Mismatch response (MMR) in neonates: beyond refractoriness

Gábor P. Háden[1], Renáta Németh[1,3], Miklós Török[4], István Winkler[1,5]

[1] Institute of Cognitive Neuroscience and Psychology, Research Centre for Natural Sciences, Hungarian Academy of Sciences, Budapest, Hungary
[3] Department of Cognitive Science, Central European University, Budapest, Hungary
[4] Department of Obstetrics-Gynaecology and Perinatal Intensive Care Unit, Military Hospital, Budapest, Hungary
[5] Institute of Psychology, University of Szeged, Szeged, Hungary

Corresponding author: Gábor P. Háden, Institute of Cognitive Neuroscience and Psychology, Research Centre for Natural Sciences, Hungarian Academy of Sciences. H-1117 Budapest, Magyar tudósok körútja 2, Hungary. E-mail: haden.gabor@ttk.mta.hu. Tel: +36 1 382 6808.

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Abstract
In the adult auditory system, deviant detection and updating the representation of the environment is reflected by the event-related potential (ERP) component termed the mismatch negativity (MMN). MMN is elicited when a rare-pitch deviant stimulus is presented amongst frequent standard pitch stimuli. The same stimuli also elicit a similar discriminative ERP component in sleeping newborn infants (termed the mismatch response: MMR). Both the MMN and the MMR can be confounded by responses generated by differential refractoriness of frequency-selective neural populations. Employing a stimulus paradigm designed to minimize this confounding effect, newborns were presented with sequences of pure tones under two conditions: In the oddball block, rare deviant tones (500 Hz; 10%) were delivered amongst frequent standards (700 Hz; 90%). In the control block, a comparison tone (500 Hz) was presented with the same probability as the deviant (10%) along with the four contextual tones (700 Hz, 980 Hz, 1372 Hz, 1920.8 Hz; 22.5% each). The significant difference found between the response elicited by the deviant and the comparison tone showed that the response elicited by the deviant in the oddball sequences cannot be fully explained by frequency-specific refractoriness of the neural generators. This shows that neonates process sounds in a context-dependent manner as well as strengthens the correspondence between the adult MMN and the infant MMR.

Introduction

The auditory system creates and maintains a veridical representation of the environment. Forming representations of the regular aspects of the environment is an important part of this function. Detecting violations of the previously extracted regularity representations allows updating these representations and to separate sound carrying new information from those that can be predicted based on what the auditory system knows about the environment (Winkler et al., 2009). The auditory deviance detection process is thought to be reflected by the event-related potential (ERP) component termed mismatch negativity (MMN). MMN is, for example, elicited by rare sounds (deviant) with a pitch that differs from that appearing frequently in the sequence (standard) (for a recent review, see Näätänen et al., 2011). Pitch-deviant stimuli presented to sleeping newborn infants also elicit a discriminative ERP component (Alho et al., 1990), which has similar features to the MMN observed in adults (termed the mismatch response; MMR). Ever since MMN was first described as a memory-based mismatch process (Näätänen et al., 1978) it has been debated whether MMN is a separate ERP component or a modulation of the auditory N1 response (e.g., May & Tiitinen, 2010). For MMN elicited by pitch deviation, it can be argued that the neural populations responding selectively either to the standard or to the deviant pitch attain different refractory states as a consequence of the difference in how often they are activated. Therefore, when comparing between the response to the standard and the deviant stimulus, at least a part of the difference can be explained by differential refractoriness (May & Tiitinen, 2010; Fishman, 2013). In order to separate the memory-comparison contribution from the effects of differential refractoriness, Schröger and his colleagues (Schröger & Wolff, 1998; Jacobsen & Schröger, 2001) have developed a stimulus paradigm designed to minimize the refractoriness-related contribution to the estimate of the MMN response. The aim of the present study is to test whether, similarly to the adult MMN, the MMR response observed in neonates cannot be fully accounted for by differential refractoriness. Finding similar neural processes underlying the MMN and the MMR would further strengthen the correspondence between these ERP components.

The MMN component is usually derived as the difference between the ERP response elicited by a deviant and the standard. However, as was noted above, this approach is susceptible to

refractory effects as the neural populations encoding the stimuli are activated with different temporal frequency. In order to control for refractory effects a stimulus identical to the deviant can be presented with the same probability as the deviant (deviant-control) but in a sequence composed of a range of randomly chosen stimuli differing in the deviant feature (Schröger & Wolff, 1998; Jacobsen & Schröger, 2001). This procedure provides a reasonable estimate of the refractory state of the neural populations responding to the deviant stimulus, while the deviant-control stimulus is not expected to elicit a memory-based mismatch response (termed "genuine MMN"), because the random stimuli do not provide a regularity which would be violated by the deviant-control. Therefore, subtracting the ERP elicited by the deviant-control from that recorded for the deviant stimulus provides an estimate of the genuine MMN elicited by the deviant in the main experimental condition.

The interpretation of the infantile MMR is not as straightforward as that of the adult MMN, because the brain is still in rapid development (Kushnerenko et al., 2002) and some adult-like components for example the N1 are completely absent (Ponton et al., 2000). The latency and polarity of infantile ERP response to deviant stimuli presented in the oddball paradigm are highly variable and while some variables have been proposed to affect them (e.g., maturity, sleep state, stimulus presentation rate, etc.) none of them explains the whole range of findings (Kushnerenko et al., 2013). Furthermore, there are possibly several overlapping components sensitive to various stimulus properties as well as deviance in these features (see, e.g., Kushnerenko et al., 2007). These components do not fully correspond to any of the ERP responses in adults and they have different developmental trajectories during infancy (He, Hotson & Trainor, 2009; Kushnerenko et al., 2013).

No previous auditory deviance detection experiment employed Schröger and colleague's (Schröger & Wolff, 1998; Jacobsen & Schröger, 2001) control procedure for refractory effects in newborn infants, which is the best currently available for oddball designs (Kujala, Tervaniemi & Schröger, 2007). Earlier attempts to control for refractory effects in newborn infants presented deviant-equivalent sounds with a 33.3% probability within equiprobable conditions (Čeponiene et al., 2002; Kushnerenko et al., 2002). This method is better than reversing the stimulus probabilities for a control of the oddball paradigm, but it still underestimates refractory effects in the MMR signal. Therefore, although the results of Čeponiene and colleagues (2002) and Kushnerenko and colleagues (2002) are compatible with the notion of a genuine memory comparison process contributing to the response to deviant sounds, they did not provide a critical test of this issue. Thus it is yet unknown whether and if so how much of the deviance related response difference can be attributed to memory-based comparison processes in neonates.

We presented newborn infants with an oddball and a comparable control stimulus block. If the response difference between the deviant and the standard stimulus is fully due to differential refractoriness between the neuronal populations responding to the two types of sounds, then we should find no differences between ERP responses elicited by the deviant and the deviant-control stimuli. In contrast, if there is a genuine MMR (i.e., a response to deviance based on detecting a

regularity violation), then the response to the deviant should differ from that to the deviant-control.

Materials and methods

Participants

EEG was recorded and analyzed from 26 (18 male) healthy full-term newborn infants during day 1-3 postpartum. One additional infant's data was recorded, but discarded due to excessive electrical artifacts. The mean gestational age was 38.80 weeks (38 weeks and ~6 days; SD=1.07), birth weight 3388 g (SD=478.61); 18 neonates were born with Caesarean section. All infants had Apgar scores of 9 and 10 (1 and 5 minutes, respectively; corresponding to the highest value in the two assessments as assigned by the protocol of the hospital ward). The hearing of 16 infants was normal, while 10 infants' hearing was not tested in the hospital due to equipment malfunction. Because the incidence of neonatal hearing problems in a normal population, such as the one our sample is taken from, is about 0.1% (Davis & Wood, 1992) therefore normal hearing can be reasonably assumed in the all or at least the large majority of the infants tested. Informed consent was obtained from one or both parents. The experiment was carried out in a dedicated experimental room at the Department of Obstetrics-Gynaecology and Perinatal Intensive Care Unit, Military Hospital, Budapest. The mother of the infant could opt to be present during the recording. The study was conducted in full accordance with the World Medical Association Helsinki Declaration and all applicable national laws; it was approved by the relevant ethics committee: Medical Research Council – Committee of Scientific and Research Ethics (ETT-TUKEB), Hungary.

Stimuli and procedure

The experimental design was based on Jacobsen et al.'s (2003). Sinusoidal tones of 70 dB SPL and 50 ms duration including 5-5 ms rise and fall times (raised cosine ramp) were presented to newborn infants. The stimulus onset asynchrony (SOA; onset-to-onset interval) was 800 ms. The tones were presented binaurally by E-Prime software (Psychology Software Tools, Inc., Pittsburgh, PA) through ER-1 headphones (Etymotic Research Inc., Elk Grove Village, IL, USA) connected via sound tubes to self-adhesive ear-couplers (Natus Medical Inc., San Carlos, CA, USA) placed over the infants' ears. Sounds were presented in pseudorandom order in two stimulus blocks corresponding to the two experimental conditions. In the oddball condition, rare 500 Hz tones (p=0.1, deviant, no repetitions allowed) were presented among 700 Hz tones (p=0.9, standard). In the control condition, 500 Hz tones (p=0.1, deviant-control) were presented among 700, 980, 1372 and 1920 Hz tones (p=0.225, standard-control). Only four standard-control tones were employed, because neonates do not distinguish small frequency differences (see, e.g., Novitsky et al., 2007) and sufficiently large frequency steps between tones would have

led to presenting tones with too high frequencies. Note that the random stimuli do not need to be presented with the same probability as the deviant-control as long as there are at least three of them and they are equiprobable among themselves (Jacobsen et al., 2003) (for further considerations regarding the choice of frequencies, etc., see Jacobsen & Schröger, 2001). Tone repetitions were not allowed in this condition. Each stimulus block consisted of 1500 tones. The order of the stimulus blocks was balanced across infants. The total duration of the stimulus presentation was approximately 40 minutes. The infants were lying on their backs with their head on a shaped pillow to minimize head movements. Sleep state was determined by observing behavioral cues (eye movements, muscle tone, and breathing patterns).

EEG recording

EEG was recorded with Ag/AgCl electrodes attached to the scalp at the F3, Fz, F4, C3, Cz, C4, P3, Pz and P4 locations according to the International 10-20 System. The common reference electrode was placed on the tip of the nose and the ground electrode on the forehead. Eye movements were monitored by measuring the voltage between an electrode placed lateral to the outer canthus of left eye and Fp1. EEG was recorded with 24 bit resolution at a sampling rate of 1000 Hz by a direct-coupled amplifier (V-Amp, Brain Products, Munich, Germany). The signals were on-line filtered with a low-pass filter with 110 Hz high cutoff frequency.

Data Analysis

EEG was filtered off-line between 1 and 30 Hz. For each stimulus, an epoch of 600 ms duration including a 100 ms pre-stimulus interval was extracted from the continuous EEG record. Epochs with a voltage change exceeding 100 μV on any EEG or EOG channel were rejected from further analysis. The remaining epochs were baseline-corrected by the average voltage in the 100 ms pre-stimulus period and averaged separately for each stimulus type. All 26 infants had more than 50% artefact free trials for all stimulus types. The mean number of artifact-free trials per infant was 129 (89-146, SD=13.64) for the deviant, 1151 (833-1295, SD=122.77) for the standard, and 130 (95-148, SD=14.57) for the deviant-control tone. Infants were in the quiet sleep state for 75%, in active sleep for 18%, and awake in 7% of the total recording time. In accordance with the procedure employed by comparable studies (e.g. Carral et al., 2005; Stefanics et al., 2007), responses were pooled across sleep states for the analyses (see Kushnerenko et al., 2013 for a review of the possible effects of sleep state on MMR). Response amplitudes were measured from 150-250 ms and 350-450 ms time windows (selected on the basis of visual inspection of the grand-average waveforms and the previous literature on pitch-deviance MMN in newborn infants e.g. Kushnerenko et al. 2007; Čeponienė et al. 2002) from the frontal and central electrode line (F3, Fz, F4, C3, Cz and C4).
Deviant effects were analyzed with three-way repeated-measures analyses of variance, separately for the deviant-minus-standard ("Classical") and the deviant-minus-deviant-control ("Refractoriness-controlled") derivations of MMN (ANOVA; Classical MMN derivation:

Stimulus [Deviant vs. Standard] × Frontality [Frontal vs. Central] × Laterality [Left vs. Midline vs. Right]; Refractoriness-controlled MMN derivation: Stimulus [Deviant vs. Deviant-control] × Frontality [Frontal vs. Central] × Laterality [Left vs. Midline vs. Right]). Greenhouse–Geisser correction was used where appropriate. Post hoc Tukey HSD tests were employed to further specify the results.
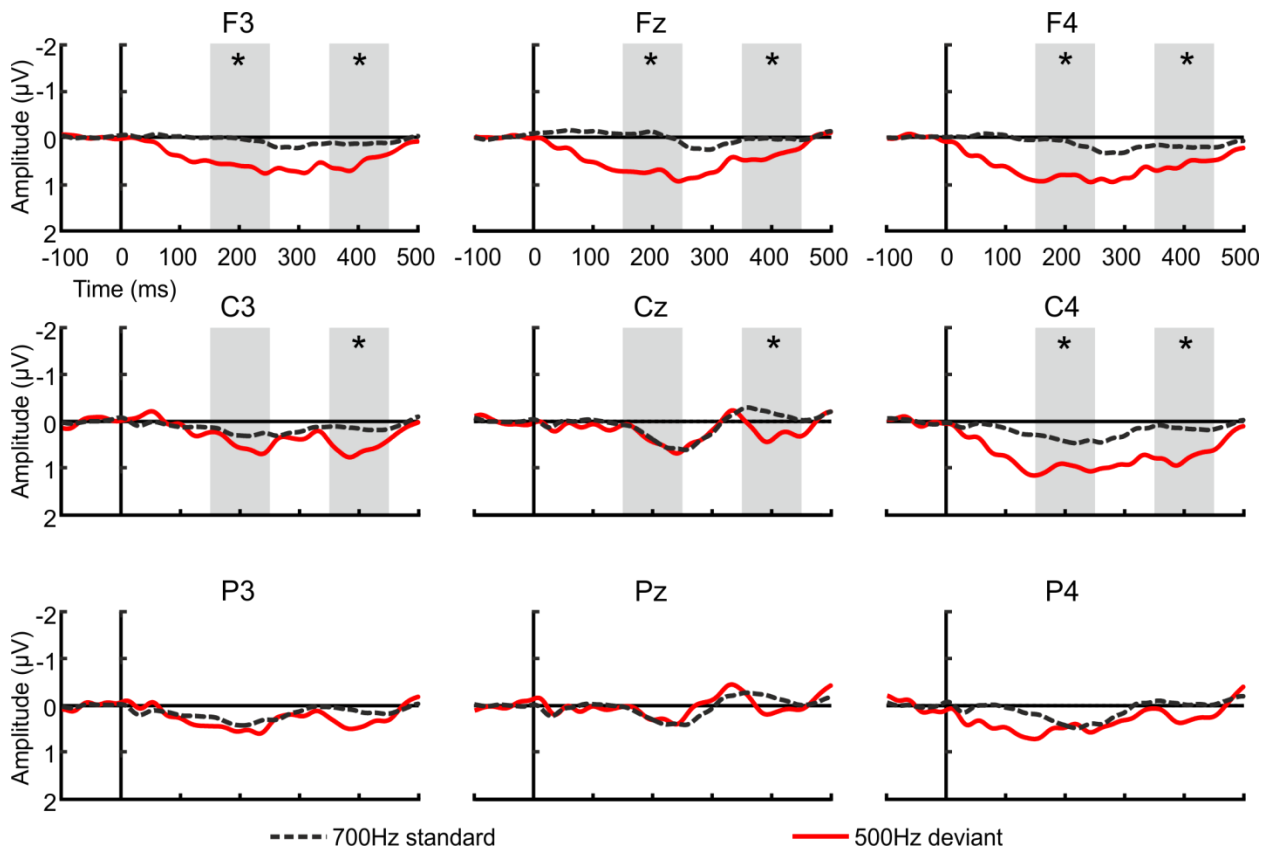
Results

Figure 1: **Group average ERP responses with the classical MMN derivation**: deviant (red continuous line) and standard tones (black dashed lines). Gray bars show measurement window (150-250 ms and 351-450 ms; F and C line); asterisks above the measurement windows mark the electrodes with significant difference (p<.05) between the standard and the deviant response amplitude.
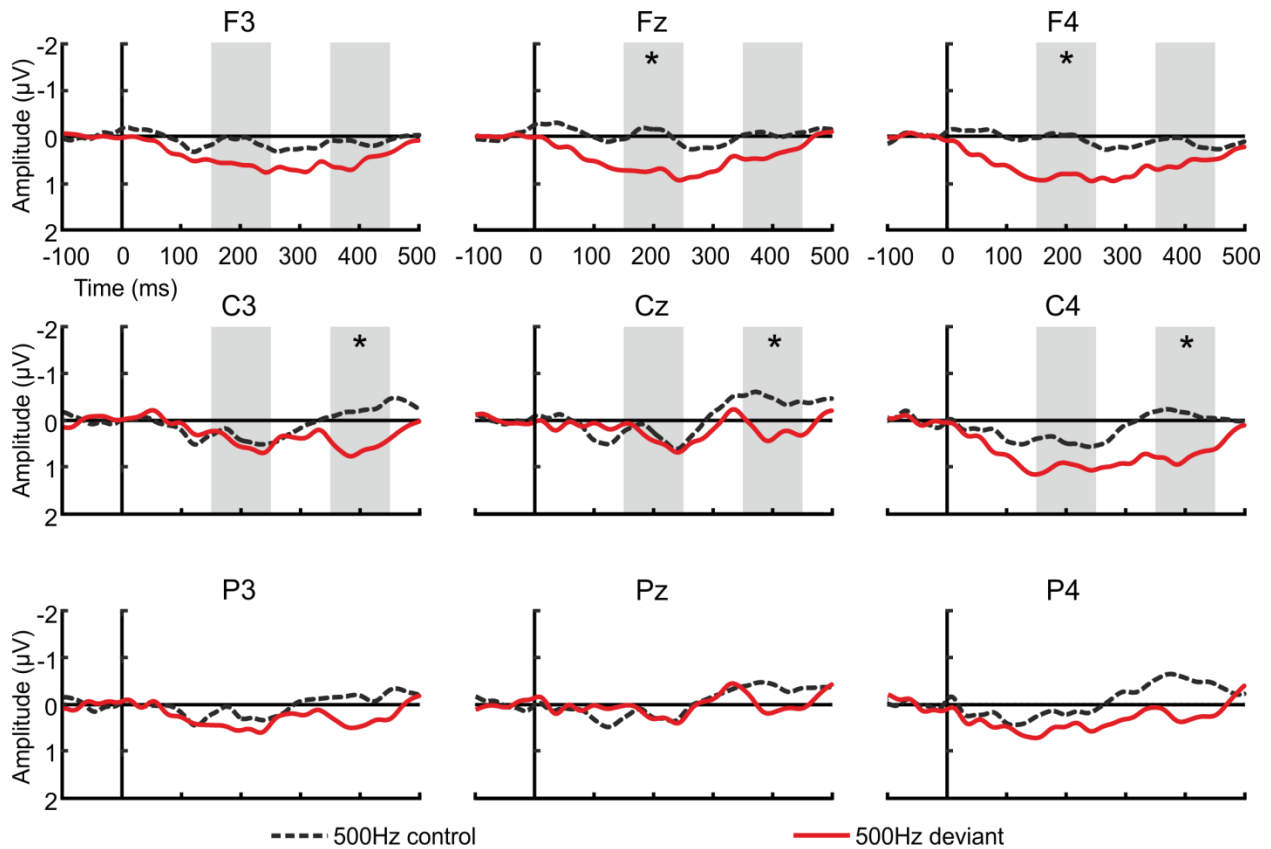
Figure 2: **Group average ERP responses with refractoriness-controlled derivation**: deviant (red continuous line) and deviant-control tones (black dashed lines). Gray bars show measurement window (150-250 ms and 351-450 ms; F and C line) ; asterisks above the measurement windows mark the electrodes with significant difference (p<.05) between the standard and the deviant response amplitude.
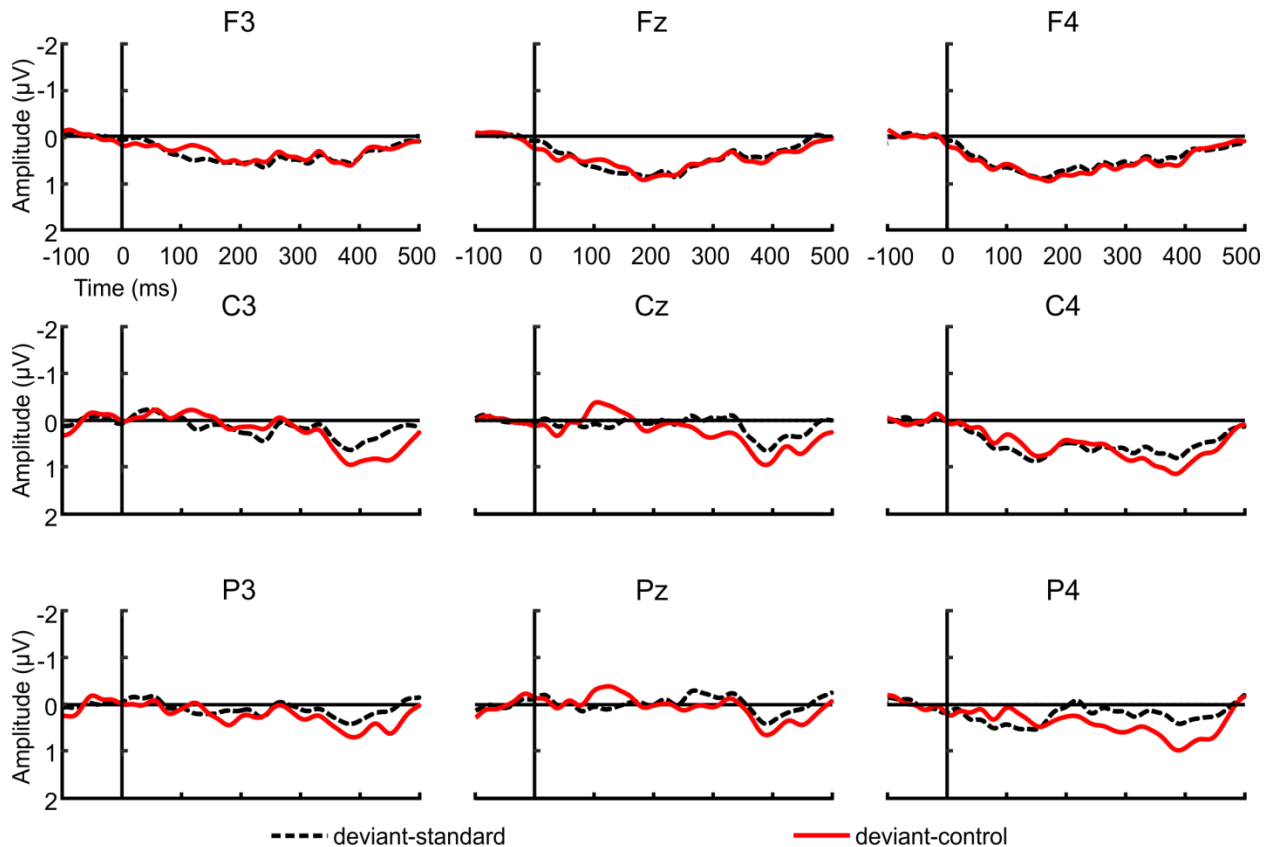
Figure 3: **Group average ERP response differences:** deviant-minus–-standard (black dashed lines) and deviant-minus-control difference waveforms (red continuous line).

All tones elicited a positive ERP response on the frontal channels peaking between 200 and 300 ms from stimulus onset. The ERP to the deviant showed a slow positive deflection commencing early (<100 ms) and terminating by ca. 500 ms post-stimulus. Of the central electrodes, only the C4 showed a similar positive deflection. Additionally, a distinct late positivity is apparent peaking at ca. 400 ms post-stimulus over the central electrodes (see Figures 1, 2, and 3).

In the 150-250 ms time window, the ANOVA for the Classical derivation yielded a significant main effect of Laterality (F(2,50)=4.02, p:<0.05, ε=0.65, η_p^2=0.14) and an interaction between Stimulus and Frontality (F(1,25)=5.66, p<0.05, η_p^2=0.18). The laterality effect was due generally larger positive response to deviants over the right side, appearing also on central and to some degree over parietal sites as opposed to the more focused frontal distribution on the left side. The interaction was due to the frontal responses to deviant stimuli being more positive than the responses to standards recorded at both frontal and central electrodes (df=25; p<0.001, all) and the central responses to deviant stimuli being more positive than the responses to standards at frontal electrodes (df=25, p<0.05). That is, the frontal and central differences were more pronounced than the parietal ones. In the same time window, the ANOVA for the Refractoriness-controlled derivation yielded an interaction between Stimulus and Frontality (F(1,25)=5.99, p<0.05, η_p^2=0.19). The interaction was due to frontal responses to deviant stimuli being more

positive than that to controls at both frontal and central electrodes (df=25; p<0.001 and p<0.01, respectively).

In the 350-450 ms time window, the ANOVA for the Classical derivation yielded a significant main effect of Stimulus ($F(1,25)=5.40$, $p<0.05$, $\eta_p^2=0.18$) and a significant three-way interaction between Stimulus, Frontality, and Laterality ($F(2,50)=5.99$, $p<0.02$, $\varepsilon=0.74$, $\eta_p^2=0.19$). The interaction was due to responses to deviant stimuli over lateral frontal, midline central, and left midline electrodes being more positive than responses to standards at most electrodes (df=50, $p<0.05$, at least). In the same time window, the ANOVA for the Refractoriness-controlled derivation yielded a main effect of Stimulus ($F(1,25)=5.35$, $p<0.05$, $\eta_p^2=0.18$).

Discussion

The goal of this study was to test whether or not the differential response observed in neonates for rare deviant sounds amongst frequent standard ones can be fully accounted for by differential refractoriness of the neuronal populations responding to the two stimuli, separately. To this end, infants were presented with an oddball and a control stimulus block, the latter containing the same tone with the same probability as the deviant appearing in the oddball sequence. The responses elicited by deviants were all positive in polarity and more pronounced on the right side in the early time window. The significant difference found between the responses elicited by the deviant and the deviant-control tones demonstrated that the response elicited by the deviant in the odd-ball sequences cannot be fully explained by the frequency-specific refractoriness. That is, the classical estimate of the MMR response likely includes contribution from a process detecting regularity violations (i.e., a "genuine MMR"; Jacobsen & Schröger, 2001; Näätänen et al., 2007; Schröger & Wolff, 1996). An alternative, but compatible description of this result is that neonates processed the current sounds in a context-dependent manner. Háden et al. (2013) arrived at a similar conclusion by comparing the responses in neonates elicited by the same sound when presented alone and within the context of a frequently presented sound (in the odd-ball paradigm), while controlling for the temporal schedule of the sound presentation. Together, the two sets of results strongly suggest that, similarly to adults, neonates process sounds in context. In the current case, deviants in the oddball paradigm evoke processes that relate the rare deviant sound to the frequent standard sound. This conclusion strengthens the link between the neonate MMR and the adult MMN.

A possible critique of the results could be that the lateral inhibition between neighboring frequencies could be stronger in the odd-ball as compared to the control condition. Indeed this is the critique put forward by May and Tiitinen (2010) regarding the control paradigm used in the current study. This issue has since been addressed in adults by the even more stringent cascadic control sequence paradigm (Ruhnau et al., 2012). The results were similar to Jacobsen et al.'s (2003), showing that the deviant response within the oddball sequences cannot be fully explained by differential refractoriness. Unfortunately, the limited duration of the experimental session in newborns prevented us from employing the cascadic control design. However, basing on the

results of the current as well as our previous study (Háden et al., 2013), one may predict with some confidence that using the cascadic control in neonates would confirm the current conclusions. The "genuine MMR" interpretation also receives support from studies where infants showed MMR responses to violations of abstract rules, such as deviance in the direction (Carral et al., 2005) and size (Stefanics et al., 2009) of pitch steps with the absolute pitch level being varied, feature conjunctions (Ruusuvirta et al., 2004), and numerical regularities (Ruusuvirta et al., 2009). In these cases, refractory effects based on the repetition of simple features do not apply. However, 1) refractoriness for higher-order features cannot be ruled out and 2) these results do not tell whether the difference responses obtained in stimulus sequences repeating primary auditory features also includes a genuine MMR contribution.

The marked morphological differences between the adult MMN and the infant MMR makes one ask as to what degree the two responses represent similar processes. Kushnerenko and colleagues (2007) suggested that the neonatal MMR consists of three different responses: an early negativity, which is only elicited by large spectral deviations, a wide positivity, which is elicited by most deviations, but responds also to stimulus intensity *per se*, and a late negativity, which may perhaps reflect categorical deviations. The maturation of the ERP responses to acoustic deviation and novelty has been discussed by Kushnerenko and colleagues (2013). It appears likely that each of these responses capture some aspect of deviance detection, albeit none of them is a pure index of it. It is also possible that the different MMR responses in infants represent different deviance detection processes, which are less easily separable in adults (but see some recent advances in adults for early (pre-MMN) ERP responses to deviance: Grimm & Escera 2012; Bendixen, San Miguel & Schröger, 2012). Further, some later processes become separated from the MMR during the first year of life (see Kushnerenko et al., 2013), such as a P3a-like response, which is associated by attentional switching or contextual evaluation in adults (Horváth et al., 2008; Polich, 2007). Due to the rapid developmental changes to infantile ERP responses to deviance, it is possible that the observed MMR deflections reflect an amalgam of several infantile responses with different developmental trajectories.

In conclusion, although the relationship between the adult MMN and the infantile MMR response is not straightforward, the current results suggest that similarly to the adult MMN, the MMR response in neonates probably cannot be fully explained by differential neuronal refractoriness. Infants process sounds in relation to their auditory context.

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