4.2. Statistical analysis

A two-tailed t-test was carried out in order to assess the differences in response latencies between the fetal responses and corresponding responses in newborns and between the response latencies to the standard and the deviant tones. One way ANOVA analysis was used to evaluate the significance between corresponding response latencies for all gestational groups. A Chi-square statistic was performed in order to test if any significant difference existed in the number of successful detected responses between the gestational groups and between responses to the deviant and standard tones from all measurements. The percent of the successful detected responses was defined as response rate. Finally, linear regression analysis was applied on all response latencies data for each response in the period from 28 week to 39 week gestational age. The statistical analysis was performed with SPSS 12.0 for Windows.

3. Results

A total of 76 fetal and 9 newborn measurements were performed. Fig. 1 shows individual magnetic response data, recorded from a fetus at 5 different gestational ages (28, 30, 32, 34 and 36 weeks). The overlay of channels located in the vicinity of the fetal head of the response to the (a) deviant tone, (b) standard tone and (c) the subtracted waveform is presented in the figure. The amplitudes of fetal brain responses to the standard tone varied from 7 fT to about 12 fT; whereas the responses to the deviant showed amplitudes above 20 fT. Further, the response amplitudes were not considered because of the influence of the factors such as different noise level and different position of the fetal head (orientation and distance to the sensor) in each measurement. After subtraction, the response waveform is similar to the response to the deviant tone (with latency around 300 ms). A late component LDN with latency above 400 ms was also observed in the 30 weeks of gestation in Fig. 1(a,c).

Fig. 2a, shows an overlay of channels with maximal magnetic field amplitudes in response to the deviant, the standard tone and the difference between them (subtracted waveform) from a fetus at 29 weeks gestation. The corresponding magnetic field distribution of the responses at the maxima is shown in Fig. 2b. The maximal activity is visible in the vicinity of the fetal head, as is evident by a marker indicating the position of the fetal head coil. The response to the standard tone is visible at 0.2 s and to the deviant at 0.4 s, which shows the different latency range of response to the standard and to the deviant tone.

Fig. 3 illustrates the responses to the deviant, standard and MMN from a 15 day old newborn. Overlay of the maximal responding channels are demonstrated in Fig. 3a. The response to the standard tone has a maximum at about 0.3 s and the response to the deviant tone has two

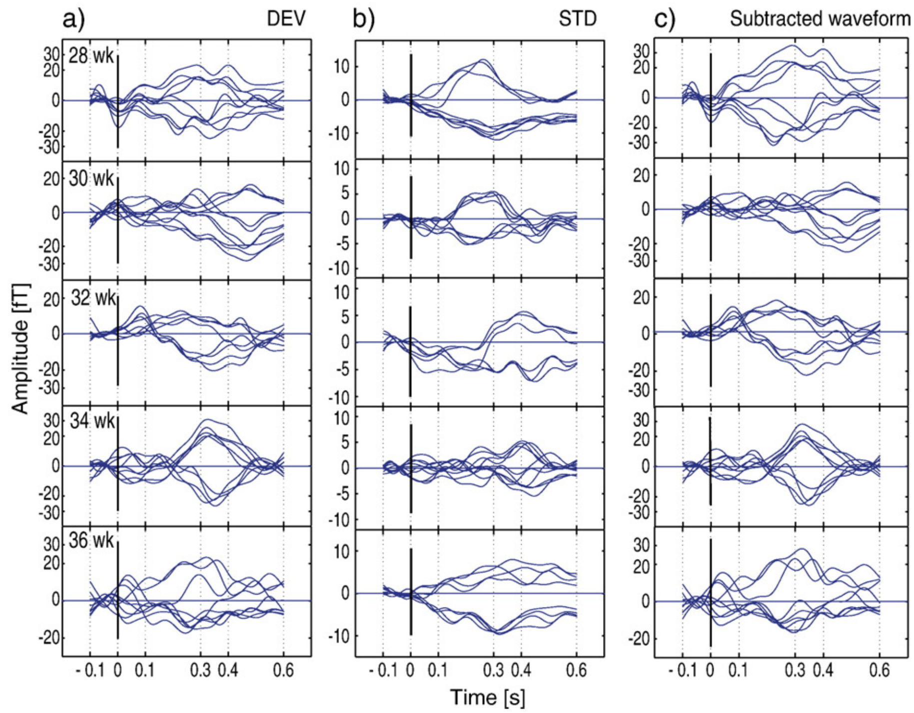

Figure 1 Fetal magnetic field responses. Overlay of the channels located in the vicinity of the fetal head of the response magnetic field to the (a) deviant tone, (b) standard tone, and (c) subtracted waveform; the rows represent fetal responses at different gestational ages.

different components. The early component is of the same latency as the response to the standard tone and the second component is observed at 0.4 s.

In Fig. 3b, the time traces of the responses for each sensor are shown. The circles denote channels with the maximal response amplitude. The signal time-course at the

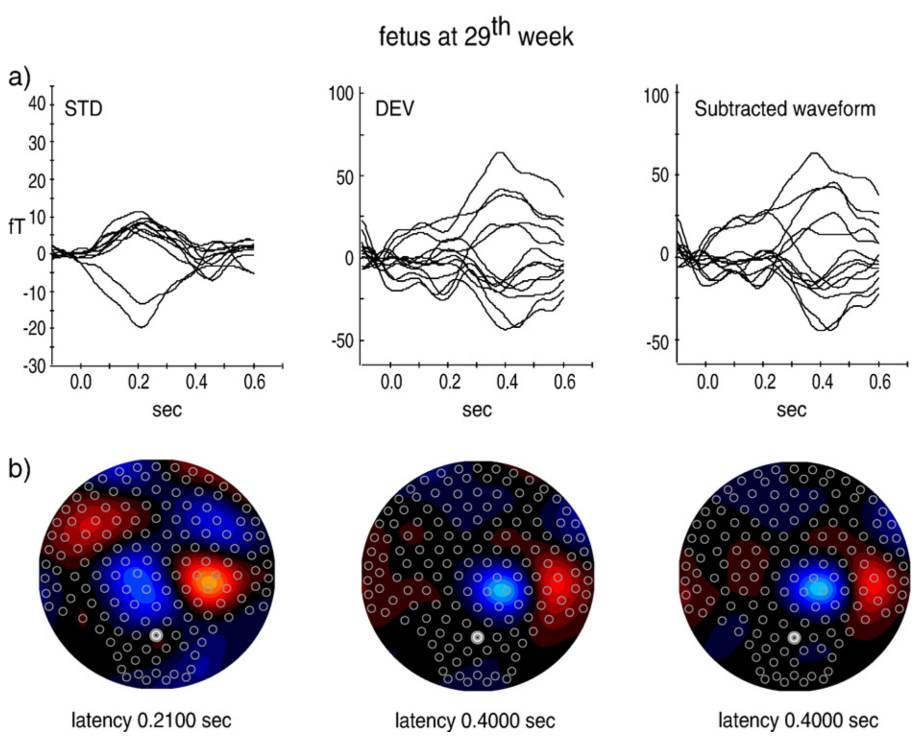

Figure 2 Magnetic field maps from a fetus at 29 weeks gestation. (a) Overlay of channels with maximal magnetic field amplitudes in response to the deviant, standard tone and subtracted waveform. (b) Magnetic field distribution of the responses at the maxima in the vicinity of the fetal head, the marker indicates the position of the fetal head coil.

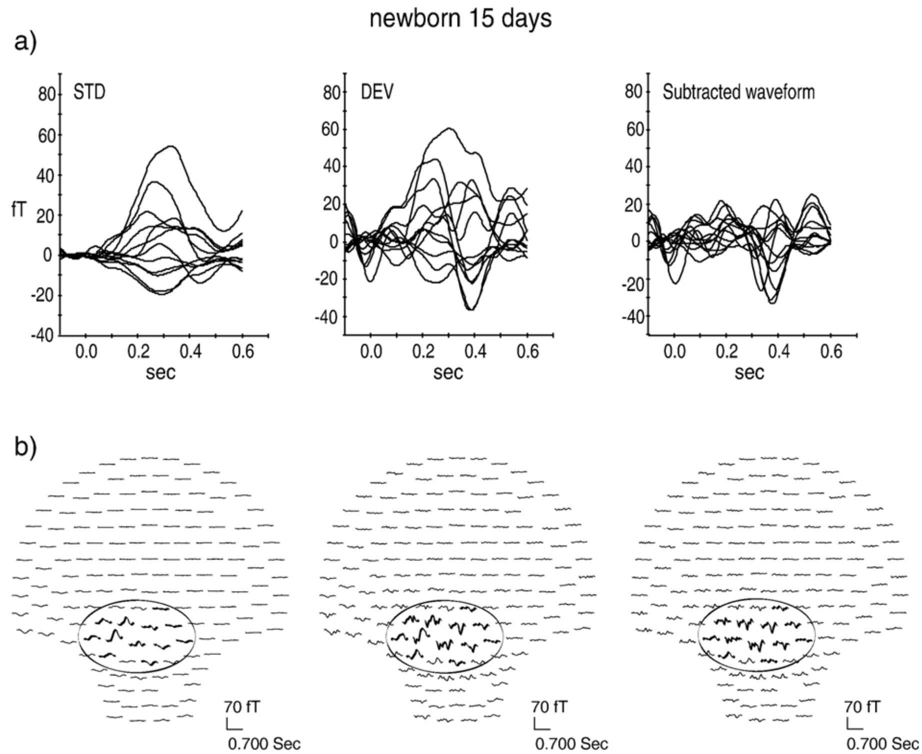

Figure 3 Magnetic field response to the deviant, standard and MMN from a 15 day old newborn. (a) Overlay of the maximal responding channels, (b) the time traces of the responses for each sensor. The circles denote channels with the maximal response amplitude.

channels, where a response to the standard appears is shown in Fig. 3b, first column. The MMN response can be seen inside the circle in Fig. 3b, third column, however the maximal response is not visible in the same channel as compared to the standard response.

Further statistics on the response rate and the response latencies were performed. A response to the standard tone was observed in 56% of the records in fetuses and 100% in newborns. Two different time ranges of this response were defined as early response (ER — 100 ms to 300 ms) and late response (LR — 300 ms to 500 ms). The early response was found in 32% of the records, averaged latency of 224 ± 42 ms (all results are given as mean and standard deviation) in fetuses and 56% in newborns, average latency 249 ± 47 ms. LR was observed in 32% of all fetal recordings, average latency of 381 ± 52 ms and 78% in newborns, latency 370 ± 84 ms (see Tables 1.1 and 1.2). For the subtracted response waveform (response to the deviant minus response to the standard tone), two different latency ranges were defined, from 200 ms to 400 ms (MMN response) and from 400 ms to 600 ms (LDN response). A response corresponding to detection of sound change (MMN, LDN or both) was found in 66% of the fetal data and 89% of the neonatal data.

An MMN response was detected in 46% of the records, average latency of 322 ± 42 ms in fetuses and 345 ± 50 ms in

Table 1.1 Response rate and response latencies recorded in 18 fetuses

Total number of records	28 to 31 weeks	32 to 35 weeks	36 to 39 weeks	28 to 39 weeks
	31	28	17	76
Response rate [%] and latencies of the responses (ER, LR) to the standard tone [ms]				
Common response rate	61 % (19 from 31)	46 % (13 from 28)	64 % (11 from 17)	56 % (43 from 76)
Response rate (ER)	39 % (12 from 31)	25 % (7 from 28)	29 % (8 from 17)	32 % (24 from 76)
Response rate (LR)	32 % (10 from 31)	21 % (6 from 28)	47 % (8 from 17)	32 % (24 from 76)
Mean (ER) latency	229 ± 48	224 ± 43	211 ± 30	224 ± 42
Mean (LR) latency	393 ± 49	373 ± 42	373 ± 65	381 ± 52
Response rate [%] and latencies of the responses of the subtracted waveform [ms]				
Common response rate	61 % (19 from 31)	67 % (19 from 28)	70 % (12 from 17)	66 % (50 from 76)
Response rate (MMN)	42 % (13 from 31)	46 % (13 from 28)	53 % (9 from 17)	46 % (35 from 76)
Response rate (LDN)	29 % (9 from 31)	43 % (13 from 28)	53 % (9 from 17)	39 % (31)
Mean (MMN) latency	326 ± 52	318 ± 37	323 ± 36	322 ± 42
Mean (LDN) latency	455 ± 35	462 ± 33	447 ± 56	456 ± 40

Table 1.2 Response rate and response latencies recorded in 9 newborns

	Response rate [%] and latencies of the responses (ER, LR) to the standard tone [ms]
Common response rate	100 % (9 from 9)
Response rate (ER)	56 % (5 from 9)
Response rate (LR)	78 % (7 from 9)
Mean (ER) latency	249 ± 47
Mean (LR) latency	370 ± 84
	Response rate [%] and latencies of the responses of the subtracted waveform [ms]
Common response rate	89 % (8 from 9)
Response rate (MMN)	56 % (5 from 9)
Response rate (LDN)	44 % (4 from 9)
Mean (MMN) latency	345 ± 50
Mean (LDN) latency	438 ± 43

newborns. In 39% of the records, an LDN response was observed, average latency of 456 ± 40 ms in fetuses and 438 ± 43 ms in newborns (see Tables 1.1 and 1.2).

The number of recordings and the percentage of the response rate of all responses in all three age groups are given in Table 1.1. A Chi-square test showed no significant difference between the response rate for MMN, LDN, ER and LR in different GA groups.

There was no significant difference in response latencies between the groups (one-way ANOVA) or between the responses of fetuses and newborns (two-tail t-test statistic). A significant difference was observed for response latencies to deviant and standard tones ($p<0.05$).

Further, a linear regression analysis was performed on the data (latencies vs. gestational age) in order to test the response latencies for maturation effect. Although not statistically significant, a decrease trend in latency was observed for all responses ER ($R^2=0.05$, $p>0.2$), LR ($R^2=0.03$, $p>0.4$), MMN ($R^2=0.007$, $p>0.6$), LDN ($R^2=0.02$, $p>0.4$) with increasing gestational age (Fig. 4a—d).

4. Discussion

One of the major findings of our study was that discriminative brain responses to sound changes can be detected at least as early as 28 weeks GA and that the detection rate did not change over GA. The earlier MMN studies did not attempt to perform recordings as early as 28 weeks of gestation and in addition the fetuses were not followed serially in a systematic fashion. Further, we demonstrated the existence of a latency classification not only for the discriminative response components (MMN and LDN), but also for the response to the standard tones (early and late response). This study also provides information about the latency trend with gestational age and response rates in different gestational groups, which can be useful in the design of further fetal studies.

The auditory nerve is well developed between 26 and 29 weeks gestation, which precedes the myelination of the brainstem and central auditory pathways by one to two weeks [36,3]. Sensory-motor structures are already developed and functional in early gestation providing a basis for cognitive development [37]. Fetal cortical evoked responses reflect cortical synaptic activity and are dependent on synapses development and synaptic density. By 24 weeks GA, neurons in the cortical subplate die while synaptic formation and dendritic growth occurs rapidly, increasing the size of the cortical plate. In humans, synapse addition occurs from 30 weeks, reaching logarithmic growth through two months post-birth. During this stage, the cortical plate has already a well laminated structure of primary sensory and motor cortex, [38]. Synaptic density of the fetal cortex and auditory pathway myelination are necessary factors for the beginning of simple cognitive function. Hence, cortical response to tone frequency change could be expected at approximately 28—30 weeks GA.

Brain evoked response (MMN, LDN) to change in stimulus frequency has been observed in fetal MEG studies by Huotilainen et al. [31] and Draganova et al. [32] but only at ≥ 33 weeks GA. Fetal sound frequency discrimination was also investigated behaviorally by Shahidullah and Hepper [39] who observed fetal movements in a habituation—dishabituation auditory task and reported no discrimination of different tones frequencies at 27 weeks GA but successful discrimination at 35 weeks. We observed fetal brain responses elicited by changes in stimulus frequency in 66% of recordings. Using the requirement that MMN or LDN response is valid only when both responses (to deviant and standard tones) were detectable restricted this to 50%. Our results showed that there is a significant difference between response latencies of the deviant and the standard tones. Hence, when a response to the standard tone was not detectable, and the latency of the subtracted response waveform was in the range of the response latency to the deviant tone, the MMN or LDN response was accepted. In all recordings standard tone responses exhibited reduced amplitudes when compared to the deviant tone responses. Similar results were reported by Huotilainen et al. [31] and Draganova et al. [32]. The small response amplitude was explained by Draganova et al. [32] as habituation effect, also demonstrated in studies of Shahidullah and Hepper [39]. The number of the averaged responses to the standard (600 trials) additionally improves signal to noise ratio but reduces the amplitude of the evoked response [40]. The difference between averaged number of responses to the deviant and standard tones could be the causal factor for the difference between the amplitudes of both responses. In future measurements, equivalent conditions for recording of deviant and standard responses should be investigated. This approach requires more insight into the habituation—dishabituation process in fetuses and newborns and could lead to better optimization of the experimental protocol.

Fetal magnetic auditory evoked response components are variable and, due to immaturity, latencies occur on a different time scale compared to evoked response components in children and adults. The response to the standard tone defined as early response (ER) was similar to fetal latencies described by Huotilainen et al. [31] and Draganova et al. [32]. A late component to the standard tone around 392 ms was also

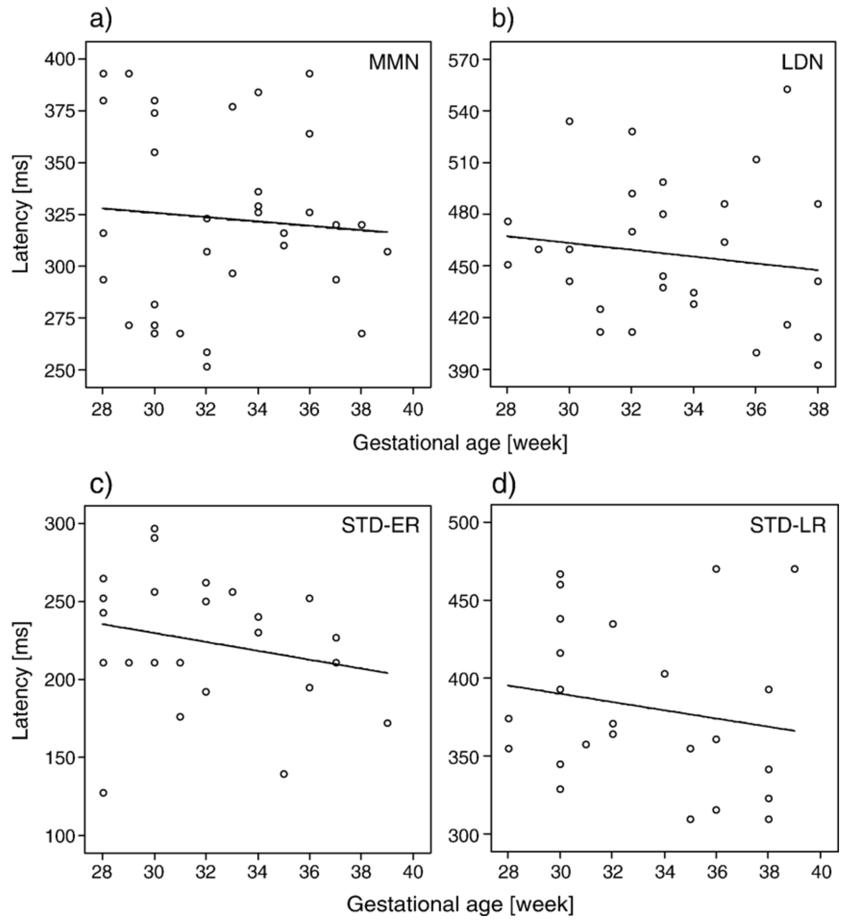

Figure 4 Linear regression analysis (decrease of the latencies vs. gestational age). (a) Early response to the standard tone (ER, r^2=0.05, p>0.2), (b) late response to the standard tone (LR, r^2=0.03, p>0.4), (c) MMN (r^2=0.007, p>0.6) and (d) LDN (r^2=0.02, p>0.4).

detected. As in adults, the short ISI may suppress elicitation of one exogenous response component but facilitate another one [41]. Thus the exact classification of fetal responses is speculative. These findings correspond with results from Eswaran et al. [42], which showed that all components of the evoked response are not present in fetuses.

The GA in which we detected an endogenous discriminative response to tone frequency change was 28 weeks. In 5 fetuses from all 10 in this GA discriminative responses were observed (Figs. 1 and 2).

Our results show MMN responses with latencies similar to other studies [31,32]. It is assumed that MMN response results from the existence of specific neurons for sound change detection and reflects a comparative process between a novel (deviant) sound and auditory memory trace (sensory memory formed by the frequent repetitive standard sound) [16,43]. In adults, sensory memory is approximately 10 s, but decreases considerably in young children and especially newborns. In neonates, sensory memory retains effectiveness for about 800 ms. Cheour et al. [25], demonstrated considerable decay of neonatal sensory memory when the ISI reached 1500 ms. Draganova et al. [32] demonstrated a randomized ISI centered at 800 ms (ISI = 800 ± 300 ms) does not disturb sensory memory and remains appropriate for perceiving the sequence of tones thus avoiding the refractory process. In the current study we used ISI of 800 ms randomized with 100 ms, providing the stimulus for eliciting the endogenous discriminative responses. Additionally, we found a late response to the deviant tone and in the subtracted waveform corresponding in latencies to the LDN, described in children and newborns by Čeponiene et al. [28,21], Korpilahti et al. [29], Shestakova et al. [30] with EEG and Huotilainen et al. [27], Draganova et al. [32] with MEG in newborns and fetuses. These studies suggest LDN is a specific response found only in early developmental stages of the auditory discriminative capability in the human since it is not detectable in adults. In our study, the LDN responses were observed in some of the fetal and neonatal data together with MMN or without MMN, which shows that LDN might be a feature of the tone frequency change discrimination in fetuses.

Although, the group between 36—39 weeks GA and 28—31 weeks GA showed the highest and the lowest response rate respectively, there was no significant difference between the groups assessed by the Chi-square test. Different factors contributed to the response rate. The first group (28—31 week) is characterized with the greatest number of recordings but with lowest response rate because of immaturity, whereas the next two groups are characterized with lower number of recordings but more detected responses. The lower number of recordings at the later GA was due to reduced participation because of maternal compliance or fetal delivery.

Different studies have reported MMN is a stable response in terms of latency and amplitude. Cheour et al. [23] showed there was no significant difference between MMN response latencies in newborns and infants three months of age. Our results showed a decrease in the trend of latencies with increase in GA for all responses to the deviant and standard tone (MMN, LDN, ER, LR), but the result was not significant. A significant difference was found only for latencies between responses to standard tone (ER, LR) and responses to frequency change (MMN and LDN), respectively. This suggests they are widely separated on the time scale.

In a serial study of standard response, Holst et al. [35] found a significant latency decrease with increasing GA in response to standard tones. The fact that we did not observe this statistical significance could be due to differences in auditory stimuli and ISI (current study: 800 ms, Holst et al. [35]: 2000 ms). Additionally, we separated responses to the standard tone into the two groups, ER and LR, whereas Holst et al. [35] selected the responses to the standard tone by the criteria of "the first highest peak" which were processed in one group. The broadness of the response waveform [44] and high noise level in fetal recordings, as well as data filtering may contribute to variability of the peak latencies. This makes calculation of latency differences not completely precise and response maturation difficult to predict. We conclude that, in the last trimester of the pregnancy, a simple cognitive process as discrimination between two tones could not be accompanied by significant changes in the response latency due to neuro-functional maturation.

In summary, we have shown that it is feasible to track development of fetal brain responses to sound frequency changes starting at least at 28 weeks of gestation and after delivery. The underlying mechanism of the discriminative ability of the auditory system is related to language learning and clinical aspects of auditory disorders. Investigation of this mechanism is important in adult research as well as that of children and infants. Of special interest is the question concerning the beginning of the process of sound discrimination, since the ability of the fetus to detect changes in sounds is a prerequisite to normal development of cognitive function. Further studies should investigate habituation processes and optimization of the stimulation paradigm for better characterization of fetal auditory sound discrimination and possible impairments.

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