

Research article

Healthy full-term infants' brain responses to emotionally and linguistically relevant sounds using a multi-feature mismatch negativity (MMN) paradigm

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ABSTRACT

We evaluated the feasibility of a multi-feature mismatch negativity (MMN) paradigm in studying auditory processing of healthy newborns. The aim was to examine the automatic change-detection and processing of semantic and emotional information in speech in newborns. Brain responses of 202 healthy newborns were recorded with a multi-feature paradigm including a Finnish bi-syllabic pseudo-word/ta-ta/as a standard stimulus, six linguistically relevant deviant stimuli and three emotionally relevant stimuli (happy, sad, angry). Clear responses to emotional sounds were found already at the early latency window 100–200 ms, whereas responses to linguistically relevant minor changes and emotional stimuli at the later latency window 300–500 ms did not reach significance. Moreover, significant interaction between gender and emotional stimuli was found in the early latency window. Further studies on using multi-feature paradigms with linguistic and emotional stimuli in newborns are needed, especially those containing of follow-ups, enabling the assessment of the predictive value of early variations between subjects.

1. Introduction

Language development requires a precise capability for sound discrimination and ability to process changes in speech. This preconscious auditory processing has traditionally been examined with event-related potentials (ERPs) of the electroencephalogram (EEG) in situations where unexpected sounds set off a neural activation, the mismatch negativity (MMN) response [1,2]. Hence, MMN is a brain response evoked by a change in auditory stimulation [1,3–6], and it exists immediately after birth [2,7] and is found even in fetuses [8].

MMN can be seen as an indicator for accuracy in auditory discrimination, representing the activity of an automatic predictive system [9]. However, contrary to behavioral measurements where co-operation with the subject is needed, the MMN measurement is suitable for studying the sensory auditory system despite possible problems with communication or task performance, for instance, with newborns [10,11]. Children with language and/or literacy problems can have

difficulties in discriminating changes in sounds [12]. These impairments can also be selective to different types of changes and, therefore, the MMN amplitude can be normal or enhanced to one deviant, but decreased to another. For example, with dyslexic individuals, the discrimination of pitch changes can be impaired while location changes are enhanced [13], whereas in autism spectrum disorders the impairment appears in the detection of emotional information [14] or in the tolerance of variation [15,16].

As MMN measurements have shown, newborns have a capability of learning speech sounds even when sleeping [11]. Therefore, this method is feasible with sleeping newborns [17–20]. Furthermore, neonates' MMN can be measured during all sleeping states, including active and quiet sleep [7,23,26,30], and also awake state [23,26,28]. MMN responses of neonates have been examined in several studies, and negative MMN-like responses to tones [10,21–24] and speech sounds have been found [7,11,20,25–27]. In adults, the MMN response is typically peaking at 150–200 ms after the beginning of the deviation

Abbreviations: EEG, electroencephalography; ERP, event-related potential; MMN, mismatch negativity

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[1,3–6], whereas in newborns the deviant deflection is peaking at more varying latencies and often later than in adults [7,10,18,22,27–31]. Furthermore, a deflection in newborn infant responses can also be positive and, thus, opposite in polarity [18,27,30–32]. In some cases, there can even occur a total absence of the MMN response [21,23]. These differences and inconsistencies in the neonatal data have been associated with maturational factors and differences in the auditory stimulation paradigms.

In the traditional one-deviant oddball paradigm, a deviant is presented rarely within a sequence of frequently presented standard stimuli. A disadvantage of this paradigm is the duration of the overall measurement, since only one deviant can be measured at a time. Näätänen et al. [33] further developed this paradigm by creating a new multi-feature MMN paradigm (Optimum-1), where five different types of deviants were used. In contrast to the one-deviant oddball paradigm where only one deviant and a standard tone were presented in a sequence, the new paradigm enabled to include more deviants and, thus, provide more information in the same recording time. The multi-feature MMN paradigm has been used in several studies with adults [34,35]; children [36–38], toddlers [39] and newborns [27,30].

Sound discrimination has been studied using the multi-feature paradigm, not only with tones, but also language-relevant sounds, like syllables [37,40] and multisyllabic pseudo-words [27,36]. These language-related sounds have introduced deviants with high relevance for speech understanding, such as changes in vowel or consonant identity, duration, or frequency. In addition to this, Pakarinen et al. [35] introduced a further developed multi-feature MMN paradigm with three types of rarely occurring emotional speech stimuli for studying attention allocation and processing of emotional information in speech.

Infants can utilize prosodic cues when structuring their native language [41,42]. This capability of extracting cues from speech is present shortly after birth [19]. In this process of language structuring individual prosodic cues such as intonation, tone, rhythm and stress reflect the emotional state of the speaker. Consequently, affective prosody is an important component of language development. In order to study the development of neonatal language and emotional perception skills a systematic study of the variations in the change-detection responses is of primary importance. Therefore, our study investigated processing of both linguistic and emotional information in speech in healthy newborns.

The first aim of this study was to evaluate the feasibility of the multi-feature MMN paradigm that Pakarinen et al. [35] introduced, in studies of healthy newborns. Second, we wanted to investigate whether newborns are capable of detecting and processing emotional information content in speech. There is a lack of systematic knowledge about newborn infants' brain responses to emotional content in speech, and an efficient paradigm to compare semantic and emotional change-detection in the newborn brain is urgently needed.

2. Methods

2.1. Participants

There were overall 207 healthy infants recruited in this study. The parents gave their written informed consent for the infants to participate in the studies, which were approved by the Ethics Committee of the Hospital District of Southwest Finland and the Ethics Committee of the Hospital District of Helsinki and Uusimaa. The study protocol followed the Declaration of Helsinki.

The infants were born full-term between 37 and 42 weeks of gestation to either native Finnish-speaking ($n = 201$) families or Swedish-speaking families ($n = 6$, speaking Finland-Swedish) and their birth weights were between 2635 and 4770 g (See Table 1). Our inclusion criteria were that the infants were healthy (Apgar score of 7–10 at 5 min), had stable physical condition and normal hearing. Five infants were excluded from participation due to prematurity (< 37 GA) or low

Table 1
Participant information (mean and ranges).

<i>n</i> =	192 (103 boys, 86 girls, **)
Gestational age at birth (weeks)	40.13 (37.43–42.29)
Weight (g)	3622.35 (2635–4770)
Height (cm)	51.02 (47–57)
Apgar [*] 1	8.70 (3–10)
Apgar 5	9.09 (7–10)
pH (uA)	7.28 (7.06–7.46)
Gestational age at measurement day (weeks)	40.67 (37.86–43.71)
Age at measurement day (days)	0–34 (4.26)

* Apgar score = newborn health assessment scale 1–10 (Appearance, Pulse, Grimace, Activity, Respiration; assessed 1 and 5 min postnatally).

** Data on the gender of 3 infants missing.

Apgar score at 5 min (< 7). The brain responses of the remaining 202 infants were recorded 0–34 days postpartum. From these, data of 10 infants were omitted from the analysis and, finally, data from 192 infants were included in the analysis (see Chapter 2.3 for details).

2.2. Stimuli

The data were measured with the multi-feature MMN paradigm including a standard stimulus and six types of linguistically relevant deviant stimuli as well as three types of emotionally uttered stimuli. The standard stimulus (46% probability, 100 in each stimulus block) was a 336 ms, bi-syllabic, naturally uttered pseudo-word/ta-ta/with the stress on the first syllable and slightly falling intonation, typical to Finnish language. The six linguistically relevant deviants were vowel duration change (/ta-ta:/, 11% probability, 25 in each stimulus block), vowel change (/ta-to/, 11% probability, 25 in each stimulus block), intensity changes (± 6 dB, 5% probability each, 11 in each stimulus block) and frequency changes (± 25.5 Hz, 6% probability each, 14 in each stimulus block). Furthermore, there were three emotionally uttered/ta-ta/stimuli (happy, angry, sad) infrequently occurring in the stimulus stream (3% probability each, 6 in each stimulus block). In all deviants the changes occurred in the second syllable of the pseudo-word. The three rare emotional variants differed from the standards and all other deviants already from the first syllable onwards as they were prosodically exaggerated natural utterances. All sounds were presented with a 650 ms stimulus onset asynchrony (SOA) and each subject was presented with 4–6 stimulus blocks. (See Tables 2 & 3 for detailed information and supplement for an excerpt of the audio stimuli file).

2.3. ERP recording and data analysis

The infants were mainly sleeping during the ERP recording. The EEG was recorded using the International 10–20 System electrode locations and a sampling frequency of 500 Hz. The stimuli were presented via loudspeakers located at a distance of approx. 1 m from the head of the infant. The data were collected from the electrodes F3, Fz, F4 (frontal), C3, Cz, and C4 (central), and Oz (back of the head). For data analysis, the data-sampling rate was decimated to 250 Hz. Data were re-referenced to the Oz electrode and band-pass filtered between 1 and 20 Hz. The data were cut into epochs beginning 100 ms before the stimulus onset and ending 650 ms after. The epochs were baseline corrected to the mean value of the signal for the period of 100–0 ms before the stimulus onset. Epochs with signal values at any channel larger than ± 150 μ V were rejected from the analysis. Data of seven participants had more than 50% of total epochs rejected and were excluded from the rest of the analysis. Additionally, data of three participants were excluded due to too few or incomplete data files.

Intervals between 100–200 ms and 300–500 ms for the emotional sounds and 300–500 ms for the deviants were chosen as descriptive of the brain responses and the averaged value of the filtered signal within

Table 2
Details of the standard, deviant and emotional stimuli (partially same as in Pakarinen et al. [35]).

Stimulus	Utterance	Total duration (ms)	1 st syllable	2nd syllable	Deviance information
Standard	/ta-ta/	336	168	168	Frequency: 175 Hz
Emotional variants					
Happy	/ta-ta:/	388	125	263	Frequencies: 276 Hz and 177 Hz Intensities: +1 dB and -2 dB
Sad	/ta:-ta:/	436	218	218	Frequencies: 276 Hz and 260 Hz Intensities: -1 dB and -2 dB
Angry	/ta-ta/	337	125	212	Frequencies: 196 Hz and 163 Hz Intensities: +3 dB and -6 dB
Deviants					
Vowel change	/ta-to/	336	168	168	Intensity difference from Std: < 1 dB Frequencies: 1 st and 2nd syllable 175 Hz and 168.5 Hz
Vowel duration	/ta-ta:/	400	168	232	Intensity difference from Std of the 1 st syllable: -2 dB Frequencies: 168 Hz and 162 Hz
Frequency change	/ta-ta/	336	168	168	Frequencies: ± 25.5 Hz (50% each): perceived as pitch changes
Intensity change	/ta-ta/	336	168	168	Intensity ± 6 dB (50% each): perceived as loudness changes

Table 3
Example of the recording sequence of standard, deviant and emotional stimuli.

Std	Sad	Std	Dev3	Std	Dev4	Std	Dev1	Std	Dev2	Std	Happy	Std
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Approx. 8s

these latency windows was collected. When the response average at an individual electrode was larger than $\pm 10 \mu\text{V}$, the response was left out from the statistical analysis as it was considered to be artefactual. After this the remaining averages from the mean amplitude values from electrodes F3, Fz and F4 as well as electrodes C3, Cz and C4 were averaged together as electrode lines F and C. The mean values were separately calculated for each infant and each stimulus type either to one or both time windows.

A one-sample *t*-test was used to determine whether the standard-subtracted mean amplitudes from the electrode lines F and C differed significantly from $0 \mu\text{V}$. We utilized two-tailed *t*-test as we did not want to presume the polarity of the MMNs. First, we tested whether the mean amplitudes of the EEG response of the three emotional stimuli from the latency window 100–200 ms differed significantly from zero. Second, the responses from latency window 300–500 ms for the six deviants and three emotional sounds were tested similarly. To evaluate the differences between the mean amplitudes of deviants and emotional stimuli, gender, and electrodes, we performed repeated-measures ANOVA (Greenhouse-Geisser corrected values are reported). The possible effect of infant age on the brain responses was tested with Pearson's correlation test.

3. Results

The waveforms of all the deviants, emotional variants and standard from electrode line F are shown in Fig. 1. Two-tailed one-sample *t*-test showed that the mean EEG amplitudes significantly differed from $0 \mu\text{V}$ in the electrode line F, in the early latency window 100–200 ms for the emotional variant *sad*: $t(185) = -2.125$, $p = 0.035$ and emotional variant *angry*: $t(185) = -2.258$, $p = 0.025$. In the electrode line C there was a significant response for the emotional variant *angry*: $t(191) = -3.101$, $p = 0.002$. In the later latency window 300–500 ms only the following emotional response in the electrode line C reached close to a significant result: *happy*: $t(189) = 1.959$, $p = 0.052$.

No significant main effect of stimuli or gender was found using repeated-measures ANOVA. However, a significant main effect of electrode was found in the later latency window 300–500 ms ($F(1, 169) = 6.010$, $p = 0.015$), due to the mean amplitudes in the central line being bigger than in the frontal line. A significant interaction effect

between gender and stimulus type was found in the early latency window 100–200 ms ($F(2, 171) = 3.681$, $p = 0.027$): The mean amplitudes for emotional stimulus *happy* were stronger in female infants (female $-0.938 \mu\text{V}$, male $-0.081 \mu\text{V}$), whereas in male infants the mean amplitudes were stronger for emotional stimuli *sad* (female $-0.109 \mu\text{V}$, male $-0.878 \mu\text{V}$) and *angry* (female $0.095 \mu\text{V}$, male $-0.874 \mu\text{V}$). The results of Pearson's correlation test showed no correlation between the two variables, age at the measurement day and the brain responses. All statistical results, mean amplitudes, standard deviations and 95% confidence intervals are reported in Table 4.

4. Discussion

The first aim of this paper was to introduce a new multi-feature MMN paradigm, that has been successfully used in studying discrimination skills of toddlers, children and adults and evaluate its usability with newborn infants. We utilized a multi-feature MMN paradigm that Pakarinen et al. [35] developed but we reduced the amount of deviant types. In addition to the six linguistically relevant deviants, the multi-feature MMN paradigm consisted of three rare emotional stimuli, which were natural utterances (*happy*, *sad* and *angry*) of the pseudo-word/*ta-ta/*.

By visual inspection we found a prominent negative deflection for all emotional stimuli that peaked around 150 ms after stimulus onset. We also found a large, later positive deflection that peaked around 400 ms for emotional stimulus *happy*, 450 ms for emotional stimulus *sad* and 500 ms for emotional stimulus *angry*. The linguistically relevant deviants had smaller negative peaks around 350 ms after stimulus onset for all other deviants except for *intensity changes* ($\pm 6 \text{ dB}$) that had minor positive deflections around 450 ms. The latencies of the negative peaks for the deviants correspond approximately to 180 ms after change onset, and that of the positive deflection for intensity change corresponds approximately to 280 ms after change onset. The results of the *t*-tests showed that most of the large negative responses elicited by the emotional stimuli were statistically significant or close to significance at the early latency window 100–200 ms. The emotional variant *angry* elicited the largest amplitudes in the early time window, most likely as a result of differences in the acoustical features. All the emotional stimuli had naturally different timbre, stress and intensity, and in *angry*

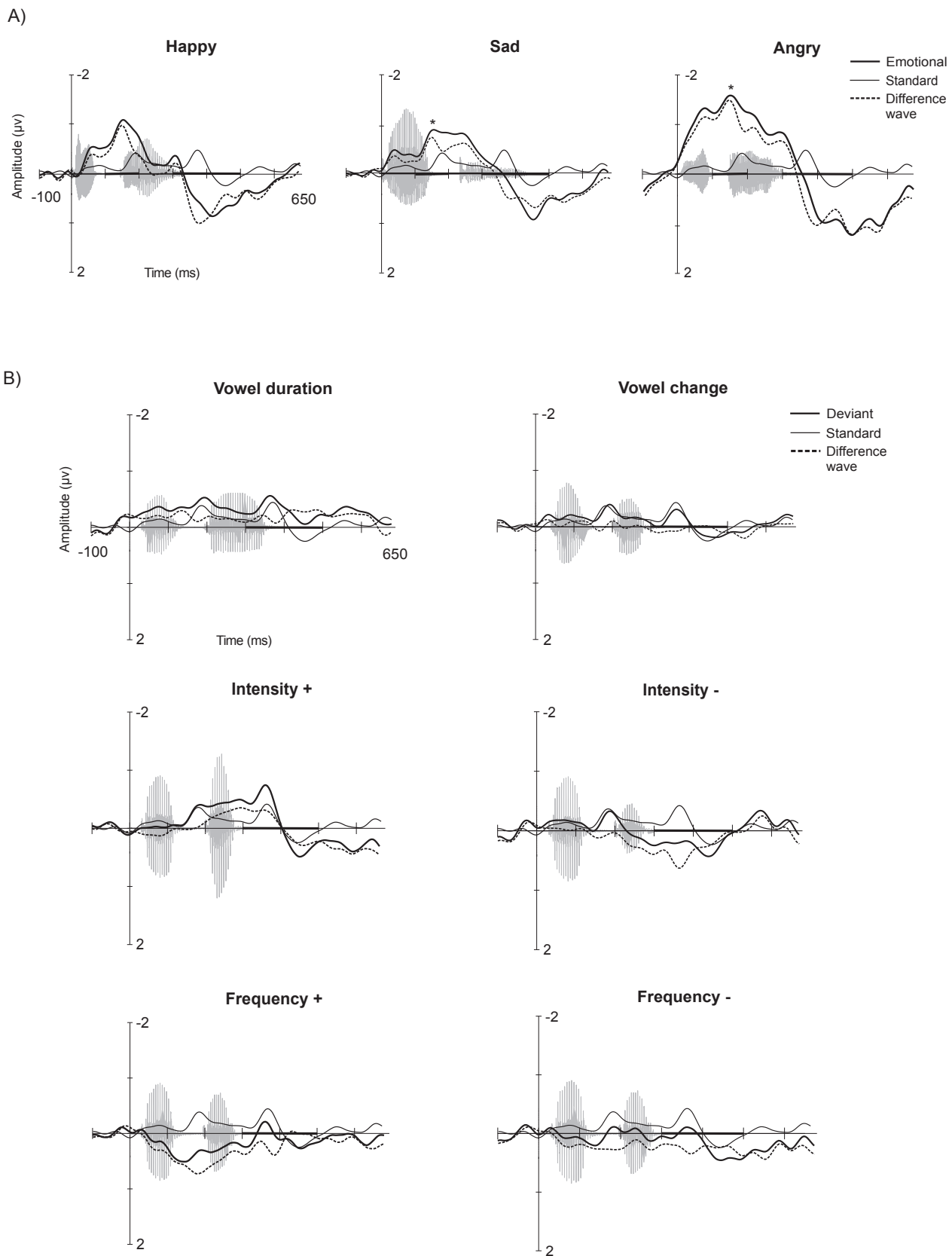


Fig. 1. The mean EEG amplitudes for the three rare emotional stimuli (A) and the six deviant stimuli (B) at frontal line (F). The bold line illustrates the emotional stimulus (A) or deviant stimulus (B), the thicker line the standard stimulus and the dotted line the difference wave (* $P < 0.05$). The sound waves of the stimuli appear in grey at the timeline and the thicker lines represent the latency windows 100–200 ms and/or 300–500 ms.

Table 4

Results of the two-tailed *t*-tests; *t*-values and *P*-values, mean amplitudes, standard deviations and 95% confidence intervals.

	<i>t</i> sig	MEAN (SD) (<i>CI</i>)		
Electrode line	F		C	
Time latency 100–200 ms				
Emotional variants				
Happy	–1,8	–0.5 (4.1) (–1.14...+0.04)	–1.8	–0.5 (3.6) (–0.99...+0.03)
Sad	–2.1*	–0.7 (4.3) (–1.3...–0.04)	–1.0	–0.2 (3.5) (–0.74...+0.25)
Angry	–2.3*	–0.6 (3.8) (–1.17...–0.07)	–3.1***	–0.8 (3.4) (–1.25...–0.27)
Time latency 300–500 ms				
Emotional variants				
Happy	1.7	0.5 (4.0) (–0.06...+1.08)	2.0	0.5 (3.6) (–0.00...+1.02)
Sad	0.7	0.2 (4.3) (–0.39...+0.86)	1.1	0.3 (3.5) (–0.23...+0.78)
Angry	1.5	0.5 (4.5) (–0.14...+1.15)	0.8	0.2 (3.9) (–0.34...+0.78)
Deviant				
Vowel duration	–1.3	–0.2 (2.3) (–0.55...+0.10)	–1.6	–0.2 (1.8) (–0.47...+0.04)
Vowel change	0.3	0.06 (2.4) (–0.28...+0.39)	–0.6	–0.08 (1.8) (–0.34...+0.18)
Intensity change (+6 dB)	–0.07	–0.02 (3.2) (–0.47...+0.44)	0.3	0.07 (2.7) (–0.31...+0.45)
Intensity change (–6 dB)	1.1	0.3 (3.6) (–0.22...+0.82)	1.4	0.3 (2.9) (–0.12...+0.70)
Frequency change (+25.5 Hz)	0.7	0.1 (3.0) (–0.28...+0.57)	–0.1	–0.02 (2.5) (–0.37...+0.33)
Frequency change (–25.5 Hz)	1.1	0.2 (2.8) (–0.17...+0.62)	1.5	0.3 (2.4) (–0.07...+0.6)

* *P* < 0.05.

*** *P* < 0.002.

stimuli these differences were occurring most strongly at the first syllable of the pseudo-word. The later positive deflections at the second time window 300–500 ms of the emotional sounds did not reach significance, nor did linguistic deviants.

The second aim of our study was to find out whether newborn infants are able to detect and process emotionally relevant information content in speech and if that can be seen in the MMNs. Although according to visual inspection responses in emotional stimuli were larger and the averaged mean amplitudes were higher when compared to deviants, our results showed statistically significant responses to emotional stimuli only in the early latency window 100–200 ms. However, when interpreting these results, one has to be aware of multiple testing. Additionally, our results demonstrated significant differences in the mean amplitudes of the emotional stimuli between genders in the early latency window. Hence, the differences in the processing of emotional sounds should be studied across genders in future studies.

In this multi-feature paradigm, emotional stimuli set off larger responses for two reasons. First, they appear less frequently in the sound stream than the standard and deviants. Second, the acoustic differences between the emotional and standard stimuli are larger than the differences between the deviants and standard. The results suggest that newborn infants' brain respond automatically and pre-attentively to emotionally relevant information in speech, and this seem to be caused by the acoustic differences that emotionally uttered speech contain. These prosodic differences in infant-directed speech are the important factors that help to get and maintain infants' attention and, thus, focus

on language learning [43,44]. Additionally, exaggerated pitch features have been shown to enhance statistical structuring of speech in newborns [45].

Our results demonstrate an extensive variation in the brain responses between the newborn infants, which can directly contribute to lower amount of significant responses at the group level. These results are in line with other studies reporting high individual differences in MMN amplitudes between neonates and lack of significant group-level responses [18,22,26]. Due to such variation in the amplitudes in individual subjects, MMN peaks have in some studies been measured individually rather than on the group level [18,19,39]. It should be noted that the variation in the data could partially be a result of maturational factors and be a feature typical to newborn infant data, as newborns' brains go through large developmental changes after birth. Some studies have shown that gestational age affects the MMN amplitude [29], however, our results showed no correlation between the responses and age at the measurement day.

The lack of group-level significant responses to deviants provokes the question whether the multi-feature paradigm is too challenging for newborns, as they need to detect changes from a sound stream consisting of a large amount of stimuli. Therefore, it would be of interest to study 3 month old infants with the same paradigm and see if the change-detection of the deviants would be more efficient. In our paradigm it might be that the emotional sounds interrupt the detection of the deviant stimuli, considering that Partanen et al. [27] used a multi-feature paradigm with multi-syllabic pseudo-word and five language-related deviants with newborns and showed significant group-level responses. In future studies emotional sounds and deviants could be recorded in separate blocks and see if the results differ compared to when all stimuli are mixed in a single block like in our study. Inter-subjective variation could also indicate relevant differences between infants predicting divergences of auditory processing or attentive skills. For this reason, follow-ups on the predictive value of the responses would be of high importance.

In conclusion, when using a multi-feature MMN paradigm with newborns there are advantages and disadvantages to take into consideration. With a multi-feature paradigm it is possible to record multiple responses in a shorter period of time. This is an important factor in developmental disorders where responses may show in one deviant but not in another, like in dyslexia [13,46,47] and children with autism spectrum disorders [15,48]. Even though variation between subjects can reduce the amount of significant responses it can also be beneficial when studying subjects with increased risk for later developmental difficulties. In future infant studies, multi-feature MMN paradigms with linguistic and emotional stimuli should be evaluated more, and examine if they could be utilized with different target groups, such as premature infants and other infants with greater risk for developmental problems.

Conflicts of interest

None of the authors have potential conflicts of interest to be disclosed.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.neulet.2018.01.039>.

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