Maturation of the auditory change detection response in infants: a longitudinal ERP study

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Mismatch negativity (MMN) is a negative component of auditory event-related potential (ERP), reflecting the brain’s automatic change detection process. In the present study we investigated the development of the pitch change detection, as indexed by the MMN, in the same infants from birth until 12 months of age. The MMN was identified in ~75% of infants at each age, being relatively stable in latency and amplitude at the group level across the ages studied. However, within the same subjects the MMN substantially varied from age to age. The inspection of individual data revealed a possible source of this variability: in a portion of 3- to 9-month-old infants, a large-amplitude positive component commenced at the latency of the MMN and thus might have masked it. The results of the additional experiment, employing distracting novel sounds in 2-year-old infants and newborns, suggested that the observed positive component could represent an infant analogue of the adult P3a response, indexing an involuntary orienting of attention. Therefore, the variability from age to age might be, at least partially, caused by the differences in degree of infants’ orienting, resulting in the reduction of the scalp recorded mismatch negativity in recordings when the orienting P3a positivity was elicited. NeuroReport 13:1843–1848 © 2002 Lippincott Williams & Wilkins.

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INTRODUCTION

The accuracy of central auditory processing can be assessed as an ability to discriminate sounds and can be objectively examined by the negative component of the auditory event-related potential called mismatch negativity (MMN). The MMN is assumed to reflect the brain’s automatic change detection process [1]. It is elicited when a deviant in some aspect of a sound occurs infrequently in a sequence of repetitive homogenous (standard) stimuli [1]. Although the MMN is well established in adults [2] and school-age children [3], the information concerning the MMN maturation in infants during the first year of life is rather controversial. In the first MMN study in newborns, Alho et al. [4] found an MMN type of negativity in response to a change in sine-tone frequency. Further, an MMN type of negativity, peaking at 200–250 ms, was elicited by phoneme changes (/y/ vs /i/) in premature and full-term newborns and in 3-month-old infants [5]. Pang et al. [6] found an MMN to a syllable change from /da/ to /ta/ in 8-month-old infants.

In contrast, several other infant studies observed a positivity in response to deviant sounds. Leppänen et al. [7] found an MMN to pitch change of a sinusoidal tone in a half of the newborns, whereas a majority of them showed a positivity in response to the deviant stimuli at about 250–350 ms. Further, Pihko et al. [8] and Leppänen et al. [9] failed to obtain an MMN in 6-month-old infants with and without a family history of dyslexia in response to syllable change from /kaa/ to /ka/. The authors therefore proposed that, in infants, a response of positive polarity might be functionally comparable to the negative polarity MMN in adults. Supporting this view, only a positive response was found in 4- to 7-month-old infants studied by Alho et al. [10] in response to sine tone frequency change, and in 3-month-old infants studied by Dehaene-Lambertz and Dehaene [11] to /ba/ vs /ga/ change. However, in 6-month-old infants studied by Trainor et al. [12], an MMN elicited by an occasional silent gap was followed by a positive response at 250–350 ms. Alho et al. [10] and Trainor et al. [12] suggested that the positivity obtained in their studies might be an analogue of the adult P3a component, indexing an involuntary attention switch to the deviant sounds.

The P3a has been proposed to be an ERP correlate of the orienting response [13]. It is a frontocentrally maximal positivity at about 250–350 ms, usually elicited by attention-catching (including rare) stimuli and often accompanied by an autonomic skin response [13] or deterioration, due to distraction, of the behavioral task performance [14].

Thus, it might appear that the changes in the auditory environment that for adults can go unnoticed (resulting only in the MMN), in infants can trigger an involuntary orienting (resulting also in the P3a).

In the present, longitudinal, study we examined the maturation of auditory change detection response in the same infants from birth to 1 year of age at 3-month intervals.
We chose a paradigm employing pitch change in a harmonic tone, which elicited a reliable MMN in 81% of the newborns in our previous study [15]. The maturation of the auditory obligatory responses to the same stimuli during the first year of life has also been examined [16].

**MATERIALS AND METHODS**

The ERPs of 12 infants (all males) were recorded 2–4 days after birth and thereafter every 3 months until the age of 12 months. All infants were born at term (39–41 weeks, 3140–4040 g), passed hearing screening with evoked otoacoustic emissions (EOAE), and were considered healthy by a neonatologist. Of these 12 infants, six were also tested at 2 years of age, together with six additional newborns, in experiment 2 (see below). The families of the studied infants did not have a history of hearing, language, or reading pathology, and none of the infants in the present study suffered from a developmental delay during the follow-up period. The study protocol was approved by the Ethical Committees of the Department of Obstetrics and Gynecology and the Hospital for Children and Adolescents of the Helsinki University Central Hospital. Informed parental consent was obtained before recruitment.

In the frequency oddball condition of experiment 1, 100 ms three-partial harmonic tones (standard of 500 Hz fundamental frequency, deviant of 750 Hz fundamental frequency, p = 0.15) were presented with an 800 ms stimulus onset asynchrony (SOA, from onset to onset). In the control (equiprobable) condition, 100 ms harmonic tones of 500, 625 and 750 Hz fundamental frequencies were equiprobably presented. The 750 Hz fundamental frequency tone from the equiprobable condition will be referred to as the control tone.

In experiment 2, in addition to the frequency oddball condition, a condition with the deviants replaced by distracting novel sounds (the novel condition), such as clicks, chirps, simulation of bird vocalizations, vowels and syllables, was conducted. Such sounds typically elicit a P3a response in children [17] and adults [14] and, in children, a subsequent negativity termed the Nc [18].

The EEG was recorded (bandpass 0.1–30 Hz, sampling rate 250 Hz) using the NeuroScan 3.0 acquisition software. Disposable electrodes were attached to eight scalp sites: F3, F4, C3, C4, P3, P4, T3, and T4 according to the International 10-20 system. The electro-oculogram (EOG) electrodes were located vertically and horizontally to the eye. All electrodes were referenced to the right mastoid. The data were off-line re-referenced to the average of the left and right mastoids and filtered at 1.0–15 Hz.

The difference waves for MMN evaluation were obtained by subtracting the response to the control stimulus from that to the deviant stimulus. The control stimuli were used in order to minimize the differences in the refractoriness levels between the responses entering the subtraction (for a detailed description of the rationale, see [15]). The MMN was defined as the largest negative deflection in the difference waveform between 80 and 300 ms after stimulus onset, greater than the average baseline voltage by 1.0 μV at any two of the four fronto-central electrodes. The subsequent positive deflection was measured from 250 to 450 ms. In the latency range of 350–750 ms, two consecutive negative peaks were observed, which were measured as the negative maxima at 350–550 ms and 550–750 ms, corresponding.

The age and electrode effects were examined with three-way ANOVAs: age (5) × electrode site (frontal, central, temporal, and parietal) × hemisphere (left, right). The sources of the significant ANOVA effects were determined by using the LSD (least significant difference) post hoc test. Greenhouse–Geisser adjustments were performed (corrected p values are reported).

**RESULTS**

The group averages of the deviant and control tone responses, together with the deviant minus control ERP difference waves, are presented in Fig. 1. Despite the fact that, at the group level, the MMN amplitude tended to increase from birth to 12 months (Fig. 1), the age effect was not statistically significant. The electrode effect was significant (F(3,33) = 10.67; p < 0.0003), due to the MMN amplitude being smaller at the temporal electrode than at any other.

Inspection of the individual difference waves revealed that the MMN was not consistently elicited across the ages studied (Fig. 2). At birth, the MMN was revealed in 10 of 12 infants. However, among the 10 infants who had an MMN at birth, three had no MMN at 3 months (infants G, H, I), and three others (F, J, L) had no MMN at 6 months of age. In contrast, the two infants (D, E) who had no MMN at birth showed it at 3 and 6 months of age.

The positivity in the difference waves following the MMN at ~300 ms was observed in the majority of infants across all ages (Fig. 2). It predominated centrally and was the largest at the age of 6 months, when a transient diminution of the MMN was observed at the frontal and central electrodes. The main age effect on difference positivity amplitude was insignificant, presumably due to the high inter-individual variability. The electrode effect was significant (F(3,33) = 5.54; p < 0.006) due to the smaller amplitude at the parietal electrodes than at any other. Late negativity was observed in the latency range 350–750 ms. Visual inspection of the individual curves revealed evidence for more than one peak in this latency window, therefore two consecutive time windows were selected: 350–550 ms for the early phase and 550–750 ms for the late phase. The main age effect for the early phase of the late negativity was significant (F(4,44) = 2.67; p < 0.05), due to its amplitude being larger at 9 months than at any younger age. The electrode effect for the early phase was significant (F(3,33) = 27.20; p < 0.0001) due to its amplitude being smaller at the temporal electrode than at any other.

The age effect on the later phase was insignificant. The electrode effect was significant (F(3,33) = 8.90; p < 0.0005), with the later phase amplitude being larger over the frontal and central than temporal and parietal areas.

Figure 3 presents the difference waves of six children of 2 years of age and of six newborns, obtained in experiment 2. At the age of 2 years, the novel sounds elicited a large amplitude clearly identifiable fronto-central P3a, peaking at ~300 ms, and a late negativity, peaking at ~700 ms. The same response pattern was seen in the newborns. A 3-way ANOVA (age × condition × electrode) revealed no age effect for the P3a and late negativity amplitudes or latencies.
Fig. 1. Grand average ERPs obtained in response to 100 ms 750 Hz deviant tone (dashed line) and the identical control tone (thin line), together with the deviant minus control difference waves (thick line) at birth (2–4 days) and at 3, 6, 9, and 12 months of age in the same infants ($n = 12$). MMN, mismatch negativity; DP, difference positivity; LNe, early phase of the late negativity; LNI, late phase of the late negativity.
Fig. 2. The individual difference waves at the C4 electrode of 12 infants at birth and at 3 and 6 months of age. Infants A, B, and C had a replicable MMN at birth and at 3 and 6 months of age. Infants D and E had no MMN at birth, but showed one at 3 and 6 months of age. Infants G, H, and I had an MMN at birth but did not have it at 3 months. Infants F, J, and L had no MMN at 6 months of age. MMN, mismatch negativity; DP, difference positivity; LNe, early phase of the late negativity; LNl, late phase of the late negativity.
elicted by the novel sounds. However, the P3a and the later phase of the subsequent negativity were significantly larger in amplitude in the novel than in the frequency oddball condition \( (F(1,10)=16.15, p<0.003; F(1,10)=6.97, p<0.03, \text{respectively}) \), whereas no condition effect was observed for change, release from refractoriness, or both. In the present study, the difference in the refractoriness levels between the responses entering the subtraction was minimized (see methods); therefore, the difference positivity appears to be related to the change detection rather than to the activation of new sensory elements. A similar positivity (P3a), elicited by novel sounds remained strikingly similar in latency (300–360 ms) and in centrally predominant scalp topography throughout the age range 4–44 years [18].

Experiment 2, employing distracting novel sounds, was carried out in an additional group of newborns in order to test the hypothesis that the P3a might have been elicited in the infants of the present study. Six of 12 longitudinally studied infants also participated in experiment 2 at the age of 2 years. As expected, the positivity in response to novel sounds was significantly larger in amplitude than that elicited by the frequency deviants. None the less, the latency of this positivity remained the same regardless of the eliciting stimulus. This is in agreement with the earlier findings that the P3a amplitude increases as a function of the magnitude of stimulus change [19] and supports the notion that the analogue of the adult P3a might be elicited starting from newborn age. In addition, the response to novel sounds in 2-year-old seems to have the second phase, largest frontally, just like the P3a in school-age children [17]. As can be seen from Fig. 3, the P3a in 2-year-old children emerges at the same latency as the MMN in response to the deviant stimuli. It might be suggested, therefore, that the large amplitude P3a masked the MMN in response to novel sounds.

Therefore, it appears that in the longitudinally studied infants, the relatively large frequency change caused involuntary orienting, resulting in an infant analogue of the adult P3a response. In part, this might account for the observed MMN variability across the ages and among the individuals, since the P3a amplitude depends on many factors, such as individual differences in arousal [20] and distractibility [21], which vary widely not only from subject to subject, but also with age. In addition, the auditory sensitivity matures throughout infancy [22] and therefore varies from infant to infant as well. Thus, the same degree of auditory change might go unnoticed for some infants, whereas in others it might be sufficient to cause orienting and result in the P3a.

Indeed, it is highly unlikely that those infants who showed MMN at birth did not generate it later in life. It is also unlikely that infants were unable to detect this frequency change, since previous behavioural studies showed that 5- to 8-month-old infants discriminate frequency changes as small as 2% [23]. Thus, it seems that at age 3 months and over, the MMN, recorded at the scalp, could be obscured due to the increasing overlap by the P3a component.

The nature of the late negativity following the positivity at 350–750 ms remains poorly understood. A second fronto-central negativity following the MMN at about 450–550 ms (called late discriminative negativity; LDN) was consistently reported in school-age children (for review see [24]). The late frontal negativity, commencing at ~600 ms, has also been reported in newborns [25] and 2- to 3-month-old infants [11,26].

In the individual difference waves of the present study, at least two negative phases were observed in the latency

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**Fig. 3.** The difference waveforms of six children of 2 years of age and of six newborns from the novel stimulus (dashed line) and frequency deviant conditions (solid line), experiment 2. MMN, mismatch negativity; DP, difference positivity; LNe, early phase of the late negativity; LNI, late phase of the late negativity.
range 350–750 ms. They exhibited different scalp distributions and maturational trajectories. The early phase peaked at about 350–450 ms, had the same scalp distribution as the MMN, and increased in amplitude during the first year of life. The later phase commenced at about 550 ms and in some infants probably continued beyond the window of the analysis epoch. The later phase was most often observed at the frontal electrodes and was anterior in scalp distribution to the early one. These findings suggest that, in infants, the late multi-phase negativity might represent several different processes.

The late negativity elicited by the novel sounds also consisted of two phases (Fig. 3). While its early peak (at about 400–500 ms) was similar in amplitude in the deviant and novel stimulus responses, the late peak (at about 600–700 ms) was significantly larger in response to the novel than to the deviant stimuli. Similarly, two phases of the late frontal negativity in response to the novel sounds were reported in adults by Escera et al. [27], with only the later phase being larger in response to the novel than to the deviant stimuli.

CONCLUSION

The auditory change detection response in infants, as indexed by the MMN component of the event-related potential, was analyzed longitudinally during the first year of life. At the group level, the MMN was relatively stable in latency and amplitude across the ages studied. On average, the MMN was elicited in 75% of infants at each age, however, a substantial MMN variability from age to age within the same individuals was observed. This variability might, at least partially, result from the reduction of the scalp-recorded mismatch negativity due to its latency overlap with the large amplitude P3a positivity, if the brain’s orienting networks were activated. Experiment 2, employing novel sounds, provided further evidence that the positivity observed in infant ERP might represent an infant analogue of the adult P3a. The closing component of the positivity observed in infant ERP might represent an infant response to an auditory stimulus change in preterm and full-term infants. In: Brunia CHM, Gaillard AWK and Kok A, eds. Psychophysiological Brain Research. Tilburg: Tilburg University Press; 1990, pp. 139–142.


