Maturation of the cortical auditory event-related brain potentials in infancy

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To my family

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ABSTRACT

Although brain development continues well into adolescence, the most rapid and impressive improvements in motor, cognitive, and perceptual abilities take place during the first and second years of life. The progress of the neuroimaging techniques provided the neuroanatomical data, showing that the most rapid postnatal neuroanatomical development also occurs in the first two years of age, followed by much more gradual changes. A link between the rapidly emerging psychological and behavioral functions and the underlying neural mechanisms might be provided by the electrical activity generated by neurons within the functioning brain. The electrical signals related to some external or internal event (event-related potentials, ERPs) provide real time indices of neural information processing, and can be followed throughout this crucial period of the most rapid neuroanatomical and functional development.

Addressing the issue of ERP maturation during infancy is not just of academic interest, but might also have wide clinical applications. To this end, it is very important to study the normal course of ERP maturation in the same infants in a fine-graded manner, in order to obtain a normative database.

The present studies therefore aimed at investigating 1) the age-related obligatory ERP changes during the first 12 months of age; 2) the infantile ERP correlates of stimulus features (pitch, duration); 3) the maturation of the central processing of stimulus change from birth to 12 months of age.

The results indicated, first, that all ERP peaks observable at the age of 12 months and later in childhood (the P150, N250, P350, and N450) could be identified as early as at birth.

The second major finding was that the infant's ERP was significantly affected by the duration of auditory stimuli at the latency zone of the N250. The pattern of the duration-

related changes observed in newborn infants was very similar to that in adults, suggesting the similarity of the underlying processes.

Third, the majority of infants already at birth possess neural mechanisms for sound frequency and duration discrimination, as was indexed by the mismatch negativity potential (MMN), reflecting the brain's automatic change-detection process.

Fourth, the positive difference component (250-350 ms) was observed, which partly overlapped the MMN and substantially varied in the same infants from age to age. The results suggested that this positive difference component might be an infant analogue of the early phase of the adult P3a component, indexing the involuntary orienting of attention to novel and distracting stimuli.

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February, 2003 Elena Kushnerenko

Supervisors: MD, PhD, R. Čeponienė, & Academy Professor R. Näätänen
Clinical supervisor: MD, PhD, V. Fellman, Associate Professor in Neonatology

List of original publications

This thesis is based on the following publications. The studies are referred to in the text by the Roman numerals I-V.

Study I.
Cheour, M., Kushnerenko, E., Čeponienė, R., Fellman, V., & Näätänen, R. (2002). Electric brain responses obtained from newborn infants to changes in duration in complex harmonic tones. *Developmental Neuropshychology*, 22, 471-479.

Study II.
Čeponienė, R., Kushnerenko, E., Fellman, V., Renlund, M., Suominen, K., & Näätänen, R. (2002). Event-related potential features indexing central auditory discrimination by newborns. *Brain Res Cogn Brain Res*, 13, 101-113.

Study III.
Kushnerenko, E., Čeponienė, R., Fellman, V., Huotilainen, M., & Winkler, I. (2001). Event-related potential correlates of sound duration: Similar pattern from birth to adulthood. *NeuroReport*, 12, 3777-3781.

Study IV.
Kushnerenko, E., Čeponienė, R., Balan, P., Fellman, V., Huotilainen, M., & Näätänen, R. (2002). Maturation of the auditory event-related potentials during the 1st year of life. *NeuroReport*, 13, 47-51.

Study V.
Kushnerenko, E., Čeponienė, R., Balan, P., Fellman, V., & Näätänen, R. (2002). Maturation of the auditory change-detection response in infants: A longitudinal ERP study. *NeuroReport*, 13, 1843-1848.

Abbreviations

AEP	auditory evoked potential
ABR	auditory brainstem response
AS	active (REM) sleep
AW	awake infant state
CNS	central nervous system
CV	consonant-vowel (syllable)
EEG	electroencephalogram
ERP	event-related potential
FF	fundamental frequency
ISI	interstimulus interval
LLAEP	long-latency auditory evoked potential
LDN	late discriminative negativity
LN	late negativity
MEG	magnetoencephalogram
MLR	middle-latency response
MMN	mismatch negativity
Nc	negative component
NSW	negative slow wave
OAE	otoacoustic emissions
OPP	observer-based psychoacoustic procedure
QS	quiet (non-REM) sleep
REM	rapid eye movements
RON	reorienting negativity
RT	reaction time
SCR	skin conductance response
SNR	signal-to-noise ratio
SOA	stimulus onset asynchrony
SP	sustained potential

Contents:

1. Introduction

Since it was discovered that human infants are able to discriminate auditory information even in utero (DeCasper and Fifer, 1980; DeCasper and Spencer, 1986) and that the electrical brain responses reflect this discrimination (Alho et al., 1990a; Kurtzberg et al., 1986), increased attention has been devoted to the infants' auditory cortical event-related potentials (ERPs) as tools to study auditory processing and discrimination. The auditory system is mature enough to function by the time of birth (Chugani and Phelps, 1986; Chugani et al., 1987; Tucci, 1996), and auditory information may enter the brain not only in the absence of attention but even in sleep. Very recently, it has been reported (Cheour et al., 2002) that newborn infants are able to learn while they are asleep. This demonstrates the importance of infant's sleep - the dominant state in neonates: they spend about 20 hours per day in sleep and still they learn and develop extremely fast. Interestingly, in neonates the electroencephalographic (EEG) patterns of active sleep often cannot be differentiated from those of the awake state (De Weerd, 1995). Further, the newborns' auditory ERPs recorded during active sleep or awake state also do not differ in waveform structure from each other (Cheour et al., 2000; Ellingson et al., 1974; Kurtzberg et al., 1984; Novak et al., 1989). This renders the recording of the auditory ERP extremely useful, as it allows one to obtain information on brain functioning even in sleeping neonates, i.e. without either requiring an active response or annoying the infant.

1.1. Neuroanatomical development of the auditory system

The human auditory system starts functioning by the 6^{th} month of gestation when the auditory mechanisms are ready to respond to a sound. By the gestational age of 30 weeks, the middle ear, cochlear, auditory nerve, and neural pathways of the brainstem are mature enough to function (for a review, see Tucci, 1996).

The subcortical structures of the auditory pathway can be clearly identified by the time of term birth and resemble their adult forms (for a review, see Johnson, 2001). The major developmental processes that occur after birth are mostly related to the maturation of the cerebral cortex. Although the chief landmarks (sulci and gyri) of the cerebral cortex are present at birth, the cortex remains relatively immature in terms of its intra- and

interregional connectivity (Johnson, 2001). The changes in brain organization continue into adolescence, though, the major changes occur during the first year of life and most of them are accomplished by the end of the second year.

Cortical development during the first year of life is characterized by an increase in synaptic density, number of synapses per neuron, and dendritic growth (Huttenlocher, 1979). At around the time of birth, there is a rapid increase in synaptogenesis in all cortical regions, resulting in more than a double increase in synaptic density (overproduction) during infancy, followed by a gradual decline (pruning) to the mature adult levels at puberty (Huttenlocher, 1979; 1984; 1990). This maturational time course closely parallels that of the cerebral energy metabolism, as measured with positron emission tomography (Chugani et al., 1987). In general, the cerebral metabolic rate for glucose rapidly rises during infancy, remains high during childhood, and decreases during adolescence (Chugani et al., 1987).

The sequence of cortical synaptogenesis appears to parallel the maturation of cortical functions: in the human primary auditory cortex (Heschl's gyrus), the synaptic density reaches its maximum at about 3 postnatal months, in the visual cortex at 8 months, and in the association area of the frontal cortex only by two years of age (Huttenlocher, 1984; Huttenlocher and Dabholkar, 1997). These structural developments are paralleled by the functional maturation: the auditory function is one of the earliest to emerge, whereas the higher cognitive functions (communicating, planning, understanding pictures (Berg, 1996)) start to appear at about 8-9 months of age. The changes in glucose utilization also follow this sequence: in neonates it is highest in the auditory and somatosensory cortices, during the second postnatal month it progressively increases over all of the cortex (Chugani and Phelps, 1986; Chugani et al., 1987), and only by approximately 8 months of age, the glucose metabolism increases in frontal and other association cortices, subserving higher cortical functions.

The same pattern of developmental changes is seen for myelogenesis: the sensorimotor regions exhibit the earliest myelinogenesis, whereas the association areas of the frontal, parietal, and temporal cortices are the last to myelinate (Vaughan and Kurtzberg, 1992). The neuroimaging techniques provided evidence that the white matter of the frontal, parietal, and occipital lobes becomes apparent by 8-12 months of age (Paus et al., 2001).

It should be noted that the extent of myelination does not directly index the functional status of the cortical networks (Vaughan and Kurtzberg, 1992) since the systems function well before each completes the myelination (Courchesne, 1990).

Myelination indeed greatly increases the speed of neural conduction (from 2 to 50 m/s (Casaer, 1993)). However, the relation of the degree of myelination to the conduction velocity is not so straightforward. The analysis of the axonal conduction time and the synaptic delay by means of auditory brainstem responses (ABR), [1] combined with the morphometric techniques, revealed that both axonal conduction and synaptic transmission are responsible for the speed of the transmission of the neural signals (Moore et al., 1996; Ponton et al., 1996). The results showed that the axonal conduction time is adult-like by 40 weeks conceptional age, which is in good agreement with the fact that the auditory nerve and brainstem auditory pathways are well myelinated by the time of term birth (Perazzo et al., 1992; Tucci, 1996; Volpe, 1995; Yakovlev and Lecours, 1967). The time required for the impulse to cross the synaptic junctions continues to shorten until about 3 years of age, however.

Since scalp-recorded evoked potentials mainly represent cortical synaptic activity, the maturational changes in synaptic density and efficacy might be the major neural substrates underlying the maturation of cortical ERPs.

1.2. Functional development of the auditory system

The fact that the auditory system is well developed by the third trimester of gestation indicates that a fetus is capable of sound perception even in the uterus. Yet the auditory stimuli reaching the fetus in the uterus are restricted to low-pitched sounds (Rubel, 1985; Gerhardt and Abrams, 1996; Sohmer and Freeman 2001). This might explain why newborns have lower auditory thresholds for low than high frequencies (Table 1) (Werner and Gillenwater, 1990), despite the fact that the development of the organ of Corti starts from the basal end where high frequencies are represented (Tucci, 1996).

[1] Auditory brainstem response (ABR) consists of six waves occurring within 15 ms after stimulation and representing the compound action potential generated along the eighth nerve (waves I and II) and the following activation of the cohlear nuclei, superior olivary complex, nuclei of the lateral lemniscus and inferior colliculus (waves III-VI) (Tucci, 1996).

Table 1. Summary of studies on the maturation of auditory sensitivity during infancy

Age	Behavioral studies	Physiological responses
Term birth	Auditory thresholds 40-50 dB higher than in adults for pure tones of 500, 1000, and 4000 Hz, with the largest difference at high frequencies (Werner and Gillenwater, 1990) (Observer-based Psychoacoustic Procedure, OPP[2]). No evidence for newborns discriminating 1000 vs. 2000 Hz frequency contrasts (Leventhal and Lipsitt, 1964; Trehub, 1973) (head turning).	Auditory thresholds 10-15 dB higher than in adults (Werner, 1996) (Otoacoustic emissions, OAE[3]; Auditory brainstem responses, ABR). Adult-like hearing thresholds in the majority of newborns for all frequencies tested (500-4000Hz) (Savio et al., 2001) (auditory steady-state response[4]). Near-term fetuses detect the pitch difference between two piano notes of fundamental frequencies 292 and 518 Hz (Lecanuet et al., 2000) (cardiac orienting). Differentiate novel speech patterns from those played during the last trimester of pregnancy (DeCasper and Spencer, 1986); differentiate mother's voice from that of other woman (DeCasper and Fifer, 1980) (sucking rate).
1-3 months	Auditory thresholds 15-30 dB higher than in adults (Olsho et al., 1988); the largest difference at high frequencies (OPP). Gap detection threshold about 70 ms (OPP) (Werner et al., 1992).	Discriminate 200-Hz tone versus 500-Hz tone (sucking rate) (Wormith et al., 1975). Discriminate duration differences of 15-55 ms in syllables and complex tones (sucking rate) (Eimas et al., 1971; Jusczyk et al., 1983; Jusczyk et al., 1980). Adult-like low-frequency tuning curves[5]

[2] Observer-based Psychoacoustic Procedure (OPP) utilizes an observer, who is unaware of a presence or absence of a signal, to determine from the infants' behavior if a stimulus has been delivered.

[3] Otoacoustic emissions (OAE) measured in the external ear canal describe responses that the cochlea generates in the form of acoustic energy. Sounds are emitted and can be detected by suitably sensitive microphones placed in the external ear. Stimulated OAE are evoked by impulsive sounds (clicks or tone pips) (Buser and Imbert, 1992; Kemp, 1978).

[4] Steady-state responses are evoked potentials that maintain a stable frequency content over time (Picton et al., 2002). The responses evoked by tones that have been amplitude modulated at rates between 75 and 110 Hz show great promise for objective audiometry, because they can track hearing thresholds, can be readily recorded in infants (Lins et al., 1996; Rickards et al., 1994) and are unaffected by sleep.

[5] Tuning curve shows liminal intensity determined at each sound frequency with the minimal liminal intensity at a frequency referred to as optimal, preferred or characteristic, above and below which the excitation threshold is increased (Buser and Imbert, 1992)

		(Folsom and Wynne, 1987) (ABR).
6–12 months	Absolute auditory thresholds 10-15 dB higher than those of adults, the difference greater at lower frequencies (Olsho et al., 1988) (OPP) (high-frequency sensitivity develops faster) (Berg, 1993; Berg, 1991; Olsho et al., 1988; Olsho et al., 1982; Trehub et al., 1980) Detect a frequency deviation of 2-3 % of a 1000 Hz tone (Olsho et al., 1987; Olsho et al., 1982) (OPP). Gap detection threshold about 70 ms (OPP) (Werner et al., 1992). 50 % of 12-month-old infants have adult-like gap detection thresholds (5-10 ms, OPP) (Werner et al., 1992).	Adult-like low-frequency and high-frequency tuning curves (Abdala and Folsom, 1995; Werner, 1996), (ABR) Adult-like hearing thresholds in the majority of infants for all frequencies tested (500-4000Hz) (Savio et al., 2001) (auditory steady-state response)

However, soon after birth, the sensitivity to the high-frequency sounds develops faster than that to low-frequency sounds (Berg, 1991, 1993; Olsho et al., 1982, 1988; Trehub et al., 1980), and the adult-like frequency sensitivity for the 500-4000 Hz tones is achieved by the 6th postnatal month (Abdala and Folsom, 1995; Werner, 1996).

he results of the behavioral studies (briefly summarized in Table 1) are somewhat at odds with the tuning curves and auditory thresholds obtained by means of auditory brainstem responses (ABR) and evoked otoacoustic emissions (OAE) (Kemp, 1978; Kemp and Ryan, 1991). That is, behavioral studies indicate that the auditory thresholds in newborns are 40-50 dB higher than those in adults (Werner and Gillenwater, 1990). However, as estimated by using OAE and ABR, the auditory thresholds were only 10-15 dB higher than those in adults (Werner, 1996). In the study of Savio et al. (Savio et al., 2001) even adult-like auditory thresholds were reported in the majority of newborns at all frequencies tested (500-4000 Hz). This pattern of results, with the objective measures indicating rather mature auditory abilities in newborns whereas behavioral measures indicate deeply immature skills, implies that a functionally mature auditory system co-exists with immature listening strategies (e.g., attention; Werner, 1996). Thus, the fact that the ability to detect sounds improves well into childhood might be, at least in part, related to the maturation of *listening* rather than to that of *hearing*.

So far, behavioral research on the ability to detect changes in the auditory environment in the first months of life has focused on orienting rather than sensory sound discrimination. Orienting to sounds depends on factors such as attention, motivation, or experience. Furthermore, the infant's response has most commonly been measured by using head turning and changes in cardiac and sucking rates. Although behavioral methods have the advantage of being more meaningful, they are very difficult to use with infants younger than 5 months of age (Benasich and Tallal, 1996; Gravel, 1989). The behavioral responses such as head turning are limited by the infant's inability to perform coordinated motor acts in the first weeks after birth, and physiological responses such as the cardiac rate or the sucking rhythm are contingent on the infant's state.

That is why, probably, some negative behavioral results were obtained in the youngest groups studied. Leventhal and Lipsitt (1964) and Trehub (1973) found no evidence for newborns discriminating 100 vs. 200 Hz, 200 vs. 500 Hz, or even 1000 vs. 2000 Hz frequency contrasts. However, when acoustically rich complex sounds such as synthetic

vowels (Clarkson and Berg, 1983) or piano notes (Lecanuet et al., 2000) were used as stimuli, newborns and even near-term fetuses responded to change by a decreasing cardiac rate.

1.3. Electrophysiological indices of auditory development

Electrophysiological responses to sound can be non-invasively, objectively, and precisely measured by using auditory evoked potentials (AEP). Electrophysiological measures, such as auditory brainstem response (ABR), are widely used to assess neonatal auditory sensitivity and to detect abnormalities of peripheral and subcortical portions of the auditory pathways. However, ABR does not provide information on cortical auditory processing.

The clinical usefulness of middle-latency response (MLR), following ABR at latencies of 10 to 50 ms, has been suggested to be limited, since the reliability of MLR is low in the first 5 years of life (Kraus et al., 1985). Long-latency auditory ERPs, following MLR, are thought to reflect responses central to the brainstem. Long-latency ERPs are more variable and are elicited less reliably near threshold than ABR. However, they offer a unique opportunity to evaluate higher-order cortical auditory processes (Stapells and Kurtzberg, 1991). Stapells and Kurtzberg (1991) found that auditory evoked potentials in a child with higher cortical dysfunction showed normal ABR and MLR results, whereas long-latency ERPs were absent. Thus, testing by the ABR or MLR alone would have missed this child's cortical dysfunction. Further, Kurtzberg and colleagues (Kurtzberg et al., 1984; 1988) and Molfese and colleagues (Molfese, 2000; Molfese and Molfese, 1997) studied infants who were at risk for language disorders and found on follow-up that those children with abnormal cortical ERPs in the neonatal period had deficiencies in language processing skills. Molfese and Molfese concluded that cortical ERPs might be meaningful predictors of further cognitive development in infants.

However, in order to be able to use ERPs widely in clinics, normative data on healthy infants' ERPs should be collected and sampled at very short time intervals, since, during infancy, cortical ERPs change qualitatively and very fast. Yet, few studies investigated the maturation of the long-latency auditory ERPs during infancy (summarized in Table 2) and even fewer studies followed ERP development in the same infants (longitudinal studies).

Long-latency auditory ERPs are usually divided into two categories: exogenous and endogenous. Exogenous (or sensory, or obligatory) components can be elicited by any

auditory stimulus (e.g. train of repetitive identical stimuli - 'standards') and represent brain response to the occurrence of the stimulus. Exogenous components typically occur within the first 100-200 ms after stimulus onset and are, to a limited extent, sensitive to the physical features of the stimulus, such as intensity, frequency, rate of stimulus presentation (Näätänen, 1992). Endogenous components mainly reflect internally generated mental events related to the cognitive assessment of the stimulus.

2. Exogenous (obligatory) auditory ERPs

2.1. Obligatory auditory ERPs in adults and school-age children

In adults, long-latency ERP deflections start with a small P1 (or P50) deflection that peaks at about 50 ms. Intracerebral recordings in humans indicate that a major source of neural activity contributing to the P1 peak originates from the lateral portion of Heschl's gyrus, i.e. the secondary auditory cortex (Liegeois-Chauvel et al., 1994).

The P1 is followed by a usually larger N1 response, peaking at about 100 ms. This peak is a sum of at least three sub-components (Näätänen and Picton, 1987): 1) the supratemporal N1 (N1b), largest fronto-centrally, originating bilaterally in the superior temporal cortex, including primary auditory cortex; 2) the non-specific N1, maximal over vertex, generated in the modality non-specific brain areas (Näätänen and Picton, 1987), partly in frontal lobe (Alcaini et al., 1994); and 3) the T–complex (Wolpaw and Penry, 1975), largest at temporal electrodes, consisting of a smaller positivity at about 100 ms and a larger negativity at about 150 ms.

In adults, the elicitation of the N1 response by threshold-level auditory stimuli correlates with behavioral sound detection (Parasuraman et al., 1982; Squires et al., 1975), and its amplitude increases with the increase of sound intensity/loudness (Picton et al., 1974, 1977). The N1 obtained in response to rare sounds is much greater in amplitude than that obtained in response to frequent sounds (Näätänen and Picton, 1987; Hari et al., 1982).

The supratemporal N1 does not represent the first volley of the afferent activity into the primary auditory cortex. Rather, it appears to reflect auditory cortical activation resulting from intra- and/or inter-hemispheric activity (Mäkelä and Hari, 1992; Mäkelä and McEvoy, 1996). This might be the reason why it is not readily obtained in children before 9 years of age (Ponton et al., 2000), because cortico-cortical connections continue to mature well into

adolescence (Courchesne, 1990 ; Vaughan and Kurtzberg, 1992; Yakovlev and Lecours, 1967). The finding that the N1 can be elicited from the age of 3 years, but only with a slow stimulation rate (Paetau et al., 1995; Sharma et al., 1997) suggests longer refractory periods of N1 generators in children, which could also be attributed to immaturity of cortico-cortical connections (Webb et al., 2001).

The N1 is followed by a P2 component peaking at approximately 180-200 ms from stimulus onset (Näätänen, 1992; Ponton et al., 2000). The source of the P2 has been located by magnetoencephalography (MEG) to the superior temporal gyri anterior to the source of the supratemporal N1 (Hari et al., 1987). In addition, some results indicate that the P2 at least partially reflects auditory driven output of the mesencephalic reticular activating system (RAS) (Knight et al., 1980; Rif et al., 1991).

The P2 peak is often followed by a negativity, labeled N2 (Picton et al., 1974). This peak has an adult latency of 220-270 ms (Ponton et al., 2000) and was suggested to be generated in the vicinity of the supratemporal planes, possibly including frontal activity (Ceponiene et al., 2002a, Gomot et al., 2000). The N2 elicited by frequent repetitive stimuli ('basic' N2; Näätänen and Picton, 1986) was reported mostly in children (Ceponiene et al., 1998; Enoki et al., 1993; Karhu et al., 1997; Korpilahti and Lang, 1994), but it was also shown in adults (Ceponiene et al., 2001; Karhu et al., 1997; Picton et al., 1974; Ponton et al., 2000), but with a smaller amplitude (Ponton et al., 2000; Ceponiene et al., 2001), and, in some reports, longer latency (Ponton et al., 2000).

In children, the N2 amplitude changes as a function of stimulus content: it was larger in response to complex rather than simple tones (Ceponiene et al., 2001) and to low rather than high-pitched tones (Korpilahti et al., in prep). Unlike the N1, children's N2 is largely insensitive to stimulus rate (Ceponiene et al., 1998; 2001). In language-impaired (Tonnquist-Uhlen, 1996b), and dysphasic children (Korpilahti and Lang, 1994), the N2 was smaller in amplitude and longer in latency than in their healthy peers.

Sustained potential (SP; Picton et al., 1978) also seems to belong to the category of obligatory, sensory-specific components. It is a long-latency negative shift continuing throughout the duration of a long-lasting auditory stimulus (Picton et al., 1978). It originates from the primary auditory cortex (Hari et al., 1987) and may commence as early as in the N1 latency zone (Scherg et al., 1989). Contrary to N1, the sustained potential has quite a short refractory period, showing a fast recovery from the previous stimulus (Picton et al., 1978). It

can be recorded even during sleep (Picton et al., 1978).

2.2. Maturation of obligatory auditory ERPs during infancy

In newborns and infants, auditory ERPs have no resemblance to adult ERP waveform. Most of the ERP studies in infants have reported a large positive deflection at midline electrodes, with a maximum at about 300 ms, followed by a negativity at about 600 ms (Barnet et al., 1975; Graziani et al., 1974; Ohlrich et al., 1978; Pasman et al., 1992; Rotteveel et al., 1987; Shucard et al., 1987).

The midline responses change from surface-negative to surface-positive during the pre-term and early post-term period (Barnet et al., 1975; Kurtzberg et al., 1984; Weitzman and Graziani, 1968). Kurtzberg et al. (1984) divided this maturational transition into 5 stages, characterized by the predominant polarity at the midline and temporal electrode sites. The majority of full-term healthy newborns show ERPs that correspond to the maturational level III as defined by Kurtzberg et al (1984), that is, with a predominantly positive component at the midline electrodes and a negative component at the temporal electrodes. The temporal response changes from surface-negative to surface-positive by 1 to 2 months post-term, thus displaying a maturational delay, compared with the response from the midline electrodes (Kurtzberg et al., 1984).

The differential maturational sequence of ERPs at the midline and temporal sites and the corresponding intracranial recordings in monkeys obtained by Steinschneider et al. (1980, 1982) led the authors to suggest different developmental courses of the underlying generators. Thus, responses recorded over the fronto-central scalp regions might be generated in the earlier maturing primary auditory cortex, whereas responses recorded from the scalp overlying the lateral surface of the temporal lobes were suggested by Kurtzberg et al. (1984) to be generated by the later maturing secondary auditory cortex.

The predominant positive deflection of infants' ERPs has most commonly been labeled as P2, and a later negative deflection at about 500-600 ms as N2. However, it should be noted that the labeling varies between laboratories and that infantile peaks do not correspond to adult peaks with the same names.

Midline P2-N2 ERP morphology seems to be typical to newborn infants, despite the differences in recording montage, stimuli, interstimulus interval, and waking state (for a review, see Thomas and Crow, 1994). The effect of state of arousal on an infant’s ERPs is a

question of debate. In some studies, infants were investigated during sleep (Barnet et al., 1975; Lenard et al., 1969; Ohlrich et al., 1978). Other studies investigated only awake infants (Shucard et al., 1987) and, in some other studies, infants were recorded both in awake state and in active sleep (Kurtzberg et al., 1984; Novak et al., 1989). In our laboratory (Fig. 1), as well as elsewhere (Ellingson et al., 1974; Kurtzberg et al., 1984; Novak et al., 1989), no significant differences in newborns' ERP waveforms were found between the awake state and active sleep.

Novak et al. (1989) followed the maturation of the auditory ERPs to speech stimuli (/da/ and /ta/ syllables) from birth to 6 months. The P2-N2 complex recorded at birth changed in morphology by the age of 3 months. The authors discerned two positive peaks in latency range of the infantile P2 (P1m and P2m) with different scalp predominance: the P1m was larger frontally than centrally, whereas the P2m was largest centrally. A discontinuity (negative trough) between these two positive peaks, at about 160-200 ms, was termed N1m by the authors. The N1m became prominent by the age of 6 months. During the first 6 months of life, the P1m and P2m increased in amplitude and gradually decreased in latency. Further, Kurtzberg et al. (1986) reported that between 6 and 9 months, the amplitude of the second major positive peak (P2m) markedly decreased, and that between 9 and 12 months, the amplitude of the preceding negativity (N1m) increased.

There are only a few studies on the development of auditory ERPs during infancy, and the results were only partially replicated. However, studies that used simple acoustic stimuli such as clicks (Barnet et al., 1975; Ohlrich and Barnet, 1972) and pure tones (Shucard et al., 1987) showed a number of similarities, when compared with ERPs elicited by speech stimuli, reported by Novak et al (1989) and Kurtzberg et al. (1986). At newborn age (below 1 month), ERP morphology was predominated by the P2-N2 configuration, with a few subjects showing the earlier P1 (60-80 ms) and a negative-going discontinuity (N1) between the P1 and P2. In addition, in sleeping infants (Barnet et al., 1975), a later positive peak at about 600 ms was observed, being most prominent by the age of 6 months. However, in awake 6-month-old infants, this late positive component was not reported (Novak et al., 1989).

Most studies on ERP maturation during infancy found increasing of peak amplitudes and shortening of peak latencies (for a review, see Thomas and Crow, 1994). Peak amplitudes, however, did not increase linearly. The amplitude of the P2 showed an inverted-U function, with a maximum at 3 months in Barnet et al's (1975) study and at 6 months in Vaughan and

Kurtzberg's (1992) study.

Latencies of ERP peaks generally decreased during infancy, however, not in all studies. In a cross-sectional study, Shucard et al. (1987) reported a non-significant latency increase from 1 to 3 months of age.

There is a lack of fine-grade longitudinal studies in infants following the development of the auditory ERP waveform until it attains the childhood morphology. Some authors (Rotteveel et al., 1987; Thomas and Crow, 1994) suggested that the ERPs of 3-month-old infants have a morphology similar to that in adults. However, the adult P50-N100-P200 is not readily identifiable in infants and children before about 10 years of age (Courchesne, 1990). In children, the auditory ERP consists of the P100, N250, and N450 peaks (Čeponienė et al., 1998, 2001; Korpilahti and Lang, 1994; Ponton et al., 2000; Sharma et al., 1997) when sounds are presented with ISIs shorter than 1 second. Only with longer ISIs, can an adult-like N1 wave be recorded in children in addition to the N250 peak (Čeponienė et al., 1998; Karhu et al., 1997). The correspondence between child and infant ERPs has not yet been established.

In our Study IV we monitored infants' ERP maturation until children's waveform morphology was attained. We employed spectrally rich, though acoustically not too complex stimuli (harmonic tones), composed of 3 partials. Previously, it was shown that human newborns react more frequently and strongly to complex tones, especially with low-frequency fundamentals (Hutt et al., 1968), and that the ERP amplitude in response to a complex tone was larger than in response to a simple tone (Lenard et al., 1969). In children and adults, acoustic complexity also resulted in increased ERP amplitudes (complex tones versus sine tones; Čeponienė et al., 2001a; Woods and Elmasian, 1986). Another reason for us to choose harmonic tones was that harmonic partials facilitate pitch discrimination in humans (Tervaniemi et al., 2000; Čeponienė et al., 2001b), and in our longitudinal Study V we also aimed at investigating the maturation of change-detection response in the same infants.

3. Endogenous discriminative components

In addition to obligatory (exogenous) ERP components, endogenous components can be elicited in the so-called oddball paradigm in response to infrequent stimuli ('deviants') randomly inserted in a train of repetitive identical stimuli ('standards').

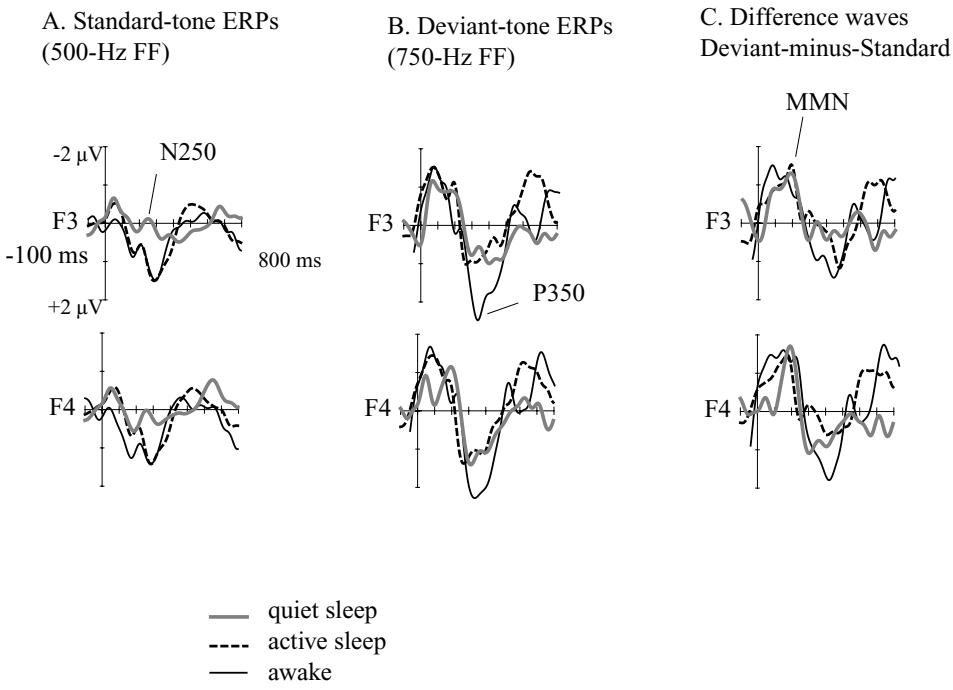

Figure 1. The effect of sleep on the newborns' obligatory and discriminative ERP components. Three groups of newborn infants, in active, quiet sleep, or awake during the recording in the Frequency oddball condition (Study II, unpublished results). Significant differences were revealed only at frontal electrodes: (A) the latency of the N250 elicited by the standard tone was significantly longer in quiet sleep than in both active sleep and awake ($F(2, 24)= 3.41$, $p<.05$), and (B) the amplitude of the P350 elicited by the deviant tone was significantly larger in awake state than in quiet sleep $F(2,24)=3.5$, $p<.05$) and tended to be larger in awake state than in active sleep ($p=0.8$).

The endogenous components, occurring after 100-200 ms from stimulus onset, reflect the processing not only of physical stimulus features, but also, depending on the paradigm and task, can index several stimulus-related cognitive processes.

As discussed above, with behavioral methods, such as head turning, it is difficult to separate attentional abilities, motivational factors and motor skills from perceptual abilities.

Among the endogenous components elicited in the oddball paradigm are the mismatch negativity (MMN), the P3a, and the late difference negativity (LDN), which are passively elicited, automatic discriminative brain responses and thus more accurate in the assessment of central auditory processing than behavioral methods.

3.1. The mismatch negativity (MMN)

The mismatch negativity (MMN, adult latency between 100 and 250 ms from change onset) was isolated from the N2 wave in an oddball paradigm by Näätänen et al. (1978). The MMN is generated by a neural mismatch process between a deviant sensory input and the neural representation, or 'sensory memory trace', formed by the repetitive standard sound. This suggestion is supported by results showing that infrequently presented stimuli against a silent background do not elicit an MMN (Cowan et al., 1993; Lounasmaa et al., 1989; Näätänen et al., 1989; Sams et al., 1985a).

The MMN is commonly derived by subtracting the ERP to the standard stimulus from that to the deviant stimulus. In adults, the MMN is maximal over the fronto-central scalp and has its major generator sources bilaterally in the auditory cortices, as indicated by the MEG studies (Huotilainen et al., 1993; Picton et al., 2000a; Tiitinen et al., 1993), electric source modelling (Scherg et al., 1989), and intracranial recordings in humans (Kropotov et al., 1995, 2000). This supratemporal MMN source was modeled as separate from, and anterior to, that of the N1 (Hari et al., 1984; Huotilainen et al., 1993).

This auditory-cortex activity reflects, presumably, an automatic pre-perceptual change-detection process, comparing the new auditory input with information stored in auditory sensory memory (Näätänen, 1992). In addition to the auditory-cortex generator, the frontal MMN generator was located in the right frontal lobe (Giard et al., 1990; Näätänen, 1992; Rinne et al., 2000), resulting in a frontal MMN subcomponent. The frontal MMN generator probably subserves involuntary call for attention to stimulus change and thus provides a link between the preattentive detection of change and subsequent attentional processes (Näätänen, 1990, 1992).

In addition, the auditory cortex MMN generator might consist of more than one source. It was originally assumed that the supratemporal dipole source results in polarity reversal of MMN below the level of the superior temporal plane at the mastoid electrodes. However, recent data (Baldeweg et al., 1999a, 2002) showed differential modulation of MMN over the

frontal and the corresponding positive phase over the sub-temporal scalp, thus assuming the contribution of additional generators.

The MMN is well-established in both adults (for a review, see Näätänen and Alho, 1995, 1997; Näätänen and Winkler, 1999) and children (Cheour et al., 2000, 2001). It can be recorded in response to any perceptually discriminable stimulus change (i.e., frequency, intensity, duration, spatial location; Näätänen, 1992) and can be used as a tool to investigate the accuracy of central auditory perception and discrimination. This notion is based on the evidence that the MMN elicitation correlates with the behavioral discrimination thresholds (Lang et al., 1990; Sams et al., 1985b). Moreover, the MMN can be obtained to barely discriminable differences in sounds (Kraus et al., 1993b), and the improved discrimination of difficult sound contrasts with training (Cheour et al., 2002; Näätänen et al., 1993) is paralleled by an increase in the MMN amplitude. The more accurate behavioral discrimination of acoustically rich sounds (harmonic tones) than of simple sinusoidal tones was also accompanied by an increased MMN amplitude and shorter latency (Tervaniemi et al., 2000). On the other hand, impaired ability to discriminate speech sounds in children with developmental language-related disorders and learning problems (Korpilahti and Lang, 1994; Kraus et al., 1996; Leppänen and Lyytinen, 1997) and impaired tone frequency discrimination in dyslexic adults (Baldeweg et al., 1999b) was associated with diminished magnitude of the MMN.

An important feature of the MMN elicitation is its independence from conscious awareness. The MMN can be elicited when the subject's attention is directed away from auditory stimulation (Näätänen, 1992), during REM sleep in adults (Nordby et al., 1996; Paavilainen et al., 1987) and in sleeping infants, regardless of sleep stage (Alho and Cheour, 1997; Alho et al., 1990a; Cheour et al., 1998, 2000; Cheour-Luhtanen et al., 1995; Leppänen et al., 1997). Moreover, no significant differences in the MMN amplitude were found in waking or sleeping newborns (Cheour et al., 2000), which renders this response especially convenient for studying infants.

3.2. Maturation of the MMN in infants

Most of the child MMN studies postulate that the MMN is developmentally a rather stable response in terms of its latency and amplitude (Csépe, 1995; Kraus et al., 1992, 1993a; for a recent review, see Cheour et al., 2000). However, some studies reported a slight MMN peak

latency decrease during the school-age years (Korpilahti and Lang, 1994; Kurtzberg et al., 1995; Shafer et al., 2000), and an amplitude decrease from childhood to adulthood (Csépe, 1995; Kraus et al., 1992, 1993a; Shafer et al., 2000). The information concerning the MMN maturation in infants during the first year of life is even more controversial.

In newborns, the MMN type of negativity was obtained to frequency change in simple tones (Alho et al., 1990a; Čeponienė et al., 2000; Cheour et al., 1999; Kurtzberg et al., 1995; Leppänen et al., 1997; Tanaka et al., 2001), to duration change in complex speech patterns (Kushnerenko et al., 2001), and to vowel change (Cheour et al., 2002; Cheour-Luhtanen et al., 1995). In older infants, the MMN was also obtained to vowel change (3 months-olds; Cheour et al., 1997; 6- and 12-months-olds; Cheour, 1998), to occasional silent gaps in tones (6-months-olds; Trainor et al., 2001), and to a consonant-vowel syllable change (8-month-olds; Pang et al., 1998; see also Table 3).

As in adults, in infants, the MMN was largest fronto-centrally (Alho and Cheour, 1997). However, in Pang et al.'s study (1998) it was largest temporally on the left and, further, a prominent MMN was also obtained over parietal areas (Cheour et al., 1998; Leppänen et al., 1997). The neonates' MMN responses differed from those of adults, by also being more spread in time, lasting sometimes even over 400 ms. In addition, a substantial MMN amplitude and latency variability across subjects (see e.g., Cheour et al., 1998) and across studies must be noted. Most puzzling, in some studies, at certain ages within the first year of life, no MMN was found (Alho et al., 1990b; Dehaene-Lambertz and Dehaene, 1994; Morr et al., 2002; Pihko et al., 1999). Instead, the deviant-stimulus ERP was positively displaced relative to the standard-ERP (e.g., Alho et al., 1990b; Dehaene-Lambertz, 2000; Dehaene-Lambertz and Baillet, 1998; Dehaene-Lambertz and Dehaene, 1994; Kurtzberg et al., 1984; Pihko et al., 1999).

An MMN-like negativity in sleeping newborn infants was first recorded by Alho et al. (1990a) who used a change in sine-tone frequency (1000 Hz vs. 1200 Hz). A control condition with the deviant tone presented alone without intervening standards was also recorded. Infrequent tones alone elicited a brief frontal negativity at about 220 ms, followed by a central positivity. The response to the deviant in the oddball condition exhibited a fronto-centrally largest negativity, lasting from 100 to 400 ms. However, under the same stimulus conditions, the authors did not obtain an MMN-like negativity in two groups of awake 4-7-month-old infants (pre-term and full-term; Alho et al., 1990b). In them, the

response to the deviant stimulus consisted of a positivity, peaking at 250-300 ms, with a pre-term group exhibiting larger positive amplitudes than did the full-term group.

In contrast, the results obtained by Cheour-Luhtanen et al. (1995) using relatively small changes in the Finnish vowels /y/ and /i/ showed a reliable MMN in a group of sleeping fullterm newborns, awake 3 month-old infants (Cheour et al., 1997), as well as in a group of pre-term infants (30-34 weeks conceptional age; Cheour-Luhtanen et al., 1996). However, the authors used acoustically rich stimuli – phonemes, which might explain the higher incidence of the MMN elicitation in their study (see also Tervaniemi et al., 2000).

The MMN amplitude, as estimated from the studies of Cheour et al. (1997, 1998a), seems to be smaller in infants than in school-age children and adults, increasing rapidly from birth to 3 months of age. The MMN latency was non-significantly longer in newborns (273 ms) than in 3-month-olds (229 ms; Cheour et al., 1998a). However, examination of the figures of another study in which vowel discrimination was also used (Cheour et al, 1998b) showed that in older infants (6- and 12-months old), the MMN peak latency was about 400 ms, which is much longer than that in newborns.

In another study (Leppänen et al., 1997) utilizing sine-tone frequency change (1000 Hz vs. 1100 Hz and 1300 Hz), a small negative deflection at a latency range of 225-255 ms was reported in only 50% of newborns, whereas almost all newborns showed a positive deflection in response to the deviant stimulus at about 250-350 ms. Subsequently, Leppänen et al. (1999) investigated the discrimination of duration changes in a vowel in consonant-vowel (CV) syllables (kaa vs. ka), and obtained negative MMN-like response neither in newborns, nor in 6-month-old infants (see also Pihko et al., 1999). The authors therefore proposed that in infants, a response of positive polarity might be functionally comparable to the MMN in adults.

Another research group (Kurtzberg et al., 1995) investigating the MMN in infants and children reported the MMN greater than 0.75 μV in amplitude only in 57% of newborns (or any sign of negativity in 75% of them) in response to the easily discriminable 1000 Hz and 1200 Hz tones. In cases where the MMN was present, its mean latency was 241 ms. The two ISI conditions (750 ms and 1000 ms) used in that study did not differ from one another in the percentage of identifiable MMNs. Using the same frequency contrast, Morr et al. (2002) failed to obtain an MMN in slightly older, 2-month-old infants, as well as in the majority of older infants and children (up to 4 years of age). Instead, a greater positivity from 150 to 300

ms was observed in response to the deviant stimulus as compared with the standard stimulus in infants younger than 12 months. However, when a larger frequency contrast was used (1000 Hz vs. 2000 Hz), the MMN-like negativity was observed in all age groups from 2 to 44 months (Morr et al., 2002). The authors suggested that neural mechanisms underlying the MMN are still immature by 3 years of age and did not rule out the possibility that the negativity observed in response to the larger frequency contrast might include a contribution of an obligatory component indexing recovery from refractoriness.

In our Study V, we attempted to follow changes of the MMN component in the same infants from birth to 1 year of age, while controlling for any possible contribution of non-refractory sensory elements to the deviant-stimulus response.

3.3. The P3a

The P3a component (250-350 ms) of the auditory ERPs, a frontocentrally maximal positivity, elicited by attention-catching, including rare, stimuli and often accompanied by an autonomic skin conductance response (Knight, 1996) was proposed by Squires et al. (1975) to be a central electrophysiological marker of the orienting response (see also Sokolov et al., 2002).

The P3a has been distinguished from P300 (P3b) by a shorter peak latency, a different (fronto-central vs. centro-parietal) scalp topography and different elicitation conditions (Squires et al., 1975). While the P3b is elicited by relevant target stimuli under active task conditions, the P3a can be also elicited by infrequent deviant stimuli even in unattended situations.

The amplitude of the P3a increases as a function of magnitude of stimulus change (Yago et al., 2001). The so-called 'novel' sounds, such as mechanical or environmental noises, are often used to elicit the P3a. Such grossly deviating sounds typically elicit a large P3a response in children (Gumenyuk et al., 2001; Čeponienė et al., under revision) and adults (Escera et al., 2000). Findings showing prolonged behavioral reaction times (RT) after stimuli that elicit a P3a, strongly support the notion that the P3a reflects involuntary attention switch (in this case, resulting in distraction from the primary task; Escera et al., 2000; Woods, 1992).

Lesion studies and intracranial recordings document the bilateral activation of the prefrontal, cingulate, temporo-parietal, and hippocampal regions during novel-event processing

(Baudena et al., 1995; Halgren et al., 1995; Knight, 1984, 1996; Kropotov et al., 1995).

Two components of the P3a (early, eP3a, and late, lP3a) have been recently identified in adults (Escera et al., 1998) and children (Gumenyuk et al., 2001). The early P3a was insensitive to attentional manipulations and its amplitude was maximal at the vertex, strongly diminishing posteriorly and laterally. The source of the MEG counterpart of the early P3a was located in the vicinity of the supratemporal MMNm source (Alho et al., 1998).

The late P3a was, in contrast, enhanced by attention. In adults, it was maximal frontally and did not invert in polarity over the scalp. Thus, the early (auditory) P3a was suggested by Escera et al. (1998) to reflect a neural process other than attentional reorientation, such as violation of a multimodal representation of the external world (Yamaguchi and Knight, 1992). The late (frontal) P3a was in turn suggested by Escera et al. (1998) to index the actual attention switch.

As far as we know, there are only two studies on infant P300, those of McIsaac and Polich (1992) and Fushigami et al. (1995). Both studies reported much longer P300 latencies in infants than in adults: 513 ms in 1-year-old infants (Fushigami et al., 1995) and 600 ms in 6-10 month-old infants (McIsaac and Polich, 1992).

However, in several infant MMN studies, a positive component at the same latency as in adults (250-350 ms) was observed in 2- to 6- month-old infants in response to deviant stimuli (Alho et al., 1990b; Dehaene-Lambertz and Dehaene, 1994; Leppänen et al., 1997; Pihko et al., 1999; Trainor et al., 2001; see also 3.2). Some authors (Alho et al., 1990b; Trainor et al., 2001) have suggested that this positivity might represent the analogue of the adult P3a, indexing attention switch to deviant stimuli.

In order to further test this hypothesis, in our Study V, we conducted an additional experiment, in which 'novel' sounds, typically used to elicit P3a in children and adults (see, e.g., Escera et al., 2000; Gumenyuk et al., 2001) were used.

3.4. Late negativities in children and adults

A prolonged negativity following the MMN in the oddball condition, with an onset at the latency zone of the N2 (ca. 300 ms), was first reported by Näätänen et al. (1982). The authors proposed that this negativity might reflect the sensitization of an organism in preparation to detect possible subsequent changes in the auditory environment or, conversely, result from sensitization arising from detection of the initial stimulus itself. A frontal negativity, even

larger and later (at about 600-700 ms) than the one described above, has been observed in response to deviants markedly different from standards ('extremes') or to selectively attended stimuli (Näätänen et al., 1982).

On the basis of the elicitation conditions, two types of late negativity can be obtained: late negativity elicited in response to novel, attention-catching (Čeponienė et al., under revision; Courchesne, 1990) and/or distracting stimuli (Gumenyuk et al., 2001), and usually accompanied by the P3a indexing involuntary attention switch, and another one elicited in response to non-novel deviant in an unattended MMN paradigm, and thus, assumed to be unrelated to attention. Indeed, in a typical MMN paradigm, deviants are repeated hundreds of times during the experiment and their novelty certainly wears off (Čeponienė et al., 1998).

3.4.1. Late negativities elicited in attended conditions

The negative component (Nc), lasting from 300 to 1000 ms was considered by Courchesne (1978, 1990) to be a sign of enhanced auditory and visual attention, since it was elicited in response to surprising, interesting, or important stimuli. A similar negativity was found when subjects had to reorient their attention back to a task after distraction by novel environmental sounds (drill, hammer, etc.; Escera et al., 2001) or unexpected frequency changes in auditory stimuli (Schröger et al., 1998, 2000). This negativity was called the reorienting negativity (RON) by Schröger et al. (1998), who suggested that it reflects activation of the prefrontal cortex networks controlling the re-direction of attention. Schröger et al. (2000) reported that the RON was absent in a passive (ignore) condition. However, in this study the authors used rather small frequency deviations as compared with the 'extremes' in Näätänen et al. (1982). A negativity similar to RON lasting from 450 to 700 ms, was obtained by Gumenyuk et al. (2001) in two groups of children (7-10 years old and 11-13 years old) in response to distracting novel sounds. The MEG data suggested that the temporal-lobe sources contribute to this negativity. This late negativity was larger in amplitude in younger children than in older ones: the same maturational profile reported previously for the Nc (Courchesne, 1983). Being of comparable latency and scalp topography, the Nc and RON might, in fact, reflect similar processes. Interestingly, the maturational time course of the Nc (amplitude increase across infancy and early childhood, followed by a gradual decline through preadolescence) was noted by Courchesne (1990) to closely parallel synaptic density changes in the frontal cortex as reported by Huttenlocher et al. (1979), and metabolic activity changes with a

maximum between 2 and 6 years, as reported by Chugani et al. (1987). Thus, the Nc might reflect the development of the higher-order cognitive functions associated with the frontal cortex.

3.4.2. Late negativities elicited in unattended conditions

A second negativity following the MMN in a passive oddball paradigm and lasting up to 450-500 ms was observed only in a few adult studies (Alho et al., 1992, 1994; Escera et al., 2001; Trejo et al., 1995). In children, it has been reported much more consistently and has been termed the MM4 by Kraus et al. (1993a), the late MMN by Korpilahti et al. (1995, 1996, 2001), Uwer and von Suchodoletz (2000), and Kilpeläinen et al. (1999b), and the LDN (late difference negativity) by Čeponienė et al. (1998).

Korpilahti et al. (2001) reported that the second negativity (late MMN, peaking ca. 430 ms) was significantly larger in 4-7-year old children for words than for pseudowords, which led the authors to propose that this late MMN might reflect the detection of a change in word meaning. However, in several other studies (Čeponienė et al., 1998, 2002b; Cheour et al., submitted; Kilpeläinen et al., 1999b; Uwer and von Suchodoletz, 2000), the LDN (400-500 ms), corresponding to the late MMN of Korpilahti et al. (2001), was also obtained in response to changes in non-speech stimuli. Enhancement, in response to deviants, of children's obligatory N450 peak which in time coincides with the LDN, was noted by Čeponienė et al. (1998) as a possible contributor to the late difference-wave negativity. Nevertheless, the authors also suggested that the LDN might reflect further processing of the detected change, since the LDN in their study was similar to the MMN with regard to the elicitation conditions, the dependence on the ISI, and the right frontal predominance. Korpilahti et al. (1995) also reported that their early and late MMNs were similar in scalp distribution, and the amplitudes of these components significantly correlated with each other. In addition, in 4-year-olds, the LDN amplitude correlated with the magnitude of stimulus change (Cheour et al., submitted), that is, it exhibited MMN-like feature. Besides, Cheour et al. (submitted) also reported that the LDN is independent of the attentional load. However, in a recent study, Čeponienė et al. (2002b) showed that unlike the MMN, the LDN was not affected by acoustic stimulus complexity and 'speechness' nature, suggesting its weak sensitivity to stimulus features.

It appears, further, that both of these late negativities can be elicited at the same time. Out of

the two phases of the late frontal negativity, the earlier phase (450 ms) did not differ between responses to deviant and novel stimuli, whereas the later phase was significantly larger in response to novels (Escera et al., 2001). Different scalp distribution of the two phases of the late frontal negativity indicated that they might reflect activity of distinct neural populations (Escera et al., 2001). The early phase was suggested to correspond to 'sensitization negativity' (Alho et al., 1994; Näätänen et al., 1982), and the later phase to the reorienting negativity (RON) (Schröger and Wolff, 1998).

Similar to the two phases of adult auditory late frontal negativity (Escera et al., 2001), in the visual modality, Nelson and Collins (1991) found in 6-month-old infants only one negative deflection (400 ms) in response to infrequent familiar face (deviant), whereas in response to infrequent unfamiliar face (novel), the second, later, negative wave was evoked, which was therefore suggested by Nelson (1994) to be related to novelty detection.

Hence, it seems that both negativities might be elicited by the same deviating stimuli. Furthermore, since the Nc latency decreases with age from approximately 700 ms at 6 months to about 500 ms at 7 years of age (Courchesne, 1990), the Nc and LDN might get closer in latency with age and, thus, start to overlap. A recent study of Čeponienė et al (under revision) indeed demonstrated that the peak latency of the Nc elicited by novel stimuli and that of the LDN elicited by deviant stimuli in 9-13-year old children were very similar (at about 600 ms). The amplitude of the Nc, however, was twice as large as that of the LDN, which might be caused, as suggested by the authors, by the greater magnitude of change signified by novel than by deviant sounds, and, thus by the different amounts of attentional resources deployed. When the amplitudes of these two negativities were normalized, the authors found no significant differences between components.

3.5. Late negativity in infants

Several studies found an LDN-like negativity in infants. Kushnerenko et al. (2001) reported two negative difference waves in newborns (at 150 ms and at 350 ms) in response to a durational change in the fricative 's' within a bisyllabic pseudoword. The second negativity, one peaking at about 370 ms, was also reported in newborns and 6-month-old infants in response to a sine-tone frequency change (Čeponienė et al., 2000). Morr et al (2002), using similar sine-tone frequency contrasts, found a second peak at about 300 ms (resulting in a

double-peaked MMN) in 31-44 months infants. It seems contradictory that the latency of infant's LDN-like negativity (300-370 ms after change onset) is shorter than that of older children and adults (450-500 ms). Thus, it appears that infant late negativity might not be an analogue of children's LDN.

Another late negativity that has been reported in newborns and infants commenced at about 600-700 ms, that is, at the latency of the Nc (Courchesne, 1990). The Nc-like, frontally maximal negativity was found in newborn infants by Kurtzberg et al. (1986), but the stimulus contrast (consonant-vowel syllables /da/ vs. /ta/) was neither very surprising nor novel. In this study, high-risk infants were also assessed: out of 15 infants with abnormal cortical responses, none showed this discriminative Nc-like response to a rare stimulus. In another study, one with a clinical subgroup, Deregnier et al. (2000), obtained a similar negative slow wave (NSW) in response to a stranger's voice compared with the maternal voice in sleeping newborns. This negative slow wave was suggested by the authors to indicate detection of novel stimuli against a background of familiar stimuli. Furthermore, this negativity was attenuated in infants with an adverse fetal environment (diabetic mothers) and its amplitude significantly correlated with the 1-year Mental Developmental Index. A similar late frontal negativity, one commencing at 680 ms, was observed in awake 2-3-month-old infants in response to the /ba/ versus /ga/ contrast by Dehaene-Lambertz and Dehaene (1994).

Thus, it appears that Nc-like negativity is elicited in young infants not only in response to very surprising and attention-capturing stimuli, as in older children (Čeponienė, under revision), but also to non-novel speech-syllable contrasts (Dehaene-Lambertz and Dehaene, 1994; Kurtzberg et al., 1984). This might indicate a maturing capacity to respond only to the most attention-getting stimuli through infancy into childhood, as was suggested by Courchesne (1990). Thus, in our Study V, we aimed at investigating similarities and differences in the orienting process in newborn infants induced by deviant and novel stimuli.

Table 2. Summary of studies on the infant obligatory auditory ERP components

Study	Subjects	State	Stimuli	ISI	Developmental findings
(Lenard et al., 1969)	14 infants at 4-8 days	Sleep	Sine and complex tones, female voice	10-15 sec	The N2 amplitude larger to complex tone and female voice than to sine tone
(Barnet et al., 1975) cross-sectional	120 full-terms at 2 weeks to 30 months	Sleep	Clicks	2.5 sec	The P2-N2 complex is a response landmark in infants. With age, complexity and amplitude increase, latency decreases. P3 (700 ms) correlated with sleep stage.
(Ohlrich et al., 1978) longitudinal	16 infants from 2 weeks to 3 years	Sleep	Clicks	2.5 sec	Peak-to-peak amplitudes increased linearly and latencies decrease by 40 months.
(Kurtzberg et al., 1984) longitudinal	35 pre-terms, 17 terms: at term, 1, 2, and 3 mo	Either awake or in active sleep	Speech sounds /da/ /ta/ and simple tones	2.7 sec	Shift from negativity to positivity with midline electrodes preceding lateral ones and full-term infants preceding pre-terms
(Shucard et al., 1987) cross-sectional	12 full-terms, at 1, 3, 6 months	Awake	Sine tones	2-4 sec	Complexity and amplitude of the ERP increase; non-significant latency increase.
(Rotteveel et al., 1987) cross-sectional	65 pre-term infants at 25 to 52 weeks CA	Awake, but sleep was not always avoided	Clicks	2 sec	The latency of the early peaks decreases, adult-like waveform achieved by 3months.
(Novak et al., 1989) longitudinal	Full-terms: 32 at term, 18 at 1 mo, 14 at 2, 15 at 3, and 6 mo	Before 1 month either awake or in active sleep; older infants – awake	Speech sounds /da/ /ta/ and the corresponding formants	2.7 sec	By 3 months, ERP at all sites predominantly positive, P1 and N1 appear, and the latency decreases.
(Vaughan and Kurtzberg, 1992) longitudinal	11 full-terms: at term to 24 months	Not stated	Speech sounds /da/ /ta/	2.7 sec	ERP complexity increases, P2 amplitude maximum at 6 months, followed by a decrease.

(Pasman et al., 1999) cross-sectional	147 infants from 28 weeks to 14 years	Awake, but sleep was not always avoided	Clicks	2 sec	Disintegration of ERP at 36-41 weeks, from 40 weeks until 4-6 years the P2-N2 complex. A second disintegration at about 6 years, adult-like P60-N100-P170 by 6-10 years.

Table 3. Summary of studies on the infant discriminative auditory ERPs

Study	Subjects (n)	State	Stimulus contrast: standard-deviant	ISI (msec)	ERP components in response to deviant
(Kurtzberg et al., 1986)	Term newborns (14)	Not stated	/da/-/ta/	3000	In response to deviant stimuli, a frontally predominant negative component (Nc, 700ms), followed by a late positive component (1300ms).
(Alho et al., 1990a)	Term newborns (8)	QS	1000 –1200 Hz	570	Fronto-central MMN-like negativity at 270-300 ms
(Alho et al., 1990b)	4-7-mo-olds pre-term (7) and full-term (7) infants	AW	1000-1200 Hz	570	In response to deviant stimuli, a positivity at 250-300 ms which was larger in pre-term than in full-term infants.
(Dehaene-Lambertz and Dehaene, 1994)	2-3-mo-olds (16)	AW	/ba/-/ga/ /ga/-/ba/	311 (5 in sequence, 3100 between sequences)	Two positive peaks at 220 ms and 390 ms, decreasing in amplitude with repetition within a sequence. The positive peak at 390 ms showed recovery in response to the deviant stimulus, whereas that at 220 ms did not. A late frontal negativity (starting at 680 ms) in response to deviant stimulus.
(Kurtzberg et al., 1995)	Term newborns (25)	AW	1000-1200 Hz	I. 750 II. 1000	I. An MMN > 0.75 ìV (mean –2.0 ìV, 241 ms) in 57%; any sign of negativity in 75% of infants. II. An MMN (mean -2.2 ìV, 298 ms) with the same incidence as with the shorter ISI.
(Cheour-Luhtanen et al.,	Term newborns (12)	QS	I.vowels /y/-/i/	700	I. Frontally dominant MMN at 200-250 ms

1995)			II./y/- boundary vowel /y/i/		II. No MMN
(Cheour-Luhtanen et al., 1996)	Preterm newborns (11)	AW AS	I.vowels /y/-/i/ II./y/- boundary vowel /y/i/	700	I. (AW) MMN 300-400 ms (F4, P4) I. (AS) MMN 400-500ms (F3, F4) II. No MMN
(Cheour et al., 1997)	3-mo-olds (6)	AW	I.vowels /y/-/i/ II./y/- boundary vowel /y/i/	700	I. Centroparietal MMN at 200-250 ms II. A small MMN with the boundary vowel
(Leppänen et al., 1997)	Term newborns (28)	QS	1000-1100 Hz 1000-1300 Hz	425	MMN in 50% of newborns, in most newborns, a positivity in response to the deviant stimulus at 250-350 ms
(Pang et al., 1998)	8-mo-olds (15)	AW	/da/ - /ta/	600	Left hemisphere (C3, T3) MMN at 200-250 ms
(Cheour, 1998)	6-mo-olds (9) 12-mo-olds (9)	AW	Finnish and Estonian vowels	700	In 6-mo-olds larger MMN (400 ms) to an Estonian vowel (physically more deviant); in 12-mo-old Finnish infants, a smaller MMN to Estonian than to Finnish vowel, in 12-mo-old Estonian infants an equal MMN for both vowels.
(Cheour et al., 1999)	Term newborns (8)	AS	1000-1100 Hz	700	MMN at 400 ms
(Pihko et al., 1999) (control groups)	I. Term newborns (31) II. 6-mo-olds (23)	QS AW	/kaa/-/ka/	425	In both groups, responses to the deviant /ka/ were more positive than those to the standard /kaa/.
(Ceponiene et al., 2000) (control groups only)	Term newborns (12); 6-8-mo-olds (8)	AS, QS, AW	1000-1100 Hz	700	Two significant MMN peaks at about 200 and 400 ms in both age groups.
(Deregnier et al., 2000) (control groups only)	Term newborns (12)	AS	Word ‘baby’ 750 ms, alternating mother’s and stranger’s voice	3900-4900/ random	The P2 peak larger to the mother’s voice, whereas the subsequent negative slow wave (NSW) larger in response to the stranger’s voice. NSW correlated with the 1-year Mental Developmental Index.
(Kushnerenko et al., 2001)	Term newborns (36)	AS	I. /asa/-/assa/ II. /assa/-/asa/ III./asssa/-/asa/	310 (SOA 600-940)	MMN at 150 and 350 ms from change onset, largest in II.

(Trainor et al., 2001)	6-7-mo-olds (28)	AW	No-gap sine tone/ (4, 8, or 12 ms) gap deviant	800 (SOA)	With all 3 gaps, an MMN at 220 ms, followed by a P3a-like positivity at about 300 ms.
(Tanaka et al., 2001) (auditory modality only)	Newborns 28-41 wk GA, 72 normal, 11 abnormal	AW	750-1000 Hz	1000	MMN at 350-400 ms in the majority of infants
(Morr et al., 2002)	2- to 47- mo-olds (63, cross-sectional)	AW	I. 1000-1200 Hz II. 1000-2000 Hz	750	I. MMN not found until 4 years of age. II. MMN at all ages, with latency decrease 1ms/mo. By 31-44 mo, MMN double-peaked (150 and 250 ms). In both I and II, a positive component (PC) at about 300 ms, decreasing in amplitude between 19 to 30 mo of age.
(Cheour et al., 2002)	Term newborns (15)	AS	/y/- boundary vowel /y/i/	700	MMN at about 250 ms after nocturnal auditory training (2.5-5 hours)
(Friederici et al., 2002)	2-mo-olds (29)	AW AS	I. /ba/-/baa/ II. /baa/-/ba/ (202-341 ms)	600	I. In awake infants frontal positivity (400-600ms), followed by right frontal negativity (800-1000ms) and in asleep infants a larger and more extended positivity. II. No positivity was observed

4. The aims of the present studies

The present studies aimed at investigating the development of the electrophysiological indices of auditory processing through early infancy. The initial stages of sound processing, reflected by obligatory responses, were examined together with the preconscious discrimination of frequency and duration change, as reflected by discriminative cortical responses. The main idea of this study was to investigate the same infants (longitudinal study) in a systematic, fine-graded manner, that is, every 3 months from birth to 1 year of age.

4.1. Studies I and II

We aimed at investigating first, whether harmonically rich stimuli facilitate sound-duration (Study I) and sound-frequency discrimination (Study II) in newborns, as in school-age children (Čeponienė et al., 2002b) and in adults (Tervaniemi et al., 2000). Study II also compared the frequency and duration MMN responses, and assessed the contribution of the non-refractory obligatory responses to the deviant-minus-standard difference wave in newborns.

4.2. Study III

Study III systematically examined the effects of the stimulus duration on the obligatory responses and compared them with those in adults. A 200-400 ms duration range (that is, longer than the upper limit of temporal loudness summation of about 200-ms; Cowan, 1984), was selected for Study III, in order to obtain a pure duration effect.

4.3. Studies IV and V

The newborns whose parents agreed to participate in the longitudinal study were repeatedly examined every 3 months until the age of 1 year in order to monitor the maturation of the obligatory (Study IV) and discriminative (Study V) responses in the same infants. In addition, Study V was designed to also control for the possible attention/orienting effects that may affect the MMN detectability in infants. To this end, in an additional condition,

frequency deviants were replaced by highly diverse novel stimuli commonly used for the elicitation of the electrophysiological correlate (the P3a) of an involuntary attention switch (Escera et al., 2000).

5. Methods

5.1. Participants

All newborns were recruited from the post-delivery wards of the Women's Hospital, Helsinki University Central Hospital, with the written consent of their parents. The studies were approved by the Ethics Committee of the Hospital.

In total, 95 newborns aged 1-6 days were enrolled in the investigation (Table 4). All infants were considered healthy by a neonatologist and passed a hearing screening using evoked otoacoustic emissions (OAE) with the ILO88 Dpi system, Otodynamics Ltd, Hatfield, UK.

In all studies but Study III, EEG records obtained in active sleep or awake state only were included in the analysis, as the EEG/ERP patterns during active sleep and awake state in infants were not found to differ essentially from each other (De Weerd, 1995; Ellingson et al., 1974; Kurtzberg et al., 1984; Novak et al., 1989). The sleep states were classified on the basis of the EEG patterns, behavioral activity, and eye movements. Quiet sleep (QS) was classified on the basis of high-voltage slow or trace-alternant patterns (Stockard-Pope et al., 1992), the absence of rapid eye movements, and behavioral quiescence. Active sleep (AS) was identified on the basis of low-voltage irregular or mixed EEG patterns, rapid eye movements, and irregular respiration.

In Study II, the data of 12 infants who spent most of the experimental time in quiet sleep stage were not reported in the original article. An additional analysis was performed comparing the ERPs of 9 out of these infants in quiet sleep with 9 of the infants recorded in active sleep and 9 infants recorded in an awake state (Fig. 1). The groups were compiled to include equal numbers of males (4 in each group).

Fifteen infants (Study IV) were repeatedly tested every 3 months until the age of 12 months. From 3 months onwards, only recordings obtained in the awake state were included in further analysis. Out of these 15 infants in Study V, 3 females were excluded in order to avoid a gender-related bias (Picton et al., 2000b). Further, 6 out of the 12 remaining infants

in Study V were recorded once more at the age of 2 years.

In Study III, 9 adults were also included (4 males, mean age 28 years).

Table 4. Newborn participants

Study	N (males)	Age range (days)	Gestational age (weeks)	Birth weight (g)
I	10 (5)	2-6	38-41	2830-4230
II	55 (17)	1-3	36-42	3060-4280
III	9 (5)	2-6	36-42	3010-5360
IV	15 (12)	2-4	38-42	3060-4040
V	(12) +6 (3)	1-6	37-41	3080-4240

5.2. Stimuli and experimental conditions

In all studies (except the additional experiment in Study V that utilized novel sounds), the three-partial harmonic tones were used. In all Oddball conditions, the standard stimulus always consisted of the 3 lowest partials of the 500-Hz fundamental frequency, FF (i.e., 500, 1000, and 1500 Hz sinusoidals), the second and third components being lower in intensity than the first one by 3 and 6 dB respectively. In all Oddball conditions, the standard stimulus occurred with a probability of 85% and the deviant tone was randomly presented with a probability of 15%. The stimulus onset asynchrony (SOA, onset-to-onset) in all studies was 800 ms. All sounds had an intensity of 70 dB sound-pressure level (SPL) at the infant's head.

5.2.1. The Frequency-oddball condition (Studies II and V)

In the Frequency-oddball condition, the deviant stimulus was a 100-ms harmonic tone consisting of the 3 lowest partials of the 750-Hz fundamental frequency (i.e., 750, 1500, and 2250 Hz sinusoidals). Both standard and deviant tones were 100 ms in duration.

5.2.2. The Duration-oddball condition (Study I, II, and unpublished results)

In the Duration-oddball condition of Study I, the deviant sounds differed from the standards in duration: in one sequence, the deviant tone was 40 ms, and in the other sequence it was 200 ms in duration.

In the Duration-oddball condition in Study II, the standard stimulus was 200 ms in duration

and the deviant tone was otherwise identical to the standard but 100 ms in duration.

This Duration contrast (200-ms standard, 100-ms deviant) was also used in the longitudinal Study V. The results of the Duration-oddball condition in Study V were not reported in the original article and are presented here as unpublished results.

5.2.3. The Equiprobable-frequency condition (Studies II, IV, and V)

The rationale for the Equiprobable condition was to equalize as much as possible the contribution of the obligatory responses to the deviant-minus-standard waveforms used to evaluate the MMN.

In the Equiprobable-frequency condition, the 100-ms three-partial harmonic tones with fundamental frequencies of 500, 625, and 750 Hz were equiprobably presented (33%) with an SOA of 800 ms. The 750-Hz FF tone served as a control stimulus. That is, the difference wave for the MMN evaluation was calculated by subtracting the ERP to the equiprobably presented 750-Hz FF tone from the 750-Hz FF tone presented as a deviant in the Frequency-oddball condition.

5.2.4. The Equiprobable-duration condition (Study II)

In the Equiprobable-duration condition, harmonic tones of 100-, 200-, and 300-ms in duration (500-Hz FF) were equiprobably presented (33%) with an SOA of 800 ms. The 100-ms tone from this condition served as a control stimulus for evaluating the MMN, obtained in the Duration-oddball condition in Study II.

Since in Study II, no difference was observed between the responses to the 100-ms tone presented as a standard in the Frequency-oddball condition and to the same tone presented in the Equiprobable-duration condition (Fig. 2 A, B), in longitudinal Study V, the standard-stimulus response from the Frequency-oddball condition served as the control response for the evaluation of the Duration MMN. Thus, the Duration difference waves were constructed by subtracting the standard-stimulus ERP from the Frequency-oddball condition (100-ms) from that to the deviant-stimulus ERP from the Duration-oddball condition (100-ms) in order to minimize the contribution of the obligatory responses to the stimuli with different durations.

5.2.5. Alternating duration condition (Study III)

In Study III, first, 6 adults were tested in order to determine whether tone duration is indexed by the obligatory ERPs, and whether the regular or random presentation of sounds with different durations and probabilities affect the morphology of the ERP responses. Therefore, the adults were tested with 4 different types of sequences: 3-duration random sequences (200-, 300-, and 400-ms tones, probabilities 33% each), 2-duration random sequences (200 and 300 ms, 300 and 400 ms, probabilities 50 % each), 2-duration alternating sequences (200 and 300, 300 and 400 ms), and a 300-ms tone presented with a 100% probability. Since none of the above manipulations had an effect on the ERP morphology, for the comparison between adults and infants, 3 alternating sequences with 2 different duration tones in each were chosen: 200 and 300 ms, 300 and 400 ms, and 200 and 400 ms.

5.2.6. Novel condition (Study V)

In the Novel condition of Study V, the 500-Hz FF standard was randomly replaced by novel sounds (15%). The novel sounds were diverse: simple tones, vowels, syllables, clicks, and chirps, mechanical and environmental noises. Each novel occurred only twice during the experiment. All stimuli were 100-ms in duration.

5.3. The EEG recording and data analysis

Neonates and 3- and 6-month-old infants were tested in a silent room in the Hospital for Children and Adolescents (HUCH). Newborn infants were lying in an infant's cot, with loudspeakers located at about 20-cm distance on both sides of the infant's head. Three- and 6-month-old infants were tested while sitting in a safety seat or on their parents' lap. Nine, 12-, and 24- months old infants and adults were recorded in a soundproof and electromagnetically shielded chamber at the Cognitive Brain Research Unit (CBRU), Department of Psychology, University of Helsinki. Infants sat on their parents' lap and were watching a silent cartoon. Adults were reading a self-chosen book. The experiments lasted about 1-1.5 hours.

Single-use electrodes were attached to the F3, F4, C3, C4, T3, T4, P3, and P4 electrode sites (in Studies III and V (Experiment 2, newborns) also to Cz), according to the International 10-

20 System (Jasper, 1958). All electrodes were referenced to the right mastoid (in Study III to the linked mastoid), and off-line re-referenced to the average of the right and left mastoids. The ground electrode was placed on the forehead. Eye movements were monitored with two electrodes, one placed below and the other on the outer corner of the right eye.

The EEG was recorded (bandpass 0.1-30 Hz, sampling rate 250 Hz) using the NeuroScan EEG recording system. The duration of the analysis epoch was 900 ms, including a 100 ms pre-stimulus time. The first 3 epochs of each block and those at any channel exceeding the absolute voltage of 150 μV were excluded from averaging. Off-line, epochs were filtered (band-pass 1.0-15 Hz), baseline corrected with respect to the mean amplitude of the pre-stimulus interval, and separately averaged according to stimulus type.

The amplitudes and latencies of the ERP peaks were measured from the latency windows defined by the latency distribution of the peak of interest across the individual infants. The mean amplitudes were then calculated over a 40-ms period centered at the peak latency at the F3/F4 electrodes for each hemisphere. The deviant-minus-standard ERP difference waveforms were computed in order to better visualize and measure the discriminative responses (MMN, LDN). In Studies II and V, deviant-minus-control (equiprobably presented tone identical to the deviant; see Methods 5.2) ERP difference waveforms were also calculated in order to minimize the differences in refractoriness levels between the responses entering the subtraction. The discriminative responses were defined as the largest negative (MMN, LDN) or positive (P3a) deflection in the corresponding latency windows of the difference waveform, greater than the average baseline voltage by 1.0 μV at any 2 out of the 4 fronto-central electrodes. The significance of the components was always tested (even when not reported in the original articles) with two-tailed t-tests for dependent samples by comparing their mean amplitudes with the 0 μV.

The statistical analyses of all the data were performed with the appropriate designs of the analysis of variance, ANOVA, and post hoc tests were applied to determine the sources of the significant ANOVA effects. All electrodes were included in the ANOVAs, unless otherwise mentioned (in some cases an ANOVA was performed for only F3, F4, C3, and C4 electrodes, since the largest and most consistent response in infants was observed over the frontal and central areas).

6. Results

6.1. Responses to the standard and equiprobable stimuli (Studies IV, III, and unpublished results)

6.1.1. ERP correlates of sound duration

Fig. 2 (A, B, C) shows group-average ERPs obtained in 13 infants in Study II.

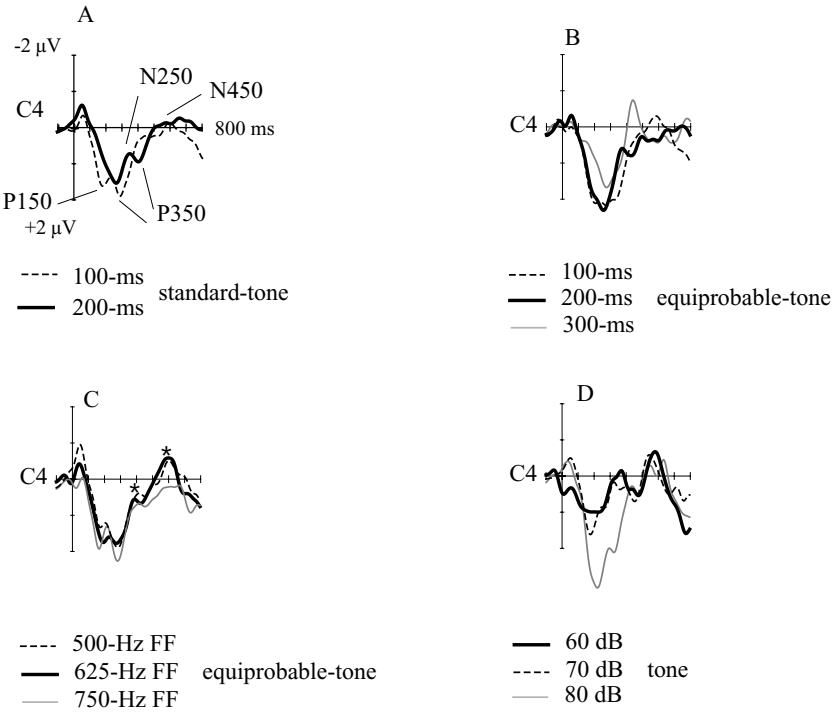

Figure 2. Obligatory responses to the harmonic tones (A) presented at a probability of 85% in the Duration and Frequency Oddball conditions (Study II, n=13); (B and C) presented at a probability of 33% in the Duration and Frequency Equiprobable conditions (Study II, n=13), and (D) presented at a 100 % probability at different intensities (unpublished data, n=6, 100-ms 500 Hz FF tone). The N250 and P350 peaks are delayed by approximately 100 ms as can be seen in response to the 200-ms harmonic tone as compared with that to the 100-ms harmonic tone (A). The response to longer tones was negatively displaced relative to the response to the shorter tone at 300-400 ms (A, B), whereas the response to the higher-intensity tone was positively displaced relative to the lower-intensity tone at the same latency range (D), whereas the responses to the 3 tones with different frequencies did not essentially differ (C). The N450 early and late phases are marked with asterisks, see 7.1.2.

The typical newborn-infant ERP was dominated by a positivity, followed by a low-amplitude

negative deflection (herein called the N450, Fig. 2, A).

A small negative deflection (herein called the N250) could be seen at about 200-250 ms after stimulus onset dividing the dominating positivity into two peaks, herein called the P150 and P350 (Fig. 2 A). Study II found significant sound duration effects on obligatory (standard-tone) ERPs in neonates. Fig. 2A shows the N250 and P350 peaks delayed by approximately 100 ms in response to the 200-ms standard tone (Duration-oddball condition) as compared with the 100-ms standard tone (Frequency-oddball condition).

During the 100-350 ms period the 200-ms standard-stimulus ERP was significantly more negative than the 100-ms standard-stimulus ERP ($F(1,12)=4.15$; $p<.03$, Fig. 2 A). Similarly, in the Equiprobable-duration condition, the responses to the longer tones were more negative during 300-500 ms as compared with the responses to the shorter tones (Fig. 2B; $F(2, 24) = 4.55$, $p<.02$). In contrast, the responses to the 3 tones in Equiprobable-frequency condition did not differ significantly from each other (Fig. 2, C).

The results of Study III, investigating the ERP correlates of sound duration with longer tones (200, 300 and 400 ms), first, replicated the results of Study II in that the longer the tone was in duration the more negative was the response at 200-500 ms. Second, the results revealed a striking similarity in the tone-duration effects on the auditory responses in newborns and adults (Fig. 3, difference waves), despite the profound differences in their waveform structure. The tone duration had a significant effect on the amplitude of the negative-going peaks in newborns ($F(2, 16)=26.37$, $p<0.0001$), the response to the 400-ms tone being negatively displaced relative to those to the 200- and 300-ms tones, and the response to the 300-ms tone being negatively displaced relative to that to the 200-ms tone.

In both groups, the latency of the negative difference peak (the ERP to the longer tone-minus- ERP to the shorter tone) was significantly shorter (by 112 ms) in the 300-200 ms than in the 400-300 ms difference wave ($F(1,8)=147.13$; $p<0.00001$, Fig. 3, right column).

The responses to the 100- and 200-ms standard tones, obtained from the same infants within each age, are shown overlaid in Fig. 4 (unpublished data). The common tendency can be clearly seen across the whole age range studied: the 200-ms standard-stimuli ERP was negatively displaced relative to the 100-ms standard-stimulus ERP at a latency range 200-400 ms. Statistically, the N250 amplitude was significantly larger in the 200-ms than in the 100-ms tone ERP ($F(1,33)=4.82$, $p<.036$), and significantly larger over frontal than central electrodes ($F(1,33)=12.28$, $p<.002$; three-way ANOVA [Age X Standard Duration X

Electrode] with only the frontal and central electrodes included). The overall age effect on the N250 amplitude in these responses was also significant ($F(4,33)=8.38$, $p<.0001$), with the post hoc test showing that the N250 at 9 and 12 months of age was significantly larger than that at birth and at 3 months of age.

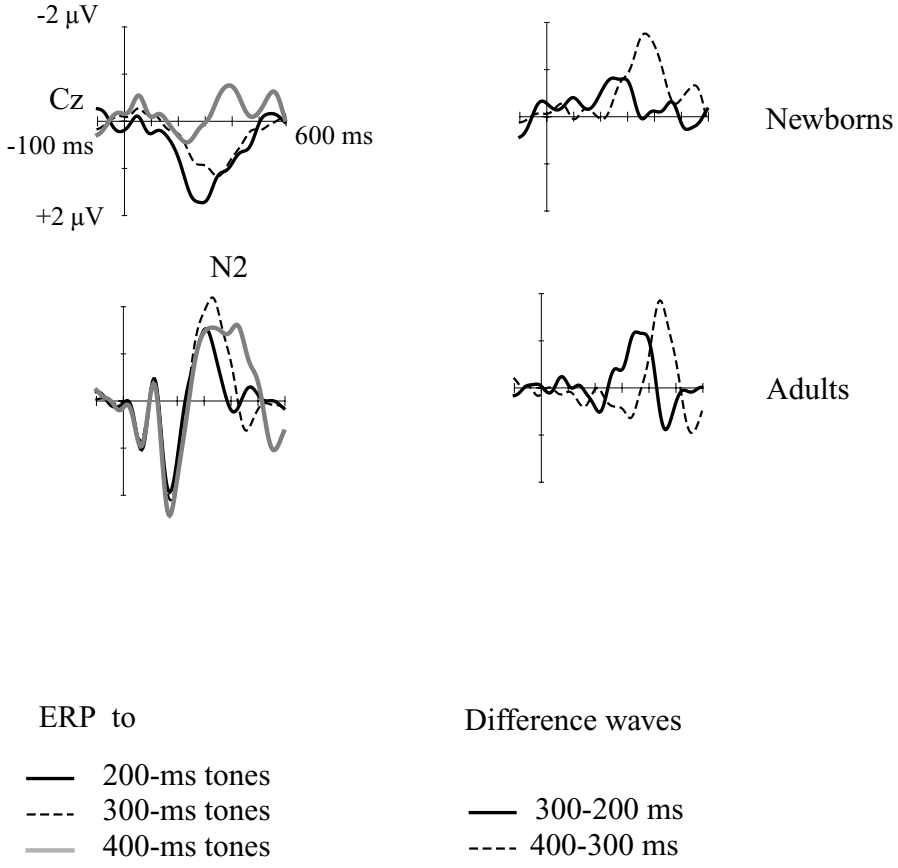

Figure 3. ERP responses in newborns (top row) and adults (bottom row) elicited by 3 different-duration tones (left column) and the corresponding difference waves obtained by subtracting the shorter tone from the longer tone (right column, Study III). The striking similarity in the difference-wave patterns can be seen between the newborns and adults (right column), despite the differences in the ERP waveform structure (left column).

6.1.2. Maturation of the obligatory ERP during infancy

The responses presented in Fig. 5 were obtained in the same infants from birth to 12 months of age (Study IV). At 24 months of age, ERP were recorded from 6 infants out of the 12 from

Study IV.

As it is seen in Fig. 5, all ERP peaks seen at the age of 12 months are identifiable already at birth. The main maturational change from birth to 3 months of age was a remarkable increase in the positive amplitudes (the P150 and P350 peaks, $F(4,56)=7.55$ and 10.56, respectively, $p<.0001$, Table 5). Between 3 and 6 months of age, the growth of the positivities stopped, and the negative N250 became robust. From 6 to 12 months of age, ERP maturation was characterized by a strong growth of the N250 and N450 negativities ($F(4,56)=12.11$ and 8.58, respectively, $p<0.0001$) which was paralleled by the diminution of the P350 amplitude ($p<0.01$). The N250 seems to further grow until 24 months of age, whereas the P150 remained largely the same. The latency of the P150 decreased from 3 to 6 months ($p<0.02$) and, further, from 6 to 9 months of age ($p<0.0002$; main age effect $F(4,56)=14.83$, $p<.00001$). The latency of the N250 remained stable at 230-270 ms, whereas the N450 latency decrease throughout the age span studied ($F(4,56)=2.88$, $p<0.04$).

Table 5. Latencies (ms) and amplitudes (μV) of the infant ERP peaks (standard deviations) at the C3 electrode.

Age (mo)	P150 latency	P150 amplitude	N250 latency	N250 amplitude	P350 latency	P350 amplitude	N450 latency	N450 amplitude
0.1	179 (31)	2.18 (1.3)	226 (25)	1.44 (1.7)	292 (30)	2.32 (1.4)	504 (61)	-0.71 (0.8)
3	192 (32)	8.76 (4.6)	234 (27)	6.87 (4.7)	326 (40)	7.84 (5.8)	494 (74)	-1.37 (2.8)
6	158 (17)	7.39 (5.3)	218 (22)	0.35 (6.3)	291 (24)	8.27 (5.3)	497 (66)	-3.28 (2.9)
9	139 (24)	8.91 (4.9)	225 (19)	-2.45 (5.1)	308 (41)	3.97 (3.4)	451 (70)	-4.02 (3.5)
12	142 (20)	6.29 (3.1)	238 (23)	-3.56 (3.6)	332 (53)	2.14 (2.8)	433 (76)	-4.57 (3.0)

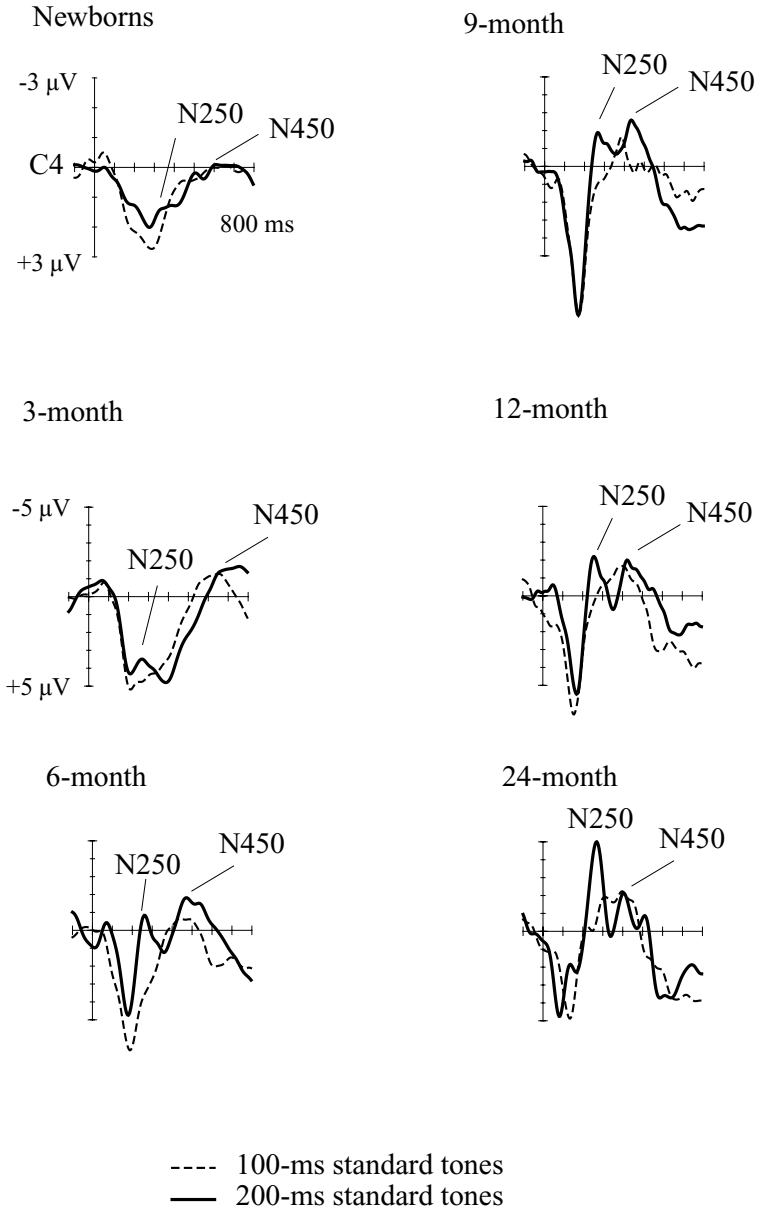

Figure 4. The maturation of the standard-stimulus ERP in response to the 100-ms and 200-ms harmonic tones. At each age, the comparison was made within the same infants out of the 12 participating in Study V (unpublished results). The enhanced N250 peak in response to the standard tones of the longer duration (200-ms) can be observed.

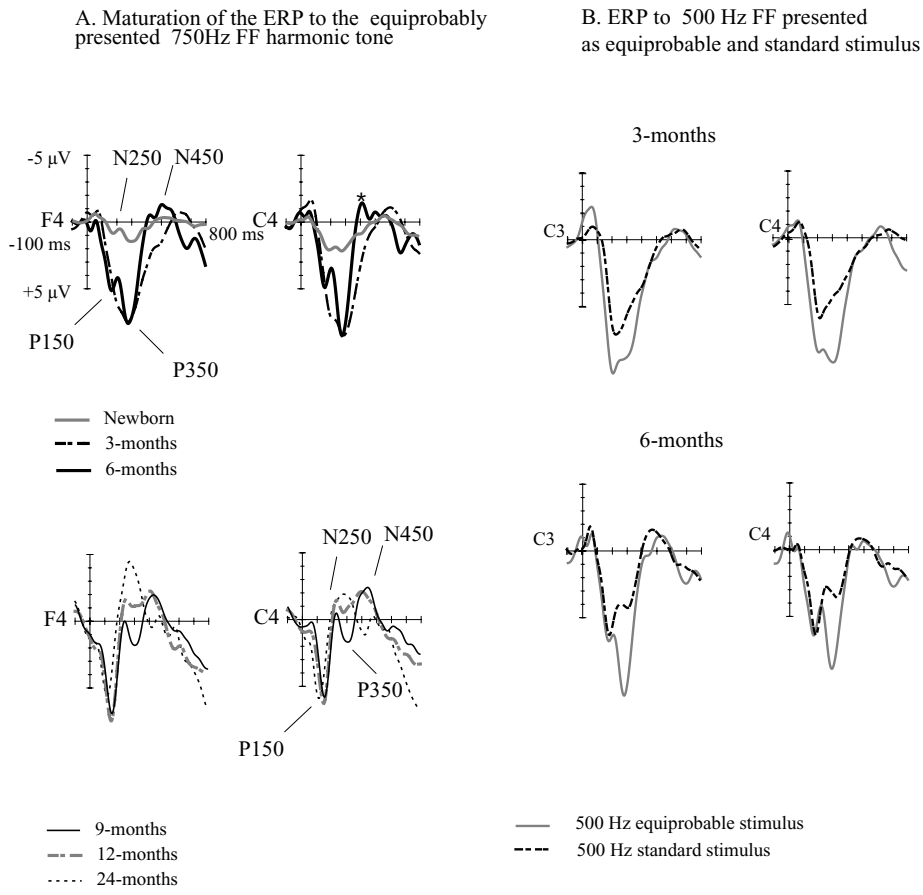

Figure 5. (A) The ERP to the equiprobably presented harmonic tones in the same infants at 2-4 days, 3, 6, 9, 12 (Study IV) and 24 months (6 out these 12; bottom row, unpublished results). The amplitude increase of the positive peaks (P150, P350) could be followed from birth to 6 months of age (top row), whereas the growth of the negative peaks was seen during the second half of the first year. The N250 continued to enhance until 2 years of life (bottom row). (B) The responses to the 100 ms 500 Hz fundamental frequency harmonic tone presented at a probability of 85% in Frequency oddball condition (dashed line) and to the same tone presented at a probability of 33% in Equiprobable frequency condition (solid line) compared in the same infants at 3 and 6 months of age. The P350 was significantly larger in amplitude in response to the tone presented in Equiprobable condition than in the Frequency oddball condition.

6.1.3. The ERP to the standard stimulus compared with that to the equiprobable stimulus

An additional comparison of the responses to the same stimuli presented as the standard in the oddball condition and as the equiprobable stimulus in the Equiprobable-frequency condition in the same infants (Fig. 5 B), revealed several significant effects: the P350 was

larger in Equiprobable-frequency condition than in Frequency-oddball condition at 3 and 6 months of age ($F(1, 14) = 6.88$, and 4.91; $p<.02$, and $p<.05$, respectively; 2-way ANOVA [Condition X Electrode] with only the frontal and central electrodes included).

6.2. Change-detection (Discriminative) responses (Studies I, II, and V)

6.2.1. The Duration and Frequency MMNs in newborns

Fig. 6 demonstrates the ERP to the standard and deviant stimuli in the Duration-oddball conditions and the corresponding deviant-minus-standard difference waves.

As it is seen in Fig. 6 A, the responses to all deviants (40-, 100- and 200-ms; Studies I and II) were negatively displaced at 150-500 ms relative to the standard-tone ERP. This effect was largest at the frontal electrodes. It is worth noting that the latency of the negative-going peak (the N250, marked with an asterisk) in both the deviant and standard ERPs seems to change with stimulus duration.

In Study I, when the MMN was determined as the negative difference wave deflection at the latency of 150-500 ms, the MMN was revealed in all 10 subjects in response to both 40- and 200-ms deviants, although a great inter-subject variation in the MMN amplitude and latency was observed. As seen from the difference waveforms in Fig. 6 B, the negative deflection is bifurcated with the smaller peak at about 150 to 250 ms and the larger one at about 300 to 400 ms. In the subsequent Study II (Fig. 6, bottom row) the first peak of the double-peaked MMN was measured from 100-350 ms and the later (called LDN) from 350-750 ms. The mean latency of the MMN peak was 257 ms and that of the LDN was 496 ms. Both peaks were significantly larger at the frontal than at the parietal electrodes ($F(5, 125)=2.41, 4.17$; $p<.04$, $p<.0015$, for the MMN and LDN, respectively).

Fig. 7 A presents the ERPs obtained in newborns in the Frequency-oddball condition (Study II).

As in the Duration condition, the MMN and LDN were significantly larger at the frontal than at the parietal electrodes ($F(5, 80)=4.32, 5.86$; $p<.002$, $p<.0001$, for the MMN and LDN, respectively). The mean latency of the MMN was 171 ms and that of the LDN 643 ms.

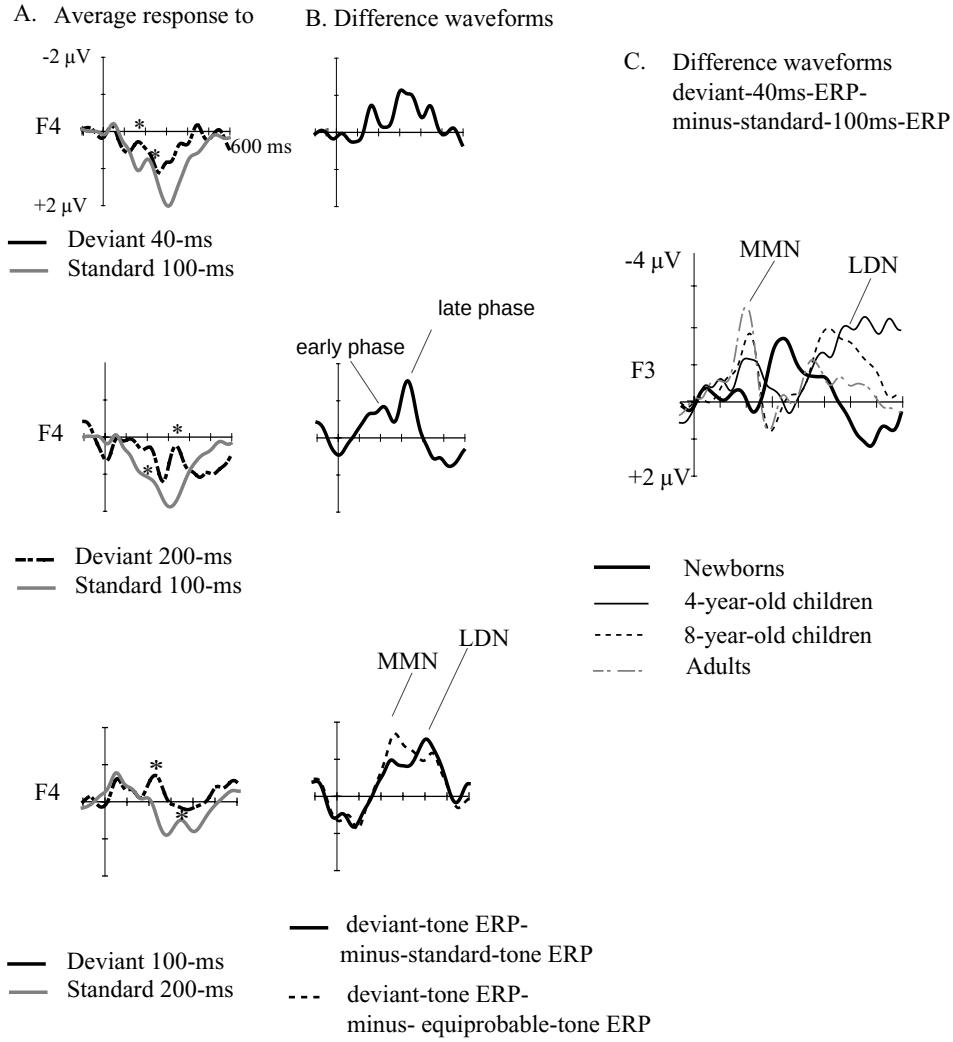

Figure 6. Newborns ERPs to standard and deviant tones in Duration oddball condition (A) and the corresponding deviant-minus-standard difference waves (B, two top rows, Study I) and deviant-minus-equiprobable difference waves (bottom row, Study II). The asterisk shows the increasing latency of the N250 peak with increasing stimulus duration. The comparison of the difference wave 40-ms deviant-ERP minus 100-ms standard-ERP is presented in (C) for newborns (Study I) and 4- and 8-year-old children and adults (Cheour et al., submitted). The newborns' difference negativity was later than the children's MMN, but earlier than the children's LDN.

Those infants who showed the MMN in both Duration and Frequency conditions were included in a between-condition comparison in Study II (Fig. 7 C). Change onset was delayed by 100 ms in the Duration-oddball condition relative to that in the Frequency-oddball condition. Correspondingly, the Duration MMN peaked on average 85 ms later than

the Frequency MMN ($F(1,9)=15.94$, $p<0.003$).

6.2.2. Subtraction-type effects

The comparison between the traditional deviant-minus-standard difference and deviant-minus-equiprobable difference obtained by subtracting the responses to stimuli of equal duration (100-ms-deviant-minus-100-ms-equiprobable; Fig. 6 B, dashed line) showed that in the Duration condition, the obligatory components significantly contributed to the deviant-minus-standard difference waves by reducing the MMN amplitude ($F(1,12)=7.44$, $p<.018$), and enhancing the LDN amplitude ($F(1,12)=8.83$, $p<.01$).

In the Frequency condition, the subtraction type affected significantly neither the MMN nor LDN.

Since the responses elicited by the standard and equiprobable tones in the Frequency condition significantly differed at 3 and 6 months of age (see 6.1.3) in the longitudinal study, both subtraction types (deviant-minus-standard and deviant-minus-equiprobable) were evaluated in this work. In the original article (Study V), only deviant-minus-equiprobable subtractions were reported.

6.2.3. Maturation of the MMN during the first year of life

Two or more negative peaks were observed across all ages studied. The first peak, at about 200 ms (Fig. 8, Table 6) was considered to be the MMN, according to Study II. The inspection of the individual difference waves revealed a substantial inter- and intra-subject variability; that is, although the MMN on average was obtained in 75% of the infants at each age, the MMN replicability within the same infants from age to age was poor. At birth, the MMN was revealed in 10 out of 12 infants. However, out of 10 infants who had an MMN at birth, 3 had no MMN at 3 months and the other 3 had no MMN at 6 months. In contrast, those 2 infants who had no MMN at birth showed it at 3 and 6 months of age. Due to the substantial variability, the age effect on MMN amplitude was insignificant (Table 6). The electrode effect was significant at $F(3, 33) = 10.67$, $p<.0003$, due to the MMN being smaller at the temporal than at any other electrode. The incidence of the MMN in the Duration-oddball condition was somewhat lower than that in the Frequency-oddball condition. That is, out of 12 infants, MMN-like negativity was observed in 9 (75%) at birth, 7 (58%) at 3 months and 6 months, 6

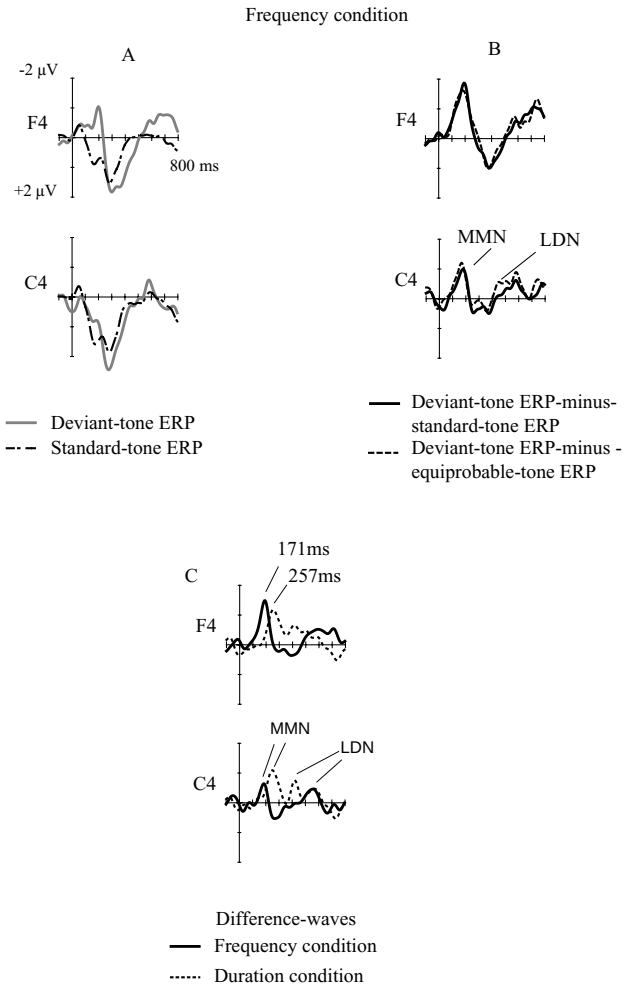

Figure 7. Newborns ERPs (A) to the standard (three-partial harmonic of 500 Hz fundamental frequency) and deviant (three-partial harmonic of 750 Hz fundamental frequency) tones, and (B) difference waves, obtained by subtracting the standard-stimulus ERP from that to deviant-stimulus (solid line) and the equiprobable-stimulus ERP from that to deviant-stimulus (dashed line). (C) The comparison of the difference waves from Duration and Frequency oddball conditions showed an MMN latency shift by about 85 ms (Study II).

(50%) at 9 months, and 8 (67%) at 12 months (Table 7, Fig. 9). Only 1 infant showed the Duration MMN at all ages.

Fig. 9 shows an additional comparison (not reported in the original article) between the Frequency and Duration MMNs during the first year of life. Only those infants who showed the MMN in Duration condition were included in this analysis.

Table 6. Latencies (ms) and amplitudes (μV) of the infant discriminative responses (standard deviations) measured from deviant-minus-equiprobable difference waves. Electrodes C3 (for DP and LNl) and C4 (for MMN and LNe).

Age (mo)	MMN latency	MMN amplitude	DP latency	DP amplitude	LNe latency	LNe amplitude	LNl latency	LNl amplitude
0.1	157 (59)	-2.21 (1.6)***	290 (69)	1.36 (1.6)*	400 (56)	-1.63 (2.5)*	674 (66)	-1.53 (2.3)*
3	169 (42)	-5.1 (5.9)*	302 (56)	3.37 (5.1)*	425 (52)	-3.19 (3.8)*	670 (84)	-2.2 (3.06)*
6	219 (62)	-5.14 (5.8)*	309 (68)	4.17 (5.6)*	417 (44)	-5.25 (4.6)***	685 (64)	-2.23 (3.4)*
9	186 (48)	-6.27 (6.9)**	343 (79)	1.55 (5.5)	369 (62)	-7.11 (7.7)***	643 (109)	-3.37 (7.8)
12	188 (57)	-5.60 (8.0)*	345 (69)	3.73 (5.5)*	365 (62)	-4.56 (6.0)*	664 (102)	-5.96 (8.9)*

* p<.05, ** p<.01, *** p<.005

Table 7. Incidence of MMN in individual subjects in Frequency (F) and Duration (D) condition.

Condition	Infant	0.1 mo	3 mo	6 mo	9 mo	12 mo
F	A	+	+	-	+	+
D	A	+	-	-	+	+
F	B	+	+	+	-	-
D	B	+	-	-	-	-
F	C	+	+	+	+	+
D	C	+	+	+	+	+
F	D	+	-	+	+	+
D	D	+	+	+	-	-
F	E	+	-	+	+	+
D	E	+	-	+	+	+
F	F	+	+	-	+	+
D	F	+	+	-	+	+
F	G	-	+	+	+	+
D	G	+	+	-	+	+
F	H	+	+	-	+	-
D	H	+	+	-	-	+
F	I	+	-	+	-	-
D	I	+	+	-	-	+
F	J	+	+	+	-	+
D	J	-	+	+	-	-
F	K	+	+	+	+	+
D	K	+	-	+	+	+
F	L	-	+	+	+	-
D	L	-	-	+	-	-

As in Study II, the MMN showed a significant latency shift by about 100 ms in the Duration

condition as compared with the Frequency condition at all ages studied ($F(1,32)=142.4$, $p<.000001$).

For the pooled data of the Duration and Frequency-oddball conditions, the age effect on the MMN amplitude was significant at $F(4, 32)=3.46$, $p<.01$, with 12-month-old infants showing larger amplitudes than any younger group, except for 9-month-olds. The Condition x Electrode effect was significant at $F(3, 96)=2.96$, $p<.04$, with the Frequency MMN amplitudes being significantly larger at the parietal electrodes than the Duration MMN amplitudes ($p<.001$).

6.2.4. The late negativities

In the latency range of 350-750 ms, in which the LDN was observed in our Study V, two negative deflections were revealed.

The earlier phase (LNe) was measured from the 350-550 ms latency window and the later phase (LNl) was measured from the 550-750 ms latency window. Both phases significantly differed from 0 μV: the early phase was most consistent at the parietal electrodes (P3 and P4) and across all ages at C4, whereas the later one at all ages was significant at the frontal electrodes (F3 and F4), and at C3 except for 9 months (Table 6). The main age effect for the LNe was significant at $F(4, 44)=2.67$, $p<.05$, with the LNe amplitude being larger at 9 months than at any younger age. The electrode effect for the LNe was significant at $F(3,33)=27.20$, $p<.0001$, due to the LNe amplitude being smaller at the temporal than any other electrode. When only fronto-central electrodes were analyzed, a significant hemisphere effect was obtained ($F(1,11)=6.62$, $p<.03$), with the LNe amplitude being larger over the right hemisphere.

The main effect on the LNe latency was significant ($F(4,44)=3.6$; $p<.02$), with the LNe latency at 9 months of age being shorter than at any younger age. The age effect on the later phase (LNl) of the multi-phase LDN was insignificant. The electrode effect was significant at $F(3, 33)=8.9$; $p<.0005$, with the LNl amplitude being larger over the frontal and central than temporal and parietal areas.

6.2.5. The positive difference-wave component (difference positivity, DP)

In addition to the negative waves, the positive difference-wave component (herein called the difference positivity, DP), following the MMN at about 300 ms, was analyzed. The DP

was centrally predominant and was largest at the age of 6 months, when also a transient diminution of the MMN was observed at the frontal and central electrodes.

The DP was observed in the majority of infants across all ages, predominantly at the central electrodes. As seen from Figure 8, both at the group and at the individual levels, the DP amplitudes were larger at 3 and 6 months than at any other age. However, due to the high inter-individual variability, the main age effect on the DP amplitude was insignificant. The electrode effect was significant at $F(3, 33)=5.54$; $p<.006$, with the DP amplitude being smaller at the parietal than at any other electrode. When only the fronto-central electrodes were analyzed, a significant hemisphere effect was obtained ($F(1, 11)=9.36$, $p<.02$), with the DP amplitude being larger over the left than right hemisphere.

When the ERPs from the Frequency and Duration-oddball conditions were compared with each other (Fig. 9), the DP latency shift was observed at the group level at 3-, 6- and 9-months of age, indicating the change-onset time locked elicitation of this component.

6.2.6. The responses to the novel sounds in infants and children

Fig. 10 shows a comparison between 2 age groups (newborns and 2 year-old children) and 2 conditions (Frequency-oddball condition versus Novel condition; see the condition description in 5.2). In the Novel condition, a clearly identifiable P3a-like positivity was elicited at about 300 ms, followed by the late Nc-like negativity (see 3.3 and 3.4).

From the comparison of the deviant and novel responses, it can be seen that in the response to novel stimuli, the MMN was apparently overlapped by the large-amplitude P3a (evident in particular at 2 years of age). No age effect was observed for the P3a or Nc amplitudes or latencies, whereas the condition effect was significant: the P3a and the late negativity (Nc) were significantly larger in the Novel than in the Frequency-oddball condition ($F(1, 10)=16.15$, $p<.003$; $F(1, 10)=6.97$), $p<.03$, respectively). No condition effect was observed for the earlier phase of the LDN (LNe).

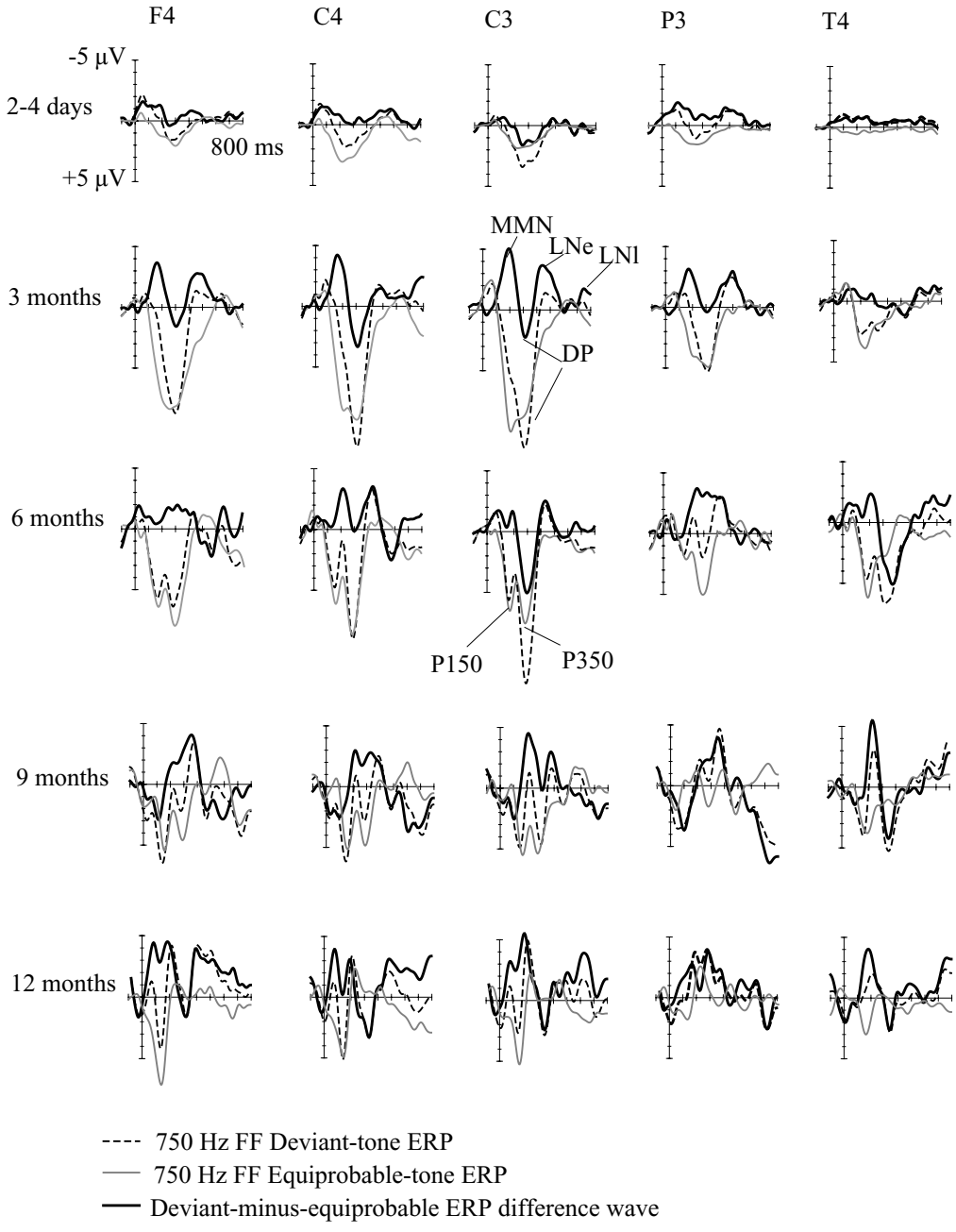

Figure 8. Grand-average ERPs obtained in response to the 100-ms 750-Hz deviant tone (dashed line), the identical control tone (thin line), and the deviant-minus-control ERP difference waves (thick line) at 2-4 days and at 3, 6, 9, and 12 months of age in the same infants (n=12).

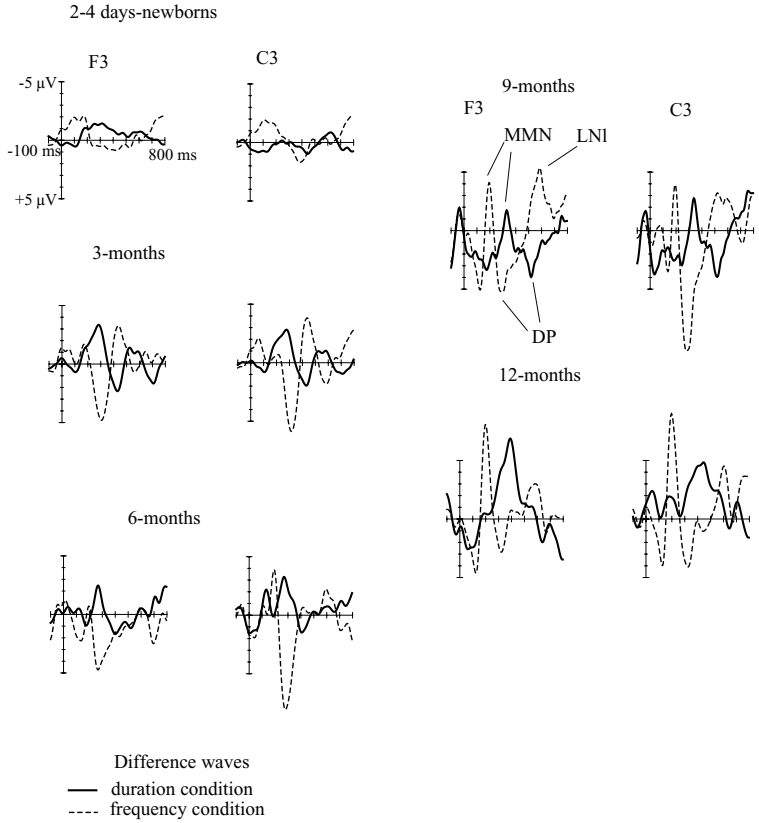

Figure 9. The Frequency and Duration MMNs in the same infants at different ages (Study V and unpublished data). Only infants who had an MMN in the Duration condition were included. The difference waves were constructed by subtracting the 100-ms standard-tone ERP from the 100-ms frequency-deviant ERP and from the 100-ms duration-deviant ERP.

7. Discussion

7.1. Maturation of the obligatory responses during infancy

Concordant with the previous studies described in Section 2.2, at birth, the ERP was predominated by a broad positivity at about 300 ms, followed by a small negativity at 450-600 ms, corresponding to the 'landmarks' of the infantile P2-N2 response (Study II, Fig. 2). In Studies II and IV, similarly as in some previous studies (Barnet et al., 1975; Cheour et al., 1999; Novak et al., 1989; Ohlrich et al., 1978), a small negative deflection (N250) riding on the positive deflection could be seen, dividing it into 2 positive peaks (P150 and P350, Figs. 1, 2, and 5).

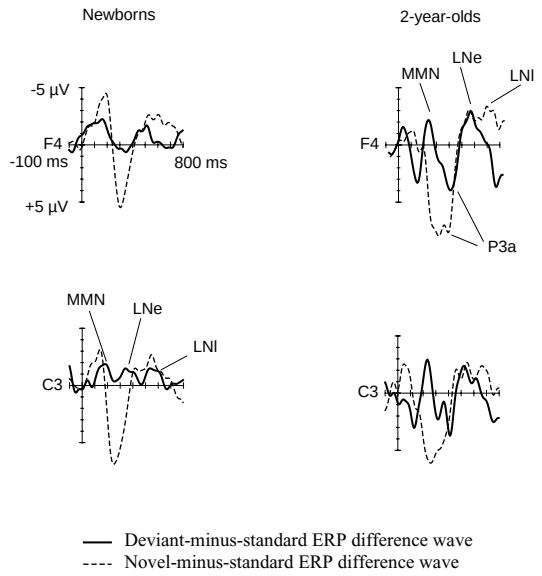

Figure 10. Difference waveforms of 6 children at 2 years of age (included also in Studies IV and V) and of 6 newborns from the Novel (dashed line) and the Frequency oddball conditions (solid line).

Importantly, in our studies, the responses to standard stimuli were robust and had a distinct morphology (e.g., Study II, Fig. 2 A) despite the fast stimulation rate (SOA of 800 ms). In previous newborn studies (Alho et al., 1990a; Cheour et al., 1999; Kurtzberg et al., 1995) using similar presentation rates, rather flat ERPs to standard stimuli were obtained. It therefore appears that spectrally rich sounds facilitate central auditory processing in infants, as they do in school-age children (Čeponienė et al., 2001) and adults (Woods and Elmasian, 1986).

7.1.1. The ERP morphology: pitch-refractoriness effects

In Study IV, the ERPs were obtained in response to tones of 3 different pitches presented equiprobably in the same block, which allowed us to avoid pitch-specific neuronal refractoriness. Indeed, the responses elicited by the same sound obtained in the Equiprobable and Frequency-oddball conditions (when this sound was presented as a standard) differed significantly from each other within the same infants: the P350 was smaller when stimuli were presented as standards at 3 and 6 months of age (Fig. 5B). This finding is in line with the previous studies showing that this positive wave is sensitive to the stimulus rate, strongly diminishing in amplitude with rapid stimulation, presumably due to refractoriness

(Čeponienė et al., 2000; Kurtzberg et al., 1995). The diminished voltage of the P350 with rapid stimulation might allow the N250 to partly merge with the ascending slope of the N450 peak (Fig. 5B), or even completely (compare 6-month-old subgroups in Figs. 4 and 5B with each other, dashed lines).

7.1.2. The ERP morphology: maturation effects

Maturational ERP changes that occurred from birth until 12 months of age consisted of an increase in the amplitude and the better definition of all peaks (P150-N250-P350-N450). Notably, the precursors of all peaks seen at the age of 12 months were discernible already at birth (Study IV, Fig. 5A).

The emergence of the N250 peak could be followed from the small-amplitude negative trough at birth and 3 month of age to the negative peak greatly increased in amplitude by 12 and further 24 months of age. The latency of the N250 remained constant across the age range studied. The similar maturational trend for this negative peak was reported previously by Kurtzberg et al. (1986), however, emerging from only about 3 month of age. The present data suggest that the generators of the N250 peak are active already at birth (Fig. 5A) and that during the second half of the first year, the relative strength of the N250 generators increases.

It might seem that the growing N250 artificially divided the predominant infant positivity into two parts (the P150 and P350). Indeed, the amplitudes of both the P150 and P350 peaks increased by the same amount from birth to 3 months of age. However, Novak et al. (1989) found that the early and late positive peaks at 3 and 6 months of age differed from each other in scalp distribution: the early peak (P1m) was largest frontally, whereas the later peak (P2m) was largest centrally. Our results also showed that these peaks are differentially sensitive to the stimulus rate. The P150 was robust in both Frequency-oddball and Equiprobable conditions (stimulus probabilities 85% and 33%, respectively), while the P350, in contrast, was significantly reduced in the Oddball condition (Fig. 5B). In addition, the maturational trajectories of these peaks began to dissociate after 6 months of age. The P150 amplitude remained unchanged not only from 6 to 12 months of age, but even further, until 24 months of age, whereas the P350 amplitude significantly diminished from 6 to 9 months of age (Fig. 5A). This finding replicates the results of Kurtzberg et al. (1988) who found an increase in the P2 amplitude until 6 months, followed by a decrement from 6 to 12 months.

Accordingly, in the group-average waveforms of the present study, at 12 months of age, the P350 could only be seen as a discontinuity between the N250 and N450 peaks. Therefore, the results of the present work together with the previous findings (Kurtzberg et al., 1988; Novak et al., 1989) suggest the existence of at least two components of the infantile P2, most probably reflecting separate neural processes.

Contrary to the widely accepted opinion that the ERP peaks essentially decrease in latency during infancy (see 6.1.2), we found a significant latency decrease with age for only the P150 and N450 peaks. The P150 latency decreased by 30 ms (see Table 5), and, as seen from Fig. 5A this latency decrement was probably mainly caused by its overlap with the growing N250. The N450, in turn, decreased in latency by 70 ms (best seen in response to standard tones, Fig. 4). However, the N450 in response to the equiprobably presented tones (Fig. 5A) was prolonged and sometimes multi-peaked, with the early phase at about 400 ms. A small protuberance on the ascending slope of the P350 at about 400 ms (marked with an asterisk in Figs. 2C and 5A) was seen already at birth (see also infants S1 and S3 in Fig. 2 of the original article IV). However, no evidence was found to consider these two phases separate components: no replicability of elicitation of both phases was revealed. Therefore, the N450 was measured as the negative maximum within the 350-600 ms period from stimulus onset. My hypothesis is that, as far as the long-latency components are concerned, it is the better synchronization with age that accounts for the most part of the N450 peak maturational changes, that is, for the observed latency shortening, amplitude growth and improving peak definition. Several lines of evidence support this assumption. The later ERP components (later than 200 ms) are much more variable in amplitude and latency than the earlier ones (Vaughan and Kurtzberg, 1992). Since ERPs are assumed to be indices of the synchronous excitation or inhibition of large neuronal populations, this variability is probably due to the decrease of neuronal synchrony with successive stages of processing (Vaughan and Kurtzberg, 1992). Thus, the multi-peaked shape of the N450 in some recordings might be due to the interindividual latency variability and/or the inter-trial latency variability within the same subjects (Kisley and Gerstein, 1999; Thomas et al., 1989; Truccolo et al., 2002). Therefore, its continuing definition until the end of the first year of life might be due to the decreasing trial-to-trial latency variability with age, in other words, due to the increasing consistency in brain response to the repeated stimuli, as also suggested by Thomas and Crow (1994).

7.1.3. Superposition of positive and negative ERP peaks

Importantly, the surface-recorded ERPs reflect the sum of the superimposed activity and might get a contribution from generators in several cerebral areas and from several layers of the cerebral cortex (Näätänen and Picton, 1987; Vaughan and Arezzo, 1988). These generators may have different maturational courses. Study IV demonstrated the interdependence of the amplitudes of the negative and positive ERP peaks during the first year of life, suggesting age-dependent changes in the relative strengths of their generators. That is, the predominant growth of the positive peaks during the first 3 months of life might have obscured a weaker activity of the N250 and N450 generators during this period. The probable increase in the strength of generators of the negative peaks in the second half of the first year of life resulted in the emergence of the robust N250 peak and the earlier, larger and better-defined N450 peak recorded at the scalp. In contrast, the amplitude of the P150 generally remained stable from 6 months onwards, and the amplitude of the P350 concurrently decreased from 6 to 12 months of age. It can therefore be suggested that the decrease of the P350 amplitude during this period was, at least partially, caused by its temporal overlap with the increasing N250- and N450-generator activities. Vice versa, at the ages younger than 9-12 months, the larger amplitudes of the P350 could have obscured an early part of the scalp-recorded N450 negativity, resulting only in a small protuberance on the P350 ascending slope.

7.2. Sound duration as reflected by obligatory ERP

Another intriguing aspect of the infant ERP was its dependence on stimulus duration. As Figs. 2 (A, B), 3, and 4 demonstrate, tone duration affected the infant's ERP at the latency range of the adult N2/child N250 peak. The ERP elicited by the longer tones was negatively displaced relative to the ERP elicited by the shorter tones. In Study III (Fig. 3), the peak latency of the negative difference waves appeared to closely follow the duration of the tones (i.e., it shifted by ~100 ms just as the durations of the eliciting tones increased by 100 ms).

The adult responses (Fig. 3, left bottom corner) to the 200- and 300- ms stimuli contained in addition to the P1/N1 peaks, the N2 peak morphologically similar to that described previously (Näätänen and Picton, 1986; Ponton et al., 2000). The N2 peak in the present

adults was prolonged in duration and it peaked slightly later to the 300-ms than 200-ms tones. In addition, the N2 peak to the 400-ms tones was double-peaked, suggesting the presence of two overlapping components. The possible candidates that could account for these duration-dependent ERP changes are 1) the offset response, 2) the sustained potential (SP), and 3) a hypothetical sound duration-specific ERP component. The latency of the second peak observed in the 400-ms tone ERP was about 430 ms which is definitely too early for the offset-N1 peaking between 80-200 ms from the stimulus offset (Picton et al., 1999). However, the positive deflection that peaked with a 150-200 ms delay from the tone offset (Study III, Fig. 3), could represent an offset P2 response (Picton et al., 1999).

In infants, similarly as in Study III, the N250 and P350 showed latency increases with the increasing tone durations in Studies II (Fig. 2, top row) and I (Fig. 6 A, marked with an asterisk). The same pattern was seen throughout the first 2 years of life (Fig. 4): in parallel with the increase in the N250 and N450 amplitudes with longer tone durations, an additional positive peak appeared in the infants' ERP at the latency corresponding to the offset-P2.

However, the presence of the offset-P2 cannot account for the duration-related ERP changes in the preceding negative wave. One possible explanation for the N2-amplitude enhancement in adults and older infants, and for the reduction of the positivity in the corresponding latency range in newborns, in response to longer tones might be the contribution of the SP. The negative responses elicited by the longer tones (see adults in Fig. 3) appear to follow the duration of the stimulus and to be maximal over the fronto-central scalp, which is characteristic of the SP. The emergence of the second negative peak in response to the 400-ms stimulus is compatible with this explanation, since in this case, the SP should extend beyond the latency range of the N2.

One could argue that in Studies II and V, the difference between the 100-ms and 200-ms standard tones might be affected by the temporal integration of sound energy, which is known to be summated over the first 200 ms of sound (Cowan, 1984; Näätänen, 1992; Yabe et al., 1997). We cannot entirely rule out this possibility, since, indeed, the response in infants seems to be generally more robust to the longer tone (Fig. 4). However, there are several lines of evidence indicating that the ERP difference represents a correlate of the duration as well. First of all, in the equiprobable condition (Study II, Fig. 2B) the pattern of duration-related changes (the reduction of the positivity at the N250 latency zone and the P350 latency increase in the ERPs to the longer tones) was the same for the durations below

the upper temporal limit for loudness summation (that is, from 100 ms to 200 ms) and for the durations above it (that is, from 200 ms to 300 ms). In the subsequent Study III, we selected a range of even longer sound durations (200-400 ms), so that the duration increments would not be accompanied by increments in perceived loudness. The duration-related response pattern observed in newborns in Study III was largely the same as that observed in Study II. That is, even when the increase in tone duration was not paralleled by an increase in its loudness, the ERPs to the longer tones were more negative than to the shorter tones at the N250 latency zone. Finally, we carried out the pilot study using the same harmonic tone but having 3 intensity levels. The results showed the opposite effect of intensity (and thus perceived loudness) to that of duration on the newborn's ERP. Increase in intensity resulted in the enhancement of the positive amplitudes (Fig. 2, D). Therefore, although the contribution of loudness to the duration effects on the infant's ERPs cannot be ruled out, I suggest that the main part of the effect is duration-dependent. Furthermore, the amazing similarity of the duration-related ERP pattern between the adults and newborns in Study III, and the consistency of the effect across several studies (Studies II, III, and the unpublished data of Study V), suggest the similarity of the sound-duration processing from birth to adulthood.

7.3. Neural mechanisms underlying the development of the infants' obligatory ERPs

The neural mechanisms underlying the above-described maturational ERP changes should be addressed with caution. Since scalp-recorded ERPs mainly represent cortical synaptic activity, the maturational changes in ERP morphology might to a large extent involve changes in intracortical synaptic organization and synaptic density (Eggermont, 1988; Vaughan and Kurtzberg, 1992).

7.3.1. The ERP peak-amplitude changes

Vaughan and Kurtzberg (1992) suggested that the ERP amplitude is proportional to the magnitude of synaptic activation. Indeed, the sequence of changes in synaptic density parallels changes in the ERP amplitude, which follow the inverted U-shape function, with rapid increase of the ERP amplitude during infancy followed by a gradual decline during

childhood. The sequence of synaptogenesis can be described to follow the same U-function: rapid increase in synaptic density during infancy is followed by gradual decline to the mature adult levels at puberty (Huttenlocher, 1979). The amplitudes of the infantile predominant positivity in our study (P150/P350), which were largest from 3 to 6 postnatal months, are in good agreement with the peak of synaptic density in the auditory cortex (Heschl's gyrus) near the postnatal age of 3 months (Huttenlocher and Dabholkar, 1997). The striking parallel between the course of synaptogenesis previously reported by Huttenlocher and Dabholkar (1997) and the ERP-peak amplitudes was also observed for visual modality in infants (Vaughan and Kurtzberg, 1992), for auditory modality in children (Ponton et al., 2000), and for both the visual and auditory modalities together (Courchesne, 1990). In contrast to the idea that synapse production is solely driven by experience, Zecevic and Rakic, (1991) suggested that this early postnatal synaptic production might be a continuation of autonomous synaptogenesis seen in the prenatal period, as synaptic density often correlates with conceptional age rather than experience. Interestingly, the P150/P350 amplitudes in prematurely born infants at the postnatal age of 3 months (conceptional age of 40 weeks) were significantly smaller than those of the full-term 3-month-old controls, and almost the same as those of newborn infants (Kushnerenko et al, 2002), indicating a correlation with conceptional age rather than with postnatal experience.

In addition, it was shown that synaptogenesis and myelination are more advanced in primary rather than in secondary auditory areas at term (Krmpotic-Nemanic et al., 1983; Yakovlev and Lecours, 1967), which is concordant with the ERP developmental lag by 1-2 months in the ERPs recorded over the temporal relative to those recorded over midline sites (Kurtzberg et al., 1984; Novak et al., 1989).

7.3.2. The ERP peak-latency changes

Changes in the synaptic efficacy during maturation may also account for the changes in the ERP peak latencies. The amounts of transmitter increase and transmitter quanta are released more synchronously, which results in a faster rise of the postsynaptic potentials at maturing synapses, and thus in decreased latencies (Eggermont, 1988). In addition, the proposed increase in consistency of brain response with age (Thomas and Crow, 1994), resulting in decrease of the trial-to-trial latency variability also contributes to the shortening of the ERP peak latencies.

As it was already discussed in 7.1.2 the latency changes in one ERP peak might also be affected by the maturational changes in another peak, overlapping peak (Ponton et al., 2001). For example, the decrease of the P150 latency was probably caused by its overlap with the growing N250. Furthermore, the latency decrease of the P150 was preceded by its slight latency increase from birth to 3 months. A similar effect was also observed by Shucard et al. (1987) and Čeponienė (2001). A possibility exists, that the disproportionally large amplitude increase of the positive peaks from birth to 3 months of age, (especially that of the P150; see Table 5) prolonged the P150 latency during this time period.

7.4. Developmental perspective of infant's auditory obligatory ERP peaks

It is difficult to unambiguously conclude whether the infantile ERP peaks are analogous to any of the adult ERP peaks. However, on the basis of their dependence on the stimuli parameters, several inferences could be made.

7.4.1. The infantile P150 as a possible precursor of the adult P1

First, the ERPs observed at 12 and 24 months of age (the P150-N250-N450 complex) seem to correspond to the P100-N250-N450 complex described in 3- to 9-year old children (Čeponienė et al., 1998; 2002a; Neville et al., 1993; Paetau et al., 1995). The persistence of the P150 peak during infancy, with a stable amplitude and steadily decreasing latency from 3 months to 5-6 years of age, suggests that it is the precursor of the childhood P100 which, in turn, develops into the adult P1 response by further decreasing in latency and diminishing in amplitude from 5 to 20 years of age (Ponton et al., 2000). Alternatively, as proposed by Ponton et al. (2000) the age-related P1 latency and amplitude decreases might actually reflect the superposition of the already mature P1 with a maturational increase of the amplitude of the N1.

7.4.1. The common properties of the infantile P350 and the adult P2

To what extent the P350 (an infantile P2) corresponds to the adult P2 remains to be determined. Pasman et al. (1999) reported that the infantile P2 disintegrates at 4-6 years of age and only by 6-10 years appears as the adult P2 (P170). Ponton et al. (2000), however, suggested that the P2 becomes adult–like by the age of 5 years, since in their study, no age-

related latency changes of this peak were observed from 5 to 20 years of age. The figures, however, showed that at 5-6 years, there was one broad positive peak lasting from 50 to 200 ms, followed by the N250 (N2). The P2, as a separate peak at the adult latency was apparent from about 9 years of age, when the emerging N1 began to intervene (Ponton et al., 2000). An interesting parallel could be observed between the children's and infant's P2: in Ponton et al's (2000) study, in 9-year-old children, the P1 was larger at Fz, whereas the P2 at Cz, just like in Novak et al's (1989) study in 6-month-old infants, the P1m was largest frontally and P2m centrally. In our study, this difference was not significant, although a similar pattern can be observed in 3- and 6-month-old infants (best seen in Fig. 1 of the original publication IV). A similar P2 maximal at the vertex was elicited by harmonic tones presented at the long ISI (mean 5 sec) in Čeponienė et al's (2002a) study in 9 year-old children and adults. Interestingly, the P2 was not observed in the same 9-year-old children with the faster stimulus rate (700 ms ISI). Similarly, a substantial reduction of the P2 amplitude with a shorter ISI (750 ms) in comparison with that elicited with an ISI of several seconds in 8 year-old children was reported by Kurtzberg et al. (1995). In adults, the P2 in the shorter-ISI condition (700 ms) was about one-third in amplitude of that in the longer-ISI (mean 5 sec) condition (Čeponienė et al., 2002a). A similar behavior of the infantile P350 was previously observed in our research group: in response to standard tones (ISI 700 ms) it was about one-third in amplitude of that in response to the rare tones (mean 6.9.sec) in newborns and 6-month-old infants (Čeponienė, 2001; Čeponienė et al., 2000). Although, in the present work, the difference between the conditions did not involve ISI, but rather the temporal probability, with regard to the pitch-specific refractoriness, however, our results support these previous findings: at 3 and 6 months of age, the P350 was significantly smaller in amplitude in response to the repeatedly presented 'standards' in the Frequency-oddball condition than in response to the same stimulus presented equiprobably with the other two. Therefore, the infantile P350 seems to share some properties with the children/adult P2 peak, that is, refractoriness pattern and scalp distribution, which lead to the tentative suggestion that the infantile P350 might be the precursor of the adult P2.

One might wonder, why the P350 is diminished in amplitude and apparently disappears from about 12 months of age, to re-appear at 5 years of age? It might be that the enhancements of the N250 and N450 entirely overlap the P2 peak. In addition, the N450 became earlier and fused with the N250 by 12 and further 24 months of age; therefore it might be assumed that

the P350 again joined the P150 peak, slightly shortening in latency from 9 months onward (see Fig. 5, electrode C4). Further, only when the N1 starts to emerge, it again divides the positive peak into the adult P1 and P2, as shown by Ponton et al. (2000).

7.4.3. The infantile N250 as a correlate of the child N250

The infantile N250 remained at the same latency from birth until 12 (24) months of age and could thus be considered the correlate of the childhood N250 (N2). Furthermore, the maturational course of the N250, gradually turning it into the adult N2 from 5 to 20 years was reported by Ponton et al. (2000). Karhu et al. (1997) averaged ERPs to consecutive tones according to their serial position in a four-tone train in 9-year-old children. It was found that with stimulus repetition, the amplitude of the N1 diminished, whereas that of the N250 increased. The authors therefore suggested that the children's N250 represents neural activity associated with sound-feature representation.

In Study III, we found a sound duration-effect on the N2 amplitude in adults, its amplitude being larger for longer tones. In newborns, we observed the same response pattern, with the reduction of the positivity at the latency zone of the adult N2 and the infantile N250 (best seen in the difference waves, Fig. 3). In longitudinally studied infants, at each age, the N250 was consistently larger in amplitude for the longer (200-ms) than for shorter (100-ms) tone and was sometimes accompanied by an N450 amplitude increase as well. This functional similarity between the infant's N250 and the adult's N2 indicates at least a partial correspondence between these components.

Several other studies also showed that the N250 reflects acoustic stimulus features such as sound frequency (Korpilahti et al., in prep), and complexity (Čeponienė et al., 2001).

Importantly, the N250 might have significant clinical value. That is, in language-impaired (Tonnquist-Uhlen, 1996a; 1996b), and dysphasic children (Korpilahti and Lang, 1994), the N250 was smaller in amplitude and longer in latency than in healthy controls. The diminished N250 amplitude or even the absence of this component was observed by our research group (Čeponienė, 2001; Balan et al., 2002) in two populations of infants with craniofacial anomalies associated with a risk for a developmental delay. In 6-month-old infants with cleft lip and palate, the negative peaks (N250-N450) were altogether missing (Čeponienė, 2001; Čeponienė et al., 2002c), and in 6-17-month-old infants with plagiocephaly the N250 amplitude was significantly smaller than in their gender and age-

matched controls (Balan et al., 2002).

7.4.4. The N450 peak

The functional significance of the N450 is not known. In some cases, it appears to be fused with the N250 (Fig. 5, 12 and 24 months of age), and is separated from it only with long ISIs (Čeponienė et al., 1998). To my knowledge, there is no evidence of the existence of the N450 in adults. The maturation of the N450 in Study IV followed the developmental course of the early phase of the late negativity (LNe; see 7.5.3), obtained in the oddball paradigm (Study V), which similarly increased in amplitude and shortened in latency from birth to 12 months of age. It was previously noted by Čeponienė et al. (1998) that a part of the LDN (corresponding to the LNe of the present work) might constitute an enhancement of the N450, since they appear at approximately the same latency, and, similarly as the N450, the LDN is mainly obtained in children. Furthermore, in children, the LDN was significantly larger in response to speech stimuli (words) than to tones (Korpilahti et al., 2001), similarly as the N450 was larger in response to vowels than that to the sinusoidal and even complex tones (Čeponienė et al., 2001). Although the functional role of the N450 remains to be determined, it might be suggested that it reflects some kind of further processing of stimulus (e.g., building neural representations, learning), which does not occur in adults under similar conditions. Indeed, the N400 was observed in adults only in paradigms, requiring an additional encoding of semantic stimulus information (Kutas and Hillyard, 1983).

7.5. Maturation of the discriminative ERP components during infancy

7.5.1. The MMN in newborns

As Studies I and II show, the majority of the neonates appear to possess effective sound-frequency and -duration discrimination mechanisms. The mismatch negativity (MMN) was obtained in all infants in Study I , both for duration increments and decrements, and in about 80% of infants in Study II, both for frequency and duration contrasts, with this incidence being higher than the highest incidence (75%) reported so far (Kurtzberg et al., 1995). This was despite the fact that the criterion for 'MMN present' in Study II was somewhat higher, -1.0 μV, as compared with the -0.75 μV, applied by Kurtzberg et al. (1995). Compared with

the latter study, in Study II, the MMN amplitude appeared to be larger and the latency shorter (171 ms vs. 220-240 ms). An MMN latency of 220-270 ms is usually reported in studies using simple tones or speech stimuli (Alho et al., 1990a; Cheour et al., 1999; Cheour-Luhtanen et al., 1995; Kurtzberg et al., 1995; Table 3). Similar amplitude and latency differences between the MMNs elicited by harmonic vs. sinusoidal tones were reported in school-age children (Čeponienė et al., 2002b) and in adults (Tervaniemi et al., 2000). It therefore appears that harmonic partials facilitate preattentive sound discrimination in newborns as they do in school-age children and in adults. This is an important conclusion, for it indicates that the negative behavioral results obtained earlier in newborns (Clarkson et al., 1989; 1991; Leventhal and Lipsitt, 1964; Trehub, 1973) can be at least partially accounted for by factors other than sensory (e.g., listening strategies, motivation, motor abilities).

The higher incidence of the duration-MMN in individual infants in Study I than in Study II might be partially accounted for by the longer analysis window (150-500 ms) used to detect the MMN. As seen in Fig. 6 B, the MMN is double-peaked as revealed in the group-averaged and also in the individual difference waves. In Study II, we measured these 2 negative peaks separately from the latency windows of 100-350 and 350-750, respectively. Thus, most probably, the later MMN peak in Study I was counted together with the earlier MMN peak, which was reported separately in Study II.

7.5.2. The subtraction type effects on the duration and frequency MMNs in newborns

The substantial sound-duration effects on the obligatory (standard-tone) ERPs in neonates (see 7.2) significantly affected the traditional deviant-minus-standard difference waves. When, in subtraction, the standard-ERP was replaced by the control-tone ERP elicited by the tone identical to the deviant, the first phase (at about 250 ms) of the duration MMN significantly increased, whereas the later phase (at about 450 ms) significantly decreased in amplitude (Fig. 6 B, bottom row). Correspondingly, when the obligatory duration effects were not controlled for, the early phase of the MMN at about 200 ms was apparently diminished when the deviant was shorter (40ms, Fig. 6, top row) than when the deviant was longer (200 ms, Fig. 6, middle row), the standard tone being the same.

For the frequency MMN, the subtraction-type effect in newborns was much smaller (non-

significant) than for the duration MMN. As discussed above, the infant responses to infrequently presented sounds result in enhanced positivity (Čeponienė et al., 2000; Kurtzberg et al., 1995). Indeed, as seen in Fig. 7 A, the response to the infrequently presented deviants is more positive than that to the standards at the latency of the P350, thus probably cutting a part of the preceding negativity lasting from 100 to 200 ms. A part of this positivity enhancement should have been eliminated by subtracting from the ERP to deviant that obtained to the same stimulus in the equiprobable condition. Thus, in the longitudinal Study V, the deviant-minus-equiprobable difference waves were computed for the MMN evaluation.

7.5.3. The maturation of the frequency and duration MMNs during the first year of life

The MMN maturation during the first year of life is shown in Figs. 8 and 9. As seen from these figures, at the group level, the MMN amplitude tended to increase with age. However, this trend was not significant mostly because the MMN was not consistent across individual infants. Although the MMN was identified in ca. 75% of infants at each age, it was not replicable within the same individuals from age to age. The inspection of the individual ERP records revealed a possible source of this variability: in some cases, the MMN was partly overlapped by the large-amplitude difference positivity (DP). This overlap was, probably, especially robust at the age of 6 months when a transient diminution of the MMN was observed (Fig. 8). Taking into consideration the substantial ERP variability in young infants, it is logical to assume that the overlap of two or more components increases this variability even more.

Supporting evidence for our suggestion that the MMN was overlapped by the large positivity was recently reported by Morr et al. (2002). The authors proposed a model illustrating the overlap between the MMN and the positive component (in their study called PC). According to that model, the sum of the MMN and PC might be either surface positive or negative, or even at the baseline, depending on the subject's age and the magnitude of change. That is, in the majority of awake infants and preschoolers in response to the 1000 vs. 1200 Hz contrast, the authors did not observe an MMN. However, in response to a larger frequency contrast (1000 Hz vs. 2000 Hz) an MMN-like negativity was elicited in all age groups from 2 to 44 months of age (Morr et al., 2002). On the grounds that it is unlikely that infants do not

discriminate the frequency contrast 1000 vs. 1200 Hz used, the authors suggested that the MMN to a smaller contrast might have been also elicited, but was masked by the large positivity in response to deviant stimuli, similarly as in our Study V.

The duration-MMN in the present Study V was also followed by the difference positivity (DP), best seen at C3 in 3-, 6-, and 9-month-old infants (Fig. 9). The duration MMN was delayed in latency compared with frequency MMN by about 100-150 ms, similarly as in Study II. Just like the duration MMN, the DP was delayed in latency to an extent corresponding to the later onset of stimulus change in Duration condition. In adults, the P3a response, following the MMN (Michie et al., 2000), was similarly delayed in latency. (The nature of the difference positivity observed in the present work was discussed in 7.5.5.)

Thus, the MMN was elicited in the majority of infants at each age studied, and it slightly increased in amplitude during the first year of life (for the pooled data of the Duration and Frequency-oddball conditions, the age effect on the MMN amplitude was significant). A typical duration-MMN latency delay compared with frequency-MMN (see Figs. 7C and 9) resembling that in adults (Joutsiniemi et al., 1998; Tervaniemi et al., 1999; Michie et al., 2000) supports the change-detection nature of the infants' MMN. Substantial inter- and intraindividual variability possibly contingent on factors other than neural sensory processing was, however, revealed in the longitudinal Study V.

7.5.3. Early and late phases of the LDN

In both Studies I and II a second negative peak in the difference waves was observed (herein called the LDN; Figs. 6 and 7). In Study II, the LDN, measured separately from the MMN, had a scalp distribution similar to that of the MMN. However, the MMN latency, being time-locked to the change onset, was significantly shorter in the Frequency than Duration condition, whereas the LDN latency was significantly shorter in the Duration rather than Frequency condition. This suggests that the LDN might not represent the same process in the Duration and Frequency conditions. Indeed, it is highly unlikely that the component of the same functional significance would occur almost 200 ms earlier for the less salient and delayed duration contrast than for the more salient and earlier frequency contrast. Another contradictory result was that the LDN, obtained under the same experimental condition in older children (Cheour et al., submitted), appeared to be longer in latency (peaking at about 500 ms) than the peak assumed to be the LDN in newborns (about 400 ms; Fig. 6C). Even

though no significant differences were reported for the LDN latency among 4- and 8-year old children and adults (Cheour et al., submitted, see also Fig. 6C), examination of these figures showed that the LDN latency tends to get shorter with age rather than longer.

Therefore it seems, that the later peak of the newborn's difference wave in Duration condition might not be identical to the child LDN but rather is a continuation of the first peak (MMN). As seen in Fig. 6 (A, B), the double-peaked structure might be artificially formed as a result of the latency shift of the N250 and/or P350 peaks in response to the standard and deviant stimuli due to their different durations. In fact, the 'comparison process' may take longer time in infants than adults, resulting in a prolonged MMN. Indeed, Näätänen et al. (1982) mentioned that just slightly differing deviants ('proximates') evoked a more prolonged MMN, which might be attributed to subjective uncertainty. The shorter and sharper MMN in the Frequency-oddball condition might be due to the more salient difference between the deviant and standard and/or to an artificial termination of the MMN by its overlap with the DP.

Further, in our longitudinally studied infants (Study V, Fig. 8) at least two consecutive negative phases of the LDN with different scalp distributions and maturational trajectories were observed in the latency range of 350-750 ms. The early phase (the LNe) peaked at about 350-450 ms and was significantly smaller at the temporal than at any other electrodes, just like the MMN in this condition. It increased in amplitude during the first year of life and decreased in latency in a similar way as the N450 did (Study IV; see also 7.4.4.).

An analysis with only frontal and central electrodes included showed that the LNe was larger over the right than left hemisphere, this right-hemisphere dominance being similar to that of the MMN (Paavilainen et al., 1991). This early LDN phase was also shorter in latency (365-400 ms, Table 6, Fig. 8), than the LDN usually reported in children (450-550 ms), and might thus be caused by the long-lasting MMN. Gomot et al. (2000) showed that the multiphase, long-lasting MMN response at 5-7 years (100-400 ms) transforms into a well-defined peak (100-250 ms) at 8-10 years and in adults (100-210 ms), possibly due to the improved synchronization of the different subcomponents of the MMN (Gomot et al., 2000) and/or to decreased trial-to-trial latency variability with age (see 7.1.2).

The later phase of the LDN (the LNl) commenced at about 550 ms and in some infants probably continued beyond the analysis window. The LNl was mostly observable at the frontal electrodes (Fig. 8, best seen in 6- and 12-month-olds). It was significantly smaller at

the temporal and parietal than at the frontal and central electrodes, that is, it was anterior in scalp-distribution to that of the LNe, which showed large negative amplitudes also parietally. I suggest that the LNl might receive a contribution from the Nc component, a frontally predominant negativity elicited by salient events and usually following the P3a at about 600-800 ms in children (Courchesne, 1990; see 3.4.1. and 7.5.4). A similar Nc-like late frontal negativity commencing at about 600 ms has been previously reported in newborns (Kurtzberg et al., 1984) and in 2-3 months-old infants (Dehaene-Lambertz and Dehaene, 1994; Deregnier et al., 2000) and was suggested by the authors to be related to novelty detection even though in these studies (Dehaene-Lambertz and Dehaene, 1994; Kurtzberg et al., 1984), the deviant stimuli were not truly 'novel' in that they were the same throughout the experiment: /ta/ in Kurtzberg et al. (1984) and /ga/ or /ba/ in Dehaene-Lambertz and Dehaene (1994) study.

7.5.4. The late negativity elicited by novel sounds

The late negativity elicited by the novel sound, also consisted of two peaks (Study V, Fig.10). 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 deviant stimuli. Similarly, Escera et al. (2001) reported two phases of the late frontal negativity in response to novel and deviant sounds in adults, with only the later phase being larger in response to the novel than deviant stimuli. Since the novel stimuli are assumed to catch the subject's attention even in the unattended paradigm, we might suggest that the later phase of the LDN in infants, enlarged in response to novel sounds, depends on the degree of orienting/distraction of the infant.

7.5.5. Difference positivity in infants – a possible analogue of the early phase of the adult P3a

In our longitudinal Study V, the deviant-minus-equiprobable difference waves for the frequency contrast were analyzed in order to minimize the contribution of the obligatory effects in the subtraction. Nevertheless, a significant positive peak at about 300 ms was observed in the deviant-minus-equiprobable difference waves (herein called the difference positivity, DP), which was especially robust at 3 and 6 months of age and the most

prominent at the central electrodes (Study V, Fig. 8).

Therefore, we suggested that the DP is probably related to change detection rather than to the activity of new sensory elements, and thus might represent the infant's analogue of the adult P3a.

One can argue that the difference positivity might still have resulted from the release from refractoriness, since the probability of the deviant stimuli was lower than that of the equiprobably presented identical stimulus (15% versus 33%). However, as Fig. 8 demonstrates, the scalp distributions of the P350 in response to the equiprobable and deviant tones are different at the parietal and temporal electrodes. While the response to the deviant tone is more positive at the latency of the P350 than that to the equiprobable tone at the central electrodes (Fig. 8), it is more negative at the same latency at the parietal electrodes, resulting in a negativity in the latter difference waves. This scalp distribution resembles that of the early phase of the P3a (150-250 ms) which is largest over the central scalp with positive amplitudes over the frontal scalp and inverted, negative amplitudes over the posterior scalp (Gumenyuk et al., 2001).

An additional experiment using 'novel' sounds was carried out in newborn and 2-year-old infants in order to further test the hypothesis that the infantile DP is an analogue of the adult P3a. The novel stimuli, known to elicit a prominent P3a in adults (Escera et al., 2000, 2001) and children (Čeponienė et al., under revision; Gumenyuk et al., 2001) were used in this additional Novel condition. As expected, the results demonstrated that the DP was significantly enhanced in response to the novel sounds as compared with that to the frequency deviants (Fig. 10). This is in good agreement with earlier findings showing that the P3a amplitude is increased as a function of the magnitude of stimulus change (Yago et al., 2001). In addition, the response to the novel sounds in 2-year-old children even showed the second phase of the P3a, which tended to be largest frontally, just like the late P3a in school-age children (Čeponienė et al., under revision; Gumenyuk et al., 2001).

Vaughan and Kurtzberg (1992) suggested that the positive components of infants at about 300 ms in latency cannot be analogue of the adult P3a, for the latencies of the obligatory ERP components are in the range of 200-300 ms during the first year; therefore, according to them, the latencies of the processing-contingent components must be longer. The present series of studies showed, however, that the processing of the frequency and duration in newborn infants is reflected by the ERPs at the same latency as in adults. In addition, the DP

latency was the same in newborns and in 2-year-old children (Fig. 10). A similar positivity at about 300-360 ms, elicited by novel sounds, was noted by Courchesne (1990) to remain strikingly similar in latency and centrally predominant scalp topography from 4 to 44 years of age.

My suggestion is that the infant DP might be an analogue of the early phase of the P3a (150-250 ms) only. The later phase of the P3a in adults, maximal frontally and enhanced by attention, was suggested by Escera et al. (1998) to index the actual attention switch. The early phase of the P3a, maximal at the vertex and strongly diminishing in amplitude posteriorly and laterally, was insensitive to attentional manipulations (Escera et al., 1998). Thus it was suggested by Escera et al., (1998) to reflect neural processes other than attentional reorientation, such as the violation of a multi-modal sensory model of the external world (Yamaguchi and Knight, 1992). Thus, the early phase of the P3a might be related to change-detection mechanism rather than an attentional switch and represent a part of the infant's change-detection response.

7.6. The maturing auditory ERPs and infants' functional development

From developmental perspective, the orienting response should be one of the first to mature since it is of critical biological significance (Pavlov, 1927) and also is the primer function for any cognitive development to occur.

The P3a component of the ERP, was proposed by Squires et al., (1975) to be a central marker of the orienting response (see also 3.3). According to the present work, the infant's analog of the adult P3a might be the difference positivity (DP), obtained from birth and remained amazingly stable in latency (about 300 ms) throughout infancy. Interestingly, the maturational profile of the infant's DP in our longitudinal Study V appears to correlate with that of the behavioral studies of orienting and attention.

Orienting in infants has most commonly been measured by using head turning, heart-rate deceleration, and motor quieting. Using these measures, infants have shown the ability to orient to sounds in the first days of life (Morrongiello and Clifton, 1984). At this age, it is the physical features of stimuli (intensity, pitch, etc.) that largely mediate stimulus preference (Gomes et al., 2000). From 1 to 3 months of age, developmental changes in orienting and attentiveness are very rapid and are paralleled by the onset of social behavior (smiling,

vocalizing) (Farroni et al., 2002; Shucard et al., 1987). Shucard et al. (1987) proposed that the development of behavioral responsivity might result in increased electrophysiological responsivity: indeed, the most remarkable ERP change (almost three-fold increase of the P150/P350 and DP amplitudes) occurs between birth and 3 months of age.

Further decrease of the DP amplitude by the age of 9-12 months parallels the evidence for the reduction in the orienting response to novel visual stimuli in 9 month-old infants (Gomes et al., 2000). This might result from the acquired experience: step-by-step infants learn what is relevant and what is not and, subsequently, learn to ignore irrelevant information. However, very young infants have not yet formed the representation of 'what is relevant', since they have no experience to base upon. Therefore, their attention might be captured by any yet unfamiliar stimulus, since it could be potentially relevant.

Therefore, it appears that in our longitudinal Study V, the relatively large frequency change carried by the acoustically rich deviant tones caused involuntary orienting in infants, resulting in the P3a-like positivity. The overlap between the negative-polarity MMN and the positive-polarity P3a (see 7.5.5) might result in the varying difference wave voltage - negative or positive, depending on the relative contributions. 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 (Geisler and Polich, 1992; Polich and Kok, 1995) and distractibility (Kaipio et al., 2000; Kilpeläinen et al., 1999a), which widely vary not only from subject to subject, but also with age. In addition, the auditory sensitivity in infants still matures through the first year of life (Tharpe and Ashmead, 2001), and therefore varies from infant to infant as well. Thus, the same auditory change might be only preconsciously registered by some infants, whereas in others, the same change can be sufficient to cause orienting/distraction, resulting in the P3a.

It is also worth noting that the infant P3a seems to depend on arousal, just as its adult analogue does (Polich and Kok, 1995). As it is seen in Fig. 1, the P350 in response to deviant stimuli (infantile P3a) was significantly larger in awake infants than in those in quiet sleep, and tended even to be larger than in infants in active sleep. This supports the proposed orienting nature of this component, since in awake state, the orienting process is much more pronounced than in sleep. Active sleep in infants has, however, been related to vigilant attention (Anders et al., 1985; Gabriel et al., 1981), whereas quiet sleep is less influenced by environmental stimuli.

7.7. Looking forward

Information clarifying the age-related parameters of the ERPs in normal individuals should help to create a tool for the assessment of developmental disorders. Although general developmental ERP trends are clear (see 8), the intersubject variability of the latencies and amplitudes in infants is large. Therefore, the distributions of the ERP values in normal and abnormal populations may overlap. However, it should be emphasized that the waveshape of the novel-sound ERPs was surprisingly consistent amongst the infants, contrary to the substantial variability of the deviant-stimulus ERP. It might be suggested that higher-energy signals (that is, acoustically rich or high in intensity) cause better synchronization of the synaptic events, and thus result in more stable responses. Therefore, it appears that high-energy sounds are the best to be employed in infant research.

On the other hand, poor replicability of the ERPs in the same infants might index inconsistency of the brain response (see 7.1.2).

Finally, it would be of great interest and importance to further test our (Study V) hypothesis of the differential auditory stimulus-change processing by 6-9 month-old infants. In our study (Kushnerenko et al., 2002) in prematurely born infants, the large positivity in response to the deviant tone was still predominant at the 12 months corrected age, whereas in the age-matched controls, the large MMN was observed at the same latency. The larger deviant-tone positivity (presumably infant's P3a) in pre-term than in full-term group was also obtained in 4-7-month-old infants by Alho et al. (Alho et al., 1990b) and was proposed by the authors to be associated with the high distractibility of pre-term infants (Astbury et al., 1983). Thus, positive amplitudes at the latency of the MMN might reflect increased distractibility in pre-term infants.

It might be beneficial, therefore, to combine the psychological and electrophysiological measures in order to determine whether the larger amplitude of the P3a in response to deviant stimuli is associated with enhanced levels of distractibility or a higher auditory sensitivity/reactivity.

8. Conclusions

I. Infant's obligatory ERPs maturation

All ERP peaks observable at the age of 12 months and later in childhood (P150, N250, P350, and N450) were identifiable already at birth. During infancy, the amplitudes of the ERP peaks increased and their latencies got slightly shorter (for P150 and N450 only). The main maturational change from birth to 3 months of age was a remarkable increase in the positive amplitudes (the P150 and P350 peaks). By 6 months of age, the growth of these peaks terminated, whereas the N250 peak became robust. The second half of the first year of life was characterized by the strong growth of the negative amplitudes (the N250 and N450 peaks). I suggest that the observed maturational changes in the ERP waveform are related to the different maturational courses of the underlying generators, with the relative strength of their activity changing during the first year of life.

II. Infant's ERP correlates of sound duration

The newborn infant's ERP was significantly influenced by the duration of the auditory stimulus at the latency zone of the N250 peak (a precursor of the adult N2). The pattern of duration-related changes observed in newborn infants was very similar to that in adults, also occurring in the latency zone of the adult N2. The results suggested that a) the infant's N250 peak might represent acoustic stimulus features as the child's N250 does; b) sound duration is processed already by neonates and in a similar way as in adulthood.

III. Maturation of infant's change-detection response

The majority of infants were found to possess neural mechanisms for sound frequency and duration discrimination, as was indexed by the mismatch negativity potential (MMN). In addition, the longitudinal investigation of the change-detection response revealed the developmental increase of the positive ERP response to stimulus change, which substantially varied in the same infants from age to age. I suggest that this positive response represents the early phase of the P3a response. This conclusion was based on the similarity in the elicitation conditions, waveshape, and latency of the infant's difference-wave positivity to that of the children and adult P3a.

The positive response emerged at the latency 250-300 ms, in infants partly overlapping the MMN. I suggest that this overlap rendered the reduction of the MMN recorded amplitude and diminished the MMN replicability in individual infants.

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