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Mismatch response (MMR) in neonates: Beyond refractoriness

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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.

1. 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, Denham, & Nelken, 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, Kujala, & Winkler, 2011). Pitch-deviant stimuli presented to sleeping newborn infants also elicit a discriminative ERP component (Alho, Sainio, Sajaniem, Reinikainen, & Näätänen, 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, Gaillard, & Mäntysalo, 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

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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, Čeponiene, Balan, Fellman, & Näätänen, 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, Van den Bergh, & Winkler, 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 et al. (2002) and Kushnerenko et al. (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.

2. Materials and methods

2.1. 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 min, 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.

2.2. Stimuli and procedure

The experimental design was based on Jacobsen, Schröger, Horenkamp, and Winkler'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., Novitski, Huotilainen, Tervaniemi, Näätänen, & Fellman, 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 min. 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).