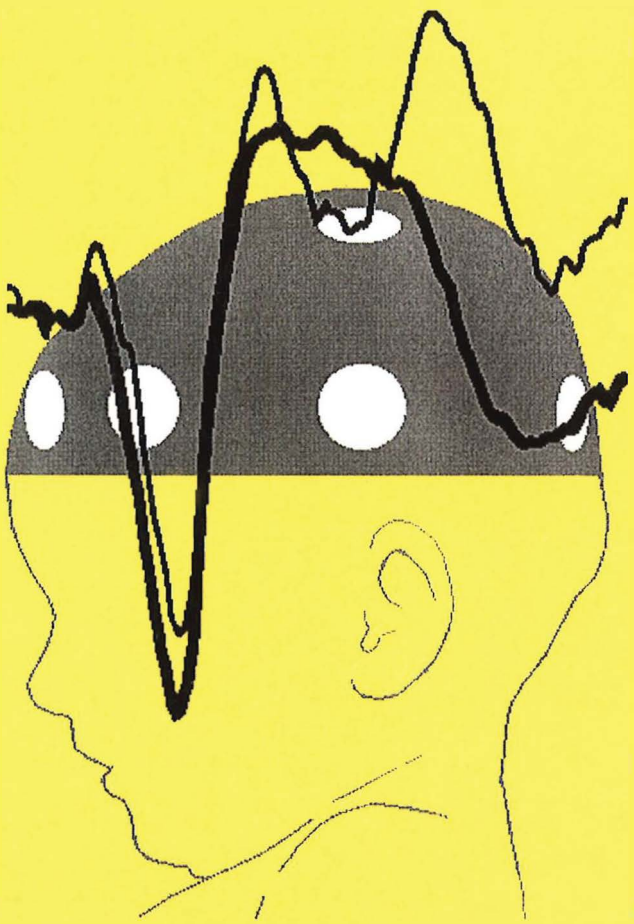
Paavo H.T. Leppänen

Brain Responses to Changes in Tone and Speech Stimuli in Infants with and without a Risk for Familial Dyslexia



UNIVERSITY OF JYVÄSKYLÄ

JYVÄSKYLÄ LONGITUDINAL STUDY OF DYSLEXIA

JYVÄSKYLÄ STUDIES IN EDUCATION, PSYCHOLOGY AND SOCIAL RESEARCH 151

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ABSTRACT

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Yhteenveto: Aivovasteet ääni- ja puheärsykkeiden muutoksiin vauvoilla, joilla on ja vauvoilla, joilla ei ole riskiä suvussa esiintyvään dysleksiaan
Diss.

Developmental dyslexia, a specific disorder of learning to read, is widely acknowledged as being often genetically transmitted, but as yet, little is known of the early precursors of the disorder. In the present study the brain electrical responses to changes in auditory oddball paradigms were studied both at birth and at the age of six months in a group of young infants from families with a genetic background of developmental dyslexia (at-risk group) and in a group of infants without such a background (control group). Both group differences and developmental features of event-related potentials (ERPs) were under focus. At birth, the ERPs to the deviating rare /ka/ stimuli with an interstimulus interval of 855 ms were different between the groups, but not with a shorter interval of 425 ms. At six months of age some differences between the groups were found in their responses to the frequent /kaa/ stimulus. At this age, more marked group differences were found in the ERPs to the duration change of a silence period, an acoustic cue for consonant lengths, embedded within a pseudoword (/ata/ vs. /atta/). The results suggest, that the at-risk group differ from the control group both in the basic responsiveness to auditory/speech stimuli and in the responses to changes in the temporal structure of speech stimuli, as well as in terms of how the stimulus presentation context affects the ERPs. The clearest developmental feature at birth was a waveform consisting of a long lasting positive deflection, which was generated by all deviant stimulus types, whether pure tones or speech stimuli differing in their temporal features. By the age of six months, this slow waveform pattern had been transformed into a wave complex with clearly distinguishable deflections, reflecting a more mature negative-positive-negative deflection structure. The responses to deviant stimuli were, typically still at this age, positively displaced in relation to those to the standard stimuli, suggesting maturational effects on early ERPs. Some evidence for an adult-like negatively displaced mismatch negativity (MMN) response was also found.

Keywords: brain event-related potentials, oddball paradigm, infants, developmental dyslexia, genetic risk, developmental effects, auditory processing, pitch, speech sound duration

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Jyväskylä Longitudinal Study of Dyslexia (JLD)

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Newark, NJ, USA
March, 1999

Paavo Leppänen

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the data presented in the following articles, which are referred to in the text by their Roman numerals (I-V).

I. Leppänen, P. H. T., & Lyytinen, H. (1997). Auditory event-related potentials in the study of developmental language-related disorders. *Audiology & Neuro-Otology*, 2, 308-340.

II. Leppänen, P. H. T., Eklund, K. M., & Lyytinen, H. (1997). Event-related brain potentials to change in rapidly presented acoustic stimuli in newborns. *Developmental Neuropsychology*, 13, 175-204.

III. Pihko, E., Leppänen, P. H. T., Eklund, K. M., Cheour, M., Guttorm, T. K., & Lyytinen, H. (1999, in press). Cortical responses of infants with and without a genetic risk for dyslexia: I. Age effects. *NeuroReport*, 10 (5).

IV. Leppänen, P. H. T., Pihko, E., Eklund, K. M., & Lyytinen, H. (1999, in press). Cortical responses of infants with and without a genetic risk for dyslexia: II. Group effects. *NeuroReport*, 10 (5).

V. Leppänen, P. H. T., Pihko, E., Eklund, K. M., Guttorm, T. K., Aro, M., Richardson, U., & Lyytinen, H. (submitted). Brain responses reveal temporal processing differences in infants at a risk for dyslexia.

ABBREVIATIONS AND TERMINOLOGY

AEPs	Auditory evoked potentials
AS	Active sleep
BAEPs	Brainstem auditory evoked potentials
CA	Conceptional age (gestational age + chronological age since birth)
CAEP	Cortical auditory evoked potentials
CV	Consonant-vowel
CNS	Central nervous system
EEG	Electroencephalography
ERPs	Event-related potentials
EMG	Electromyography
GA	Gestational age
HVS	High-voltage slow waves
ISI	Interstimulus interval
LVI	Low-voltage irregular
MEG	Magnetoencephalography
MGN	Medial geniculate nucleus
MLAEPs	Middle latency auditory evoked potentials
MMN	Mismatch negativity
MRI	Magnetic resonance imaging
PET	Positron emission tomography
QS	Quiet sleep
REM	Rapid eye movements
SOA	Stimulus onset asynchrony
TA	Trace alternate

CONTENTS

INTRODUCTION

In the present study the purpose was to investigate the differences in the brain event-related activation of groups of infants from families with or without a familial background of developmental dyslexia. Dyslexia, a difficulty to learn to read fluently, is one of the major specific learning disabilities causing severe handicap in many children and affecting not only their school achievement but also increasingly their career choices. Reading is based on a complex set of skills and cognitive processes, some of which have been identified, such as phonological processing. The underlying causes for the failure to acquire these skills still remain, however, largely unknown.

There is strong evidence that dyslexia, at least its common forms, are genetically transmitted (Gilger, Pennington, & DeFries, 1991; Pennington, 1991a, b, 1995; Wood, Flowers, Buchsbaum, & Tallal, 1991). Therefore, infants born to families with affected parent/parents (and close relatives) are at elevated risk for the disorder (see e. g. Lyytinen, Leinonen, Nikula, Aro, & Leiwo, 1995) and one way to trace early precursors or markers of dyslexia is to study these infants. Prospective studies make it also possible to better differentiate between factors present already at birth or at very early infancy, from acquired ones, or from ones which are more prone to be a complex result of interaction with learning, and affected by ways of compensating for possible processing weaknesses. One reasonable approach would be to study phenotypic functions that have been shown to be deficient in affected populations. In many cases the study of such functions is complicated in very young infants due to task demands, like focused attention and problem solving skills. At the same time there are good reasons to try to go behind these higher level skills and explore the more basic 'lower level' cognitive and perceptual processes on which the development of these skills can be thought to depend.

Perhaps the most widely studied, and generally acknowledged, phenotypic deficit of dyslexia is linked to phonological processing difficulties (Bradley, 1992; Bradley & Bryant, 1978, 1983; Goswami & Bryant, 1990; Lundberg, Olofsson, & Wall, 1980; Wagner & Torgesen, 1987; Wagner, Torgesen, & Rashotte, 1994; for reviews, see e. g.; Lyon, 1995; Pennington, 1991a). This deficit can, in turn, result from underlying auditory and/or speech

processing deviations, such as altered perceptual or discrimination processes. Recent electrophysiological brain research, behavioural auditory and speech perception studies, as well as some neurobiological findings (discussed in the review included here, Article I, Leppänen & Lyytinen, 1997) seem to support the lower processing level assumption, though perhaps not exclusively (see also McBride-Chang, 1995).

Accumulating evidence for a more specific basic level processing deficit behind phonological problems has recently raised considerable interest. This is a deficit related to the perception of rapid changes and the temporal structure of auditory and speech elements (Hari & Kiesilä, 1996; McAnally & Stein, 1997; Reed, 1989; Stark & Tallal, 1988; Tallal, 1980; for reviews, see Farmer & Klein, 1995; Richardson, 1998; Tallal & Curtiss, 1990; Tallal, Miller, & Fitch, 1993).[1] In the context of the Finnish language this kind of a difficulty could be related to the differentiation of short and long vowels and consonants, which requires both exact timing and perception of the temporal structure of speech elements and which has also been found to be problematic for Finnish dyslexics (Lyytinen, Ahonen, & Räsänen, 1994; Lyytinen et al., 1995; Richardson, 1998).

Based on these considerations the main focus of this work is in the processing of changes in the temporal structure of speech elements as revealed by the auditory event-related potential (ERP) experiments. This study is a part of the Jyväskylä Longitudinal Study of Dyslexia (JLD; for a more detailed description of this research project, see Lyytinen, 1997; Lyytinen et al., 1994; Lyytinen et al., 1995) and within its framework, the ultimate goal is to investigate the predictive value of the developmentally studied auditory ERPs as early markers of language development and precursors of familial dyslexia. At this early stage of the longitudinal research, this predictive aspect is limited to the investigation of ERP-differences between the at-risk group and control groups both at birth and at the age of six months. The ERP-technique is particularly suitable for detection of early processing deviations, because it makes it possible to follow a course of certain brain processes over time with the precision of tens of milliseconds. Additionally, with multiple electrode sites, one can locate brain areas involved in the processing of the stimulus information within a certain time range. Further, the method works well with infants, because no overt behavioural response is required.

The first publication included in this work, Article I (Leppänen & Lyytinen, 1997), gives a general overview of the ERP studies involving clinical populations with language impairment and developmental dyslexia. In addition, Article I outlines the rationale for the approach used in this work, of which a summary with an update is presented in the chapters below. The empirical work is presented in Articles II-V. The paradigm used in the ERP-experiments is a typical oddball paradigm, in which a well-studied component, the mismatch negativity (MMN; Näätänen, 1992; Näätänen & Alho, 1997;

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1 Recent research suggests, though, that the question may be of a deficit seen also in fast motor-sensory and visual processing (Lovegrove, 1993; Stein & Fowler, 1985; Stein & Walsh, 1997).

Näätänen, Gaillard, & Mäntysalo, 1978), is usually generated in adults. Because very little was known of the responses in young infants obtained with this paradigm at the time of initiating the present research, the first empirical study (Article II; Leppänen, Eklund, & Lyytinen, 1997) comprises of a methodological experiment to facilitate the interpretation of the data representing responses to the temporal aspects, and the findings are therefore, reported only from the control group infants. The second and third studies (Article III; Pihko, Leppänen, Eklund, Cheour, Guttorm, & Lyytinen, 1999, and Article IV; Leppänen, Pihko, Eklund, & Lyytinen, 1999) focus on developmental changes and group differences between at-risk and control infants in the brain electrical activation generated by a syllable/vowel duration change measured during sleep at the birth and during wakefulness at the age of six months. The fourth study (Article V; Leppänen, Pihko, Eklund, Guttorm, Aro, Richardson, & Lyytinen, submitted) focuses on the group differences in the ERPs elicited by changes in consonant duration embedded in pseudowords in six-month-old at-risk and control infants.

Development of the brain and auditory system

Below a brief description of the development of the brain, the auditory system and perceptual abilities related to the stimulation used in the current experiments is presented in order to provide a general background to the factors affecting the developmental aspects of electrical brain responses. The overview also shows that the auditory system is, though in a developing state, relatively well 'equipped' already at birth.

Cortical development

The cerebral cortex of humans develops in two major phases (for reviews on neural and cortical development, see e. g. Casaer, 1993; Creutzfeldt, 1995; Dekaban, 1970; Huttenlocher, 1994; Johnson, 1998; Rakic, 1991; Spreen, Risser, & Edgell, 1995). In the first phase during the prenatal period cortical neurons are formed and assembled into a multilayered laminar structure. Precursors of neurons are born near the cerebral ventricles, from where they migrate to the cortical plate: the first arriving neurons form the lower cortical layers and the neurons born later pass these earlier neurons and form the upper layers (Huttenlocher, 1994). This development starts at the gestational age (GA) of about 10 weeks and by around the 7th month of gestation the vast majority of cerebral cortex neurons have reached their location at the cortical plate, which at this stage has the appearance of a primitive, three-layered cortex, with an outer marginal zone (later layer I), the cortical plate itself, and below it the inner plexiform layer (part of the subcortical intermediary zone; Creutzfeldt, 1995; Huttenlocher, 1994; Johnson, 1998).

The second major phase, starting during the second trimester of gestation and continuing during the postnatal period, is the development of cortical connections involving the growth of axons, dendrites and the complexity of their tree-structure, and synaptic circuits (Huttenlocher, 1994). At birth the average weight of the brain is about 335 gm (Dekaban, 1970), the volume being about one-third of that of the adult brain. The following increase in the size of the brain is largely due to the growth of neurons and their connections (Huttenlocher, 1994). The lamination of the cerebral cortex is also poorly defined at birth (Dekaban, 1970). At the age of six months the brain weighs about 660 gm and the general configuration of the brain and relative length of the frontal and temporal lobes are now more mature (Dekaban, 1970).

Synaptic overproduction, synapse elimination and neuronal loss. During the first postnatal year there are rapid bursts of increase in synaptic density that occur at different ages for different cortical areas. For example, in the visual cortex the most dramatic increase of synapses occurs between two and four months with a similar timetable for the primary auditory cortex. In these areas, the peak in the number of synapses is reached by the end of the first year, in contrast to the prefrontal areas, where the peak is not reached until after the first year (Huttenlocher, 1994; Johnson, 1998). It is interesting that, for example in the visual cortex, the total number of synapses at the age of six months is much larger than in adulthood, which Huttenlocher (1994) regards as an indication of the overproduction of synapses in the cerebral cortex and holds this overproduction as an anatomical substrate for some of the functional properties of the infant brain. The overproduction is followed by synaptic elimination, both by axon withdrawal and the pruning of axon collaterals, starting around the age of one year (Creutzfeldt, 1995; Huttenlocher, 1994) and extending beyond the age of 3 years (Spreen et al., 1995).

In addition, whole neurons are eliminated during early development. Evidence from animal studies suggests that brain cell death is related to the inability of neurons to find their target areas (Casaer, 1993; see also Creutzfeldt, 1995). According to Huttenlocher (1994), neuronal death is less important in the increasingly complex neural systems (e. g. when comparing the spinal cord to the visual cortex), while synapse elimination, in contrast, seems to increase with the increasing of the complexity of the neural systems. He suggests that large pools of functionally unspecified synapses may be necessary for the development of the complex neural circuits that underlie functions such as language and memory. Casaer (1993) suggests that this kind of synaptic redundancy secures many complex short- and long-distance connections; functionally inappropriate afferent and efferent cortical fibres are either withdrawn or pruned (see also Creutzfeldt, 1995). This period of the overproduction and elimination of synapses coincides with the period of functional plasticity in infants suggesting a relation between the two developmental phenomena (Huttenlocher, 1994).

Myelination. During the early postnatal period, starting just prior to birth, neuronal pathways become increasingly surrounded by the fatty sheath consisting of glial cell membranes. This process, called myelination, increases the efficiency of information transmission from about 2 m/s to 50 m/s in a fully

myelinated axon (Casaer, 1993; Johnson, 1998). At birth the white matter of the cortex for the most part is not yet myelinated with the exception of some fibers of the primary afferent projection systems, including a proportion of somatic sensory fibers, as well as visual and auditory fibers from the thalamic areas to the corresponding cortical areas (Dekaban, 1970). Myelination continues throughout the first three to four months after birth, the sensory areas myelinating before the motor and cortical association areas, the myelination of the latter not reaching adult level until early puberty (Johnson, 1998).

It is not, as yet, clearly understood how myelination of a given cortical area is related to its function. Synaptic activity of the cortex is present well before myelination begins (Creutzfeldt, 1995). What is known is that myelination affects the conduction velocity of the fibres, which has been related to the latency decrease of cortical evoked potentials from infancy to adulthood (Casaer, 1993; Creutzfeldt, 1995). According to Creutzfeldt (1995) the late and temporally asynchronous myelination of different areas indicates that the undeveloped and insufficiently myelinated brain responds more slowly, and that brain activities in different areas are differently correlated in infants compared to adults. Casaer (1993) interestingly suggests, that it is not myelination as such which is important but rather that interacting brain centres are provided with fast signal-conducting pathways.

Development of the auditory system

In the mature auditory system air vibration, which sounds consist of, is transmitted to the fluid within the cochlea producing vibratory movement of the basilar membrane in the inner ear and bending the hair cells lying between the basilar and stiffer tectorial membrane (e. g. Spreen et al., 1995; for a comprehensive description of the auditory system, see Edelman, Gall, & Cowan, 1988). The hair cell receptors stimulate the fibres of the eighth (auditory nerve), the axons of which ascend into the dorsal and ventral cochlear nuclei of the medulla, and from there through the superior olivary nucleus to the contra- and ipsilateral side of the brain via the lateral lemniscus tract on each side of the brainstem. Passing the lateral lemniscus the auditory signal arrives into the inferior colliculus of the midbrain and the medial geniculate body of the thalamus before projecting to the auditory cortex of the temporal lobe.

According to the review by Spreen et al. (1995) on the development of the auditory system, the ear starts to develop at around 22 GA days at which time otic placodes, or the ectodermal auditory precursors of the inner ear and the vestibular system emerge. By 4 to 5 GA weeks the cochlear and labyrinth lobes (forming a part of the vestibular system) are differentiated and by around 5 weeks the external auditory meatus (canal) originates. At 6 weeks, the cochlea is a short curved tube and at about 7 weeks the middle ear ossicles appear reaching their final size by 6-8 GA months. The hair cells in the organ Corti develop at around 4 to 5 GA months. The peripheral auditory system is thus developed and functionally complete at birth. The auditory nerve is also developed and fairly well myelinated at birth. The brainstem and thalamic

pathway development is also relatively complete by birth, but the myelination of the projection fibers to the cortex is not complete. By the age of six months the thalamo-olivary tract, the majority of the thalamic nuclei and the auditory projection fibers to the primary auditory cortex are relatively well myelinated (Dekaban, 1970); however, the myelination of the auditory system continues to the age of 4 years (Spreen et al., 1995).

Development of pitch and duration differentiation in early infancy

Next, I briefly describe the development of pitch- and duration-perception based on evidence obtained with a variety of, mostly behavioural, methods.

Auditory development has been extensively studied, especially during the past two decades, with several methods, including elicited motor responses, cardiac and electrodermal responses, visual fixation responses, high amplitude sucking measures and conditioning paradigms (for elaborate reviews, see e. g. Aslin, Jusczyk, & Pisoni, 1998; Aslin, Pisoni, & Jusczyk, 1983; Morse, 1974, 1979; for procedures, see e. g. Gravel, 1989; Nozza, 1987). We know now, for example, that a variety of sounds are available to the fetus within the uterus during the prenatal period, of which the dominant biological sound is generated by the mother's heart beat (for a review, see e. g. DeCasper & Spence, 1991). Newborns are also known to be more responsive to speech passages that had been recited aloud during their prenatal period than to novel passages, suggesting that the fetuses had learned and remembered something about the environmental acoustic cues (DeCasper & Spence, 1988). Infants exhibit also a preference for the parental language very soon after birth (see Eimas, 1996).

Another widely studied general basic aspect of infant audition is absolute sensitivity, or thresholds, to certain tone frequencies, which in other vertebrates is related to the developmental changes of the external and middle ears, changes in the structure and electrochemistry of the inner ear as well as the developmental time course of the cochlea (Werner & Bargones, 1992). In 2-week-old infants the absolute threshold is about 50 dB poorer, in 1-to-6-month-olds 35-40 dB poorer, and in 6-to-12-month olds 10-15 dB poorer than in adults (see Aslin et al., 1998; see also Werner & Bargones, 1992; Werner & Gillenwater, 1990). Infant-adult differences are dependent on stimulus frequencies; neonates have in general better sensitivity at low frequencies, but due to progressive improvement in high-frequency sensitivity, by the age of six months infants approach adult level in higher frequencies while improving more slowly in low frequency sensitivity (Werner & Bargones, 1992). Early abilities to deal with phonetic information is yet another widely studied area. Developmental studies of phonetic discrimination have shown that by the age of six months, infants are able to discriminate between nearly every phonetic contrast on which they have been tested (see e. g. (Werker & Polka, 1993). I now turn to more specific research related to the stimulation used in this work.

Pitch differentiation. Response sensitivity for different frequencies, for example, have been typically studied using habituation paradigms, in which gross motor behaviour or sucking or heart rate has been monitored during

signal changes (Werner & Bargones, 1992). Early behavioural studies failed to demonstrate that newborn infants could discriminate between tones with different frequencies embedded in stimulus streams (for reviews, see Aslin et al., 1983; Morse, 1974). One-month-olds, on the other hand, have been demonstrated to be able to discriminate between frequencies of for instance 200 vs. 500 Hz, and 6-week-olds between frequencies within a range such as 150-250 Hz vs. 1500-2500 Hz and 4-month-olds differences between 1100 vs. 1900 Hz. At a little older than six-months, infants can discriminate between pitch differences as small as 2 % (see Olsho, Schoon, Sakai, Turpin, & Sperduto, 1982). In general, infants are better in discriminating between high frequencies (such as between 4000 vs. 8000 Hz) as compared to low frequencies (e. g. 250-2000 Hz; see Werner & Bargones, 1992). Interestingly, little new evidence has come forth about the basic pitch discrimination abilities of young infants in more recent studies (for a review see, Aslin et al., 1998). It has been shown, for example, that with high stimulus intensities and high frequencies (up to 4000 Hz) 3-month-old infants can reach a discrimination threshold of 3 %, which is only somewhat higher than that of 1 % for adults (see Aslin et al., 1998). It has been suggested that frequency discrimination is not solely dependent on the frequency information of the used stimuli; for example, temporal information is suggested as being used in discriminating between low frequencies (Werner, 1992), suggesting the complexity of such a seemingly simple auditory process as low level discrimination.

Perception of durational features. Durational cues are important, for example, in segmenting speech signal as well as dealing with prosodic information. There is, however, much less early behavioural research on infants' abilities to differentiate between durational elements than on frequency discrimination. Findings show that 10-week-olds are sensitive to temporal-order information and detect changes in the relative timing of two events at stimulus onset and that 2-3-month old infants can discriminate between short temporal patterns consisting of different groupings of pure tones, such as those consisting of 4 tones and extending up to one second (Morrongiello, 1988). Five-month-olds are able to differentiate between longer patterns, such as a 2-4-tone grouping vs. 4-2-tone grouping spanning 2.6 seconds, but it is not until the age of one year that infants are capable of reliably discriminating more complex pattern changes, such as in the number of elements per group as well as in the number of these groups (Morrongiello, 1988). These measures do not, however, directly reflect an ability to differentiate between durations as such. Eilers, Bull, Oller and Lewis (1984) found that 5-11-month-old infants could discriminate between speech-like stimuli, which differed only in vowel duration. The infants performed above the chance level for identifying the lengthening a vowel at the level of 33, 67 and 100 %, respectively. The discrimination of vowel durations with difference ratios of less than 67 % seemed, however, to be difficult for the infants (Eilers et al., 1984). Werner (1992) has reviewed other few existing related studies. For example, 3-month-old infants show much poorer temporal resolution than adults in conditions in which a probe tone has to be detected, when it is preceded by a noise masker. Also, 3-, 6-, and 12-month-olds' gap detection thresholds are much greater (varying in different studies from around

25 to 60-80 ms) than those of adults (varying from 10 to 20 ms; see also Aslin et al., 1998; Benasich & Tallal, 1996). On the other hand, even 1-4-month-olds can discriminate as small as 20 ms differences in voice onset time (VOT), when this difference provides information that is sufficient to distinguish two-syllable initial stop consonants from different voicing categories (e. g. /b/ vs. /p^h/; see Eimas, 1996). Performance both on VOT and gap detection tasks depends on temporal acuity, perhaps more so in the latter if no other discriminative cues are present.

Overall, substantial developmental changes take place within early infancy in the basic auditory functions. Frequency differences, which young infants have been capable of discriminating between in behavioural studies have, for example, been relatively high. These differences are also higher in comparison to the pitch differences used in the current experiments. However, as Aslin and colleagues (1998) point out, by the age of six months infants are, generally speaking only mildly poorer than adults across most of the basic auditory capacities, taking into consideration the methodological limitations. It is interesting, for example that newborn infants' relatively poor performance in early studies of discrimination was, in Morse's (1974) view, more dependent on the information processing constraints of paradigms used rather than the infants' discriminative abilities (see also Aslin et al., 1998). Also, according to Schneider and Trehub (1992), much of the variation, for example in threshold measures, between infant and adult performance can be attributed to methodological factors, such as differences in false-alarm rates in infant and adult responses as well as differences between sound-field and earphone test conditions. Therefore, one may expect better discriminative responses with psychophysiological measures, that are not dependent on the infants' overt response.

ERPs in the study of auditory processing in infants

In the study of early auditory cognition and basic processes that might be impaired, for example, in groups of infants at risk for developmental language related disorders, the event-related potential (ERP) technique offers information that behavioural methods do not. ERPs are measured with the usual EEG-techniques. EEG is usually thought to result from brain electrical activation, current flow, related to summated postsynaptic potentials in vertically oriented pyramidal neuron populations. From the EEG it is, however, difficult to see any reliably distinguishable responses to a certain external event, for example a sound stimulus, because event-related responses are small in amplitude (typically 1-15 μV) and are obscured by much larger deflections (usually 30-150 μV) of the ongoing background EEG. However, by averaging numerous time-locked EEG-epochs, usually from twenty-thirty to more than a hundred, across a stimulus event, the response to a given stimulus can be clearly differentiated,

as other spontaneous and random activity not time-locked to that specific stimulus cancels itself and summates as zero (for a detailed description of the technique, its rationale and applications, see Regan, 1989)[2]. With ERPs it is possible to follow a course of the brain's activity in time with the precision of tens of milliseconds and, thus, to obtain knowledge, not only of the end product of processing, but also of the sequence, timing, and stages of specific processes. ERPs also render valuable information concerning auditory cognition, even in cases, when no conscious attention is directed to the stimulus event (Näätänen, 1992). Thus, this technique is suitable for studying early developmental as well as pre-attentive auditory functions related to discrimination and perception.

Maturational factors affect greatly, as is evident on the basis of the short overview of the brain development above, electrophysiological activity, like EEG or the ERPs of the developing brain. For example, conduction velocity varies with the diameter of the nerve fibre, the length of the nerve, as well as with the thickness of the myelin sheath and distance between Ranvier nodes, and is thus affected by developmental changes in myelination, which is also seen at the level of the peripheral nervous system (Parano, Uncini, De Vivo, & Lovelace, 1993). Other maturational factors also affect early ERPs, such as changes in the location, type and geometric relations of pre- and postsynaptic elements, the response variability of neural ensembles, cognitive developmental/functional changes, and the developmental time-table of their interaction (Courchesne, 1990; Kurtzberg et al., 1984b; van der Molen & Molenaar, 1994; for ERP variability in development, see Thomas et al., 1997). Therefore, one has to be aware of the maturational factors on electrophysiological correlates one uses, when interpreting early cognitive functions. Furthermore, if one also intends to use ERPs to investigate differences in cognitive processing not due to age variation between, say, control and clinical populations, it has to be shown that ERPs are sensitive to the variation in specific processing demands that the experimental conditions/assigned tasks impose on the subjects (van der Molen & Molenaar, 1994).

Infant spontaneous EEG and arousal states

Early findings of infant EEG (reviewed by Dreyfus-Brisac, 1964) revealed that the morphology and topographical distribution of premature EEG changes rapidly between the fifth and seventh months of gestation, and that waking and

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2 In the ERP-technique, it is assumed that 1) the background EEG acts as noise for the ERP-signal, 2) the signal waveform is generated by a process that stays stationary from trial to trial, 3) the noise, background EEG, is produced by a stationary random process, and that 4) the noise samples are uncorrelated from trial to trial (Regan, 1989). Several other reviews and textbooks are available (for general description and theoretical discussion on the technique and different components, see e. g. Mendel (1980); Papanicolaou & Johnstone (1984); Gevins & Cutillo (1986); Squires & Ollo (1986); Coles, Gratton, & Fabiani (1990); Näätänen (1992), Ritter & Ruchkin (1992); for general articles on the development of ERPs, see e. g. Courchesne (1990); Friedman (1991); Thomas & Crow (1994).

sleep patterns are not differentiated in EEG before the eighth GA month. Electrical activity is also discontinuous in these prenatal months. By the eighth month both differentiation of wakefulness and sleep EEGs, and a continuous pattern of EEG emerge. From the eighth to ninth months on, three distinct arousal states related to EEG patterns can be seen: drowsiness, sleep, and wakefulness EEGs.

At birth, in full term infants the EEG has distinct patterns that alternate in different arousal states (see Anders, Embde, & Parmelee, 1971; Lombroso, 1985): Low voltage irregular (LVI) EEG, which is characterised with both theta (5-8 Hz) and slow (1-5 Hz) activity, a voltage between 14 - 35 μV, and which is similar in all scalp regions and with little variation during a one minute epoch. Trace alternate (TA) is characterised with bursts of high voltage slow waves (0.3 - 3 Hz), with occasional rapid low voltage waves superimposed on and sharp 2 - 4 Hz waves interspersed between the slow waves. The bursts last 3 - 8 seconds followed by 4 - 8 seconds of mixed frequency activity. High voltage slow wave (HVS) pattern, in turn, is a continuous, moderately rhythmic 0.5 - 4 Hz EEG with a voltage up to 50 - 150 μV. Mixed (M) EEG pattern has high voltage and low voltage polyrhythmic waves, intermingled shortly after each other and the amplitude is lower than in the HVS pattern.

Newborn infants generally go from a waking state, via a short transition for 15-20 minutes, into active sleep, with LVI and M as the most typical EEG patterns, and then through a short transition for another 15-20 minutes into quiet sleep characterised with TA and HVS (Anders et al., 1971; Lombroso, 1985; Zeskind & Marshall, 1991). Quiet sleep is a controlled state characterised by behavioural quiescence, regularity of physiological activity, and the lack of eye movements (Anders et al., 1971). The proportion of quiet sleep to total sleep time grows with an infant's conceptional age reaching about 40 % between 39-42 conceptional weeks (see e. g. Kohyama & Iwakawa, 1990; cf. also Chamberlain, 1987, who in his review on newborns reports the equivalent proportion to be ca. 50 %). However, individual differences in early postnatal life, both in the proportional pattern of sleep states as well as in the duration of sleep states have been reported (e. g. Thoman & Whitney, 1989).

At birth, the waking state EEG pattern resembles that of active sleep (Lombroso, 1985). According to Samson-Dollfus, Forthomme, and Caprion (1964), by the age of three months the basic wakefulness EEG varies between 4-6 Hz. By five months, EEG is well organised, rhythmical, differentiated in occipital lead activity, and has 50-100 μV voltage with the eyes closed, the rhythmical activity disappearing when the eyes are opened (see also Bell & Fox, 1994). After the age of six months the EEG has a rhythm of 5-8 Hz with a rapidly changing amplitude. These infant EEG rhythms are slower than the typical adult beta activity of 13/14 - 30 Hz during an alert and wakefulness state (Shagass, 1972).

However, no consistent correlation has been established between auditory evoked potentials and background EEG activity (see e. g. Arlinger & Walker, 1975; Engel & Mistein, 1971; Graziani, Katz, Cracco, Cracco, & Weitzman, 1974). Furthermore, according to Duclaux, Challamel, Collet, Roullet-Solignac, and Revol (1991), modifications in auditory evoked potentials according to

hemispheres (found in their study), and differences in the responses to deviant, and standard stimuli cannot be explained by differences in background EEG.

Infant ERPs elicited by equiprobable stimuli presented with slow rates

Early attempts to record auditory evoked potentials with newborn infants failed, with no reliable responses found at the temporal or vertex scalp areas for broad-spectrum noise stimuli (Ellingson, 1964). However, since then several auditory evoked potential or ERP[3] studies (for reviews, see Kurtzberg, 1982; Molfese & Betz, 1988; Thomas & Crow, 1994) with neonates and young infants have been published, showing that infant ERPs respond differentially to a number of various types of auditory stimuli, like tone pips and speech sounds (see e. g. Kurtzberg, Stone, & Vaughan, 1986; Molfese, Burger-Judisch, & Hans, 1991; Molfese & Molfese, 1985, 1986; Novak, Kurtzberg, Kreuzer, & Vaughan, 1989; Thomas, Shucard, Shucard, & Campos, 1989).

Typical to these studies has been that the stimuli have been presented with equal probabilities and with rather long interstimulus intervals (ISI), running from around two seconds to more than eight seconds. The ERPs of full-term infants to auditory stimuli presented in these kind of conditions, and when measured within a few days from birth, typically have a rather shallow waveform, in comparison to typical adult ERPs, with a major positive deflection at around 200-300 ms, often followed by a later negativity peaking after about 500 ms (e. g. Barnet, Ohlrich, Weiss, & Shanks, 1975; Ellingson, Danahy, Nelson, & Lathrop, 1974; Graziani et al., 1974; Kurtzberg, Hilpert, Kruezer, & Vaughan, 1984a; Kurtzberg et al., 1986; Novak et al., 1989; Pasman, Rotteveel, de Graaf, Stegeman, & Visco, 1992; Rotteveel et al., 1986; Weitzman & Graziani, 1968). This response with a slow positive-negative deflection pattern reflects the basic or obligatory auditory response to an auditory stimulus independent of the nature of the stimulus (e. g. speech sound or pure tone).

The ERPs undergo developmental changes throughout early infancy; from slow immature long lasting deflections, a mature waveform with clearly distinguishable peaks gradually emerges. Kurtzberg et al. (1984a; see also Novak et al., 1989) have described five maturational levels through which the ERPs of young infants evolve until the age of three months: the least mature ERPs, like those of pre-terms, show negative polarity at midline and lateral

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3 I have excluded here auditory evoked potential studies dealing with brainstem responses (ABR, elicited within 10 ms from the stimulus onset) thought to be generated in the afferent sensory pathways that transmit the signal to the central processing systems, as well as middle latency responses (MLR, within a latency of ca. 50 ms) that are also classified as exogenous evoked potentials (Coles et al., 1990; Loveless, 1983; Picton, Stapells, & Campbell, 1981). These early exogenous components are invariably elicited whenever the sensory system is intact (Coles et al., 1990) and are, therefore, often used for clinical purposes in the diagnosis of neurological diseases, and are one of the exclusionary criteria for developmental dyslexia (for reviews on ABR and MLR, see e. g. Mendel, 1980; Musiek, Geurkink, Weider, & Donnelly, 1984; Picton & Durieux-Smith, 1988; on assessment of infants and children, see also Kileny & Robertson, 1985; Guerit, 1985; Pettigrew, Henderson-Smart, & Edwards, 1990; Stapells & Kurtzberg, 1991).

sites, and the most mature ERPs positive polarity at both these sites. The mature ERPs of full-terms show positive polarity at midline electrode locations and negative at temporal locations. Pre-term infants have an immature morphology more often than full-terms even though the age at measurement is corrected to term. These findings replicate the early results by Weitzman & Graziani (1968); in their study, the positive response at a latency of about 300 ms was prominent in full-terms at both the lateral (between temporal and midline sites) and midline electrodes. These developmental changes are understandable in the light of the earlier described maturational changes in the brain. The existence of poorly myelinated auditory pathways and primary cortical reception areas with immature synaptic connectivity fits well with the newborn shallow ERP waveform.

Infant ERPs elicited in oddball paradigms

The above described exogenous auditory ERPs do not, however, reflect the discriminative processes of young infants, especially those based on comparison processes between prior auditory input and new deviating auditory events. These kind of processes, which are dependent on the sound stream context and which are capable of flexibly utilising the context information for dealing with new input, are obviously necessary for learning language. Recently, increasing interest has arisen in infant ERP studies for utilising variations of an experimental procedure, the MMN paradigm, that has been widely and extensively used to study adult passive discrimination abilities. In adults, ERPs to stimulus change are usually studied using oddball paradigms, in which a rarely occurring deviating stimulus embedded among a repeated frequent stimulus, typically generates an MMN ERP component (Näätänen et al., 1978; for reviews, see Näätänen, 1990, 1992, 1995; Näätänen & Alho, 1995, 1997). This interest has been facilitated by the occurrence of the response to almost any kind of deviating feature of auditory stimuli in adults, and by the fact that MMN can be recorded even when no attention is paid to the stimuli (Alho, Woods, & Algazi, 1992; Lyytinen, Blomberg, & Näätänen, 1992; Näätänen, 1992; Näätänen, Paavilainen, Tiitinen, Jiang, & Alho, 1993; Paavilainen, Tiitinen, Alho, & Näätänen, 1993; Sams, Paavilainen, Alho, & Näätänen, 1985a). Since an ERP-wave may reflect a summation of many simultaneous brain processes (Näätänen & Picton, 1987), a so-called difference wave obtained by subtracting the response to a frequently presented standard stimulus from the response to an infrequent deviant stimulus, is thought to best represent the MMN-response (Näätänen, 1990).

The MMN-component is thought to reflect an auditory detection change process based on the functioning of sensory memory. According to a theory proposed by Näätänen (1984, 1992), a frequently repeated tone in a series of tones forms a memory trace or neural model of the acoustic features of this tone in the sensory memory. This trace can last up to about eight to ten seconds (Böttcher-Gandor & Ullsperger, 1992; Mäntysalo & Näätänen, 1987). It is then assumed that the sensory input generated by a deviating tone does not fit with

the existing model or memory trace, thereby resulting in a mismatch process reflected in a negative deflection reaching its maximum at ca. 200 ms over the frontal and central areas of the scalp (Giard, Perrin, Pernier, & Bouchet, 1990; Näätänen, 1990, 1992; Paavilainen, Alho, Reinikainen, Sams, & Näätänen, 1991). MMN is, thus, thought to indicate a discriminative response to a change in a stimulus sequence, not a response to some stimulus per se. The major source for this response is shown to reside in the supratemporal auditory cortex (Giard et al., 1990; Hari et al., 1984; Kaukoranta, Sams, Hari, Hämäläinen, & Näätänen, 1989; Sams et al., 1985b). This mismatch process may, then, also initiate brain processes triggering higher executive cognitive functions related to attention, long term memory, and other mechanisms under voluntary control, for example the conscious discrimination of change in auditory information (Näätänen, 1988, 1991, 1992; Paavilainen et al., 1991; Sams et al., 1985a; Öhman, 1979).

Recent evidence also suggests that MMN is affected by long term memory traces, such as language specific speech representations; MMN is larger to deviant speech stimuli involving critical cues relevant in one's own language context as opposed to stimuli with irrelevant or unfamiliar speech elements (Näätänen et al., 1997). For example, Finnish adults have an attenuated MMN when an Estonian vowel, which does not belong to the Finnish vowel-system, is presented as the deviant stimulus, whereas no such attenuation occurs in Estonian persons or when using a vowel that belongs to both Estonian and Finnish vowel-systems.

Studies of child MMN are, however, relatively few and recent. MMN has been observed both in normal children (e. g. Ceponiene, Cheour, & Näätänen, in press; Kraus, McGee, Sharma, Carrell, & Nicol, 1992; Kraus et al., 1993; Kurtzberg, Vaughan, Kreuzer, & Fliegler, 1995; Leppänen, Laukkonen, & Lyytinen, 1992; Lyytinen & Lorys-Vernon, 1989) and clinical groups of children (e. g. Cheour et al., 1997b; Korpilahti, 1996; Korpilahti & Lang, 1994; Kraus et al., 1996; Winsberg, Javitt, Silipo, & Doneshka, 1993). In normal children of school age, the MMN-response resembles a typical adult MMN in that it has approximately an equal latency, peak amplitude of the difference wave, as well as a fronto-central scalp distribution. However, some differences also exist between child and adult ERPs measured in typical MMN paradigms; for example, unlike in adults, a fairly large response to a frequently presented standard stimulus has been observed in children (e. g. Korpilahti & Lang, 1994; Leppänen et al., 1992).

ERP-studies in infants around or below the age of six months are also relatively recent and few (for reviews, see Cheour, 1998; Cheour et al., 1998a). Alho, Sainio, Sajaniemi, Reinikainen, and Näätänen (1990a) have reported an adult MMN-like response in newborns to a deviant tone of 1200 Hz (with a probability of 10 %) embedded amongst standard tones of 1000 Hz. The effect was seen in six out of eight subjects. The negatively displaced deviant deflection peaked at ca. 270-300 ms (at Fz and Cz), and thus, somewhat later than typically seen in adults, in whom the corresponding latency is usually around or less than 200 ms. The midline distribution of the negativity, however, resembled that of a typical adult response. The response to the standard tone was very

small, which according to the authors was due to the fast stimulus rate employed (onset-to-onset ISI of 610 ms). In their review article, Kurtzberg et al. (1995) also reported a MMN-like response to a pitch change in 14 of 25 newborns (1200 Hz, 15 % vs. 1000 Hz) using ISIs of 750 and 1000 ms. The MMN was defined as any negative deflection of the difference wave (deviant- minus standard-response) greater than 0.75 μV occurring between 150-450 ms at Fz. The peak latencies of negativity were 241 and 298 ms for the 750 and 1000 ms onset-to-onset ISIs, respectively.

A MMN-like response in newborn ERPs has also been reported to a change in phonetic elements, a deviant vowel /i/, the end point of the Finnish (Klatt-synthesized) /i/-/y/ continuum, when presented among frequently occurring /y/-vowels during quiet sleep (Cheour-Luhtanen et al., 1995). These vowels were presented with a fixed onset-to-onset ISI of 800 ms. The negative difference wave deflection peaked at 200-250 ms with a maximum at the frontal and central scalp areas. It was also observed that the MMN-like negativity was smaller, when the deviant was a boundary /y/i/ stimulus, i.e., when the difference between the deviating and standard stimuli was not so clear. This latter finding is consistent with the observations in adult studies showing that the amplitude of MMN is enhanced when the difference between deviating and standard stimuli is increased (e. g. Sams et al., 1985a). Using the same stimuli Cheour et al. (1997a) also reported a negative displacement to the deviant stimuli in three-month-olds. Similarly, in six-month-old infants a negative difference wave to a vowel change was reported (Cheour et al., 1998b), when using vowels common to both the Finnish and Estonian language (/ö/, 10% vs. /e/). However, at the age of 12 months, MMN was reported to be smaller to an Estonian vowel /õ/, not present in Finnish, in comparison to the Finnish /ö/. This result was taken as evidence of language-dependent memory traces being present in infants already before the age of one year.

Cheour-Luhtanen et al. (1996) have reported a MMN-like negativity, even in 11 preterm infants aged 30-35 conceptional weeks using the same stimuli and onset-to-onset ISI as in their earlier study (Cheour-Luhtanen et al., 1995). They interpreted their results as evidence for MMN being the ontogenetically earliest discriminative response. However, the standard /y/ stimulus also generated a response, which was more negative than the corresponding response at birth, especially at the central leads, suggesting a more immature waveform than in newborns (cf. Cheour-Luhtanen et al., 1995; see also the discussion above on the maturational effects on ERPs). Therefore, an alternative explanation cannot be totally excluded on the basis of their data. Namely, the response to the deviant /i/, being presented with long inter-deviant intervals, could also reflect a non-refractory less mature exogenous response to the formant frequencies of the deviant stimulus.

There are also oddball studies, in which no MMN-like response has been reported. Kurtzberg et al. (1986) have reported, for example, a negative response to rarely occurring speech sounds (/da/ or /ta/, 14 % vs. /ta/ or /da/) at a latency of 800 - 900 ms in newborns. This was not, however, suggested to be a representation of the MMN-response but rather a modality non-specific Nc-response to novelty which has its own developmental time

course (for a review, see Courchesne, 1990). Duclaux et al. (1991) have reported, on the other hand, that responses to a 2000 Hz deviant stimulus (with a probability of 20 % among 1000 Hz standard tones and a presentation rate of 1 tone/2 sec) measured in 6-week-olds were positively displaced in relation to responses to the standard stimuli in quiet sleep, reaching significance only at the left hemisphere. At this hemisphere the positive deflection generated by the deviant stimulus had a bifasic peak at a latency of ca. 350-400 ms; the smaller positivity of the corresponding standard response peaked ca. 20 ms earlier. McIsaac and Polich (1992) have also reported a somewhat similar discriminative positive response at a latency of ca. 600 ms in 5-10-month-old infants to a pitch deviant tone (2000 Hz vs. 1000 Hz standard tone) while awake. Comparable late positive responses to deviant tones were also reported in full-term infants (with CA ranging from 44-55 weeks) by Tokioka, Pearce, and Crowell (1995). Common to all these studies have been long ISIs ranging from 2-3.3 seconds. McIsaac and Polich (1992) related the late positivity to long term memory processes, rather than to the sensory memory processes thought to be reflected in MMN, which is reasonable in view of the long latencies used. Also, in their review article, Alho and Cheour (1997) point out that a relatively long ISI might lead to a failure to record MMN, as for example in the study by Kurtzberg et al. (1986), because MMN is known to attenuate with an increasing ISI (e. g. Mäntysalo & Näätänen, 1987).

However, failures to demonstrate MMN in oddball paradigms are not limited to paradigms with long ISIs. For example, in the above cited study of Kurtzberg et al. (1995), in which ISIs of 750 and 1000 ms were used, more than half of the infants failed to show a MMN-like response and a considerable number showed predominantly positive responses. Alho, Sajaniemi, Niittyvuopio, Sainio, and Näätänen (1990b) have also found positive displacements for pitch deviations in 4-7-month-old infants, Dehaene-Lambertz and Dehaene (1994) in 2-3-month-olds, and Dehaene-Lambertz and Baillet (1998) have reported dipoles reflecting frontal positivity in 2- to 3- month old infants for deviating speech sounds. In all these studies relatively short onset-to-onset ISIs (610, 600 and 600 ms, respectively) were used. As infants were awake in these studies, Alho and Cheour (1997) suggest that the observed positivities in the studies of Alho et al. (1990b) and Dehaene-Lambertz & Dehaene (1994) might be related to attention, and that these positivities might then obscure overlapping MMN. However, it is not excluded that the lack of a clear MMN and observed positivities could also reflect genuine maturational differences in ERPs between infants and adults (for a discussion on this issue in relation to the present data, see General discussion).

The effect of arousal state development on ERPs

It has been known for a long time that the ERPs of newborns are affected by sleep states (e. g. Ellingson et al., 1974; see also the above discussion on EEG). Ellingson et. al. (1974) reported, for example, that auditory evoked potentials to 1000 Hz pure-tones presented with irregular intervals of 8 sec or more were

generally clearest and of highest amplitude during quiet sleep. Duclaux et al. (1991) also reported, that ERPs to pitch change (2000 Hz, 20 % vs. 1000 Hz) in 6-week-olds were larger in quiet sleep than in active sleep. In addition, the response to the deviant tone differed from that to the standard tone only during quiet sleep. Thus, if a MMN-like response is expected to be present during sleep in newborns, it is not unreasonable to expect it to occur during this state. In adults, a MMN-like deflection has been reported to occur during sleep stage 2 in conjunction with K-complexes (Sallinen, Kaartinen, & Lyytinen, 1994; cf. Paavilainen et al., 1987, who failed to find MMN in sleep; they classified sleep only into various global stages without looking for a response in specific microstates, as in the one characterised by the occurrence of K-complexes). It is also quiet sleep, from which K-complexes emerge later in infancy (Metcalfe, Mondale, & Butler, 1971).

Taken together, in the light of maturational changes in brain morphology and the functional connectivity of neural networks in developing brains, we should not be surprised to see responses that do not correspond to adult ERPs. Further, from the above overview it is evident that infant ERP-deflections cannot be interpreted in a straightforward manner as functionally corresponding to adult ERPs at the equivalent latencies.

Developmental dyslexia and genetic risk

Developmental dyslexia: defining the participant population

The participants in the experiments of the present work were young infants born to parents with familial developmental dyslexia, and is the main factor which has determined the stimulus material used in these studies. On the basis of the screening of dyslexic parents for the JLD prospective study, the proportion of middle age dyslexic adults in the Finnish population is estimated to be comparable to the proportions for other nationalities (Lyytinen et al., 1995; cf. Pennington, 1995). The total occurrence rate of dyslexia that affects every day living is ca. 6 % of the Finnish population and the prevalence of familial dyslexia is ca. 3 %.

The DSM-IV (Diagnostic and Statistical Manual of Mental Disorders™, 1994) uses the term *reading disorder* (RD; 315.00) for *dyslexia* and the ICD-10 classification (1993) uses the term *specific reading disorder* (F81.0) for one of the learning disabilities belonging to a main category of disorders of psychological development (F80-89).[4] Developmental dyslexia was defined in 1968 by The

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4 The terms *'dyslexia'* or *'reading disorder'* (RD) are used in this work instead of reading impairment, reading difficulties and reading disability. Other terms also appear regularly in the literature. A related disability in the classification systems is the *disorder of written expression* (the DSM-IV, 1994: 315.2 and the ICD-10, 1993: F81.1). In practice, many dyslexics have also writing problems, but as a diagnostic category of its own this disability is not reviewed in this work.

Research Group on Developmental Dyslexia of the World Federation of Neurology as "a disorder manifested by difficulty in learning to read despite conventional instruction, adequate intelligence, and socio-cultural opportunity ... and dependent upon fundamental cognitive disabilities which are frequently of constitutional origin" (Critchley, 1970, p. 11). This is a typical, often employed definition of exclusion (used also by the two former classification systems). Accordingly, the etiology is not thought to be explained by mental retardation, central nervous system (CNS) damage or external brain injury, nor by delayed maturation resulting from emotional or physical factors other than CNS problems (Pennington, 1991a). Dyslexia is rather assumed to result from a combination of complicated interwoven genetic and environmental factors (Pennington, 1995).

The basic assumptions of the exclusionary definition have prevailed in dyslexia diagnosis (Pennington, 1991a). For example, a typical IQ criterion has usually been a score of at least 80 to 85 as either a performance or total score. It should be noted, though, that recently the IQ discrepancy criterion has been strongly criticised as an unnecessary addition to the deviation from the expected reading age level (Siegel, 1989; Stanovich, 1991). Recently, attempts have also been made to formulate a definition that is composed of inclusionary statements, which have strong empirical support (Lyon, 1995). Such definitions serve to summarise the most commonly accepted characteristics based on recent research findings. Currently dyslexia is regarded as a language-based disorder that is characterised by difficulties in single word decoding (Lyon, 1995).

Although the developmental language disorders (DLD) as a diagnostic group are not in the focus of this work, it is possible that the same underlying factors also contribute, at least partly, to these problems and they are, therefore, dealt with in Article I[5]. It is also not excluded that there might exist a kind of continuum with language impairments at one end and reading problems at the other, at least at the level of processing difficulties related to these problems. For example, children with DLD have been reported to manifest, similarly to dyslexics, problems in auditory discrimination and perception, especially in noisy conditions, and in the perception of rapidly presented sequential information (Elliot & Hammer, 1988; Elliot, Hammer, & Scholl, 1989; Morgan, 1984; Tallal & Newcombe, 1978; Tallal & Piercy, 1973; Tallal, Stark, & Mellits, 1985a; Tallal, Stark, & Mellits, 1985b; Wright et al., 1997; for reviews on the latter, see Tallal & Curtiss, 1990; Curtiss & Tallal, 1991). Auditory processing

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5 DLD is a communication disorder characterised by failure to acquire language at a normal age and at a normal rate (for a summary, see Miller, 1991; Baker & Cantwell, 1989). The DSM-IV (1994) defines five different diagnostic categories of communication disorders, of which *expressive* and *mixed receptive-expressive language disorders* (315.31) and *phonological disorder* (315.39) are the closest to developmental language disorders. In the ICD-10 classification (1993) learning disabilities belong to a main category of disorders of psychological development (F80-89). Three sub-groupings of *specific developmental speech and language disorders* (F80), *including specific speech articulation disorder* (F80.0), *expressive language disorder* (F80.1), and *receptive language disorder* (F80.2), correspond to the criteria used in selecting DLD participants for the review Article I.

problems have, in fact, been proposed as one of the causal explanations for the disorder (Miller, 1991), much in a similar way as for dyslexia (see below). However, the issue of the relationship between the two disorders is beyond the scope of this dissertation (for a discussion on their relationship, see e. g. Catts, 1993).

Genetic risk for dyslexia

The rationale for comparing infants born to dyslexic parents and infants with no indication of dyslexia in the family is based on the assumption that dyslexia runs in families in proportions much higher than would be expected on the basis of occurrence rates in the general population. The median increase in risk for a child who has an affected parent to become dyslexic him-/herself, is about eight times the population risk which is estimated at 5 % (parent recurrence ranges from 27 - 49 %; Pennington, 1995). This increase is understandable in the light of the evidence, briefly discussed below, indicating that developmental forms of dyslexia are often genetically transmitted (e. g. Gilger et al., 1991; Pennington, 1995; Pennington & Smith, 1983). These findings have lead to a growing interest in the search for the early precursors of dyslexia with a predictive value in children who are at risk for the disorder.

Two approaches could be possible in studying the genetic effects on learning disabilities (see Pennington & Smith, 1983). According to the first approach, the disorder with evidence of familiality is first identified and then subtypes that appear consistently in families are sought for. The second option would be to identify a population sharing a common genetic risk-factor, for example a sex-chromosome anomaly, and then to observe how many of that population will eventually develop a learning difficulty. Dyslexia studies would typically fall into the first category. Pennington (1995) outlines four successive steps in moving from phenotype to genotype: *familiality, heritability* (twin and adoption studies), *mode of transmission* (segregation analysis), and *gene locations* (linkage analysis).

Already at the beginning of this century it was well known, for example, from many case studies that dyslexic children had relatives that were also affected (for a review, see Pennington & Smith, 1983, see also Pennington, 1995). Two important aspects of dyslexia, reported in these cases and substantiated by subsequent research, are that dyslexia is rather specific in a sense that affected persons manifest intact skills in other domains, such as mathematics and spatial tasks, and that severity of the disorder varies individually and that it persists into adulthood. In these early studies, the average recurrence rate among first-degree relatives has been as high as 30%. Transmission across two or more generations has also been often reported, and further, that dyslexia often co-occurs with other language-disorders.

Studies of the familiality of dyslexia provide important and necessary, but not in themselves sufficient, information for demonstrating genetic influence. Pennington (1995) has reviewed four studies by Finucci, Guthrie, Childs, Abbey, and Childs (1976), Hallgren (1950), Vogler, DeFries, and Decker (1985),

and Gilger et al. (1991), that have addressed the rates of recurrence and possible mechanisms of transmission. Taken together, sibling recurrence is consistent in these studies ranging between 38.5-43%, as is also a parental recurrence rate ranging from 27% to 49%. The median relative increase in risk to become a dyslexic if a child has a dyslexic parent is about eight times that of the population risk which is estimated at 5%. These data would fit a simple autosomal dominant model of transmission, although, as Pennington (1995) points out, other transmission mechanisms are also consistent with the data. He further notifies that the fact, that the parent and sibling recurrence rates are almost equal, speaks against a simple autosomal recessive model.

Twin studies provide further support for the genetic origins of dyslexia. As monozygotic (MZ) twins possess twice the genetic similarity of dizygotic (DZ) twins (whose coefficient of genetic relationship is .50), they should show about double as much of a resemblance at a behavioural level for a genetically determined trait (e. g. Plomin, Owen, McGuffin, 1994). To put it in another way: if a trait is totally due to genes, the expected concordance rate for MZs is 100 %. Thus, smaller concordance rates indicate environmental effects.[6] Pennington (1995) has reviewed two methodologically adequate twin studies of dyslexia. In the Twin Family Reading study both poor reading and poor spelling heritability scores were high, .44 (±.11) and .62 (±.14), respectively. They were even higher, .75 (±.15), for problems in nonword reading, which has been regarded as the best single estimate or diagnostic sign for dyslexia. In another twin study at the Institute for Psychiatry in London the spelling deficit was also significantly heritable (the heritability score being .61 ± .39). In the latter reading was not heritable. According to Pennington (1995) the reason for this is not clear, but he points out that the sample was much larger in the Twin Family Reading study. These heritability scores, which describe the proportion of phenotypic variance in a population that can be attributed to genetic influence (e. g. Plomin et al., 1994), are fairly high providing strong support for a genetic influence on dyslexia.

The strongest evidence that leaves little room for doubt about the genetic transmission of some disorders comes from quantitative genetics. The latest

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6 An important assumption in the twin method is that environmental effects are approximately equal for MZs and DZs thus cancelling themselves in the comparison process (Brody, 1988). However, as pointed out by the critics of the twin studies, evidence suggest that MZs experience a more similar environment than DZs in some respects (Brody, 1988). Brody (1988) outlines several objections against this critic. For example, the critic can be held as valid only if it can be shown that the greater environmental similarities MZs experience affect the relevant phenotypic characteristics. Further, the greater environmental similarities for MZs might themselves also be attributed to genetic influence (the idea of 'choosing' an environment according to one's genetically determined temperament factors). Thus, the twin studies provide a natural experiment in which the genetic basis for phenotypic resemblance can be estimated. According to Pennington (1995), while early twin studies found greater MZ- than DZ-concordance for dyslexia, they had methodological weaknesses, such as a lack of formal diagnosis and a failure to analyse separately same- and opposite-sex DZs (analysing them together may decrease the DZ concordance if the examined trait has a sex difference in prevalence).

linkage methods, such as 'affected-relative-pair' linkage designs, are fairly robust in revealing genetic base in that they do not depend on assumptions about the mode of transmission (Plomin et al., 1994). Using modern linkage analyses dyslexia has been linked to markers on chromosome 15 and also possibly to those on chromosome 6 (see e. g. Plomin et al., 1994).

Characteristics associated with auditory processing among individuals with developmental dyslexia

Auditory and/or speech processing deviations in dyslexics

Performance on phonological awareness tasks has been known to be one of the best predictors of early reading skills, and in line with this, problems in phonological processing are widely thought to be one possible crucial factor contributing to the emergence of developmental dyslexia (Bradley, 1992; Bradley & Bryant, 1978, 1983; Goswami & Bryant, 1990; Lundberg et al., 1980; Lyon, 1995; Pennington, 1991a; Wagner & Torgesen, 1987; Wagner et al., 1994). Problems in phonological processing are also very persistent, even in adulthood (Bruck, 1992), suggesting that the question is not so much of a developmental lag, but rather of a more persisting processing deviation or deficit. Poor phonological processing is usually related to difficulties in word recognition that requires the phonological recoding skills necessary for grapheme-phoneme conversion (Rack, Snowling, & Olson, 1992). Phonological recoding skills are especially needed in the early stages of learning to read, and in cases of unfamiliar words, in contrast to mature reading, where especially familiar words are recoded automatically and fast on a visual basis (for a study and discussion on the relationship of phonological skills and text reading, see Leinonen et al., submitted).

Word decoding and phonological processing problems may be assumed, in turn, to result at least partly from more basic lower level processing or speech perception deficits (de Gelder & Vroomen, 1998; McBride-Chang, 1995; Reed, 1989; Tallal, 1980). Dyslexics are reported to differ, for example, in perception of speech sounds in noise (Brady, Shankweiler, & Mann, 1983), in their nonspeech frequency discrimination (Weirdt, 1988), in rhythmic pattern discrimination (Zurif & Carson, 1970), in processing of brief auditory cues or rapidly changing sequential or amplitude information (Hari & Kiesilä, 1996; McAnally & Stein, 1997; Reed, 1989; Stark & Tallal, 1988; Tallal, 1980; for reviews, see Farmer & Klein, 1995; Richardson, 1998; Tallal & Curtiss, 1990; Tallal et al., 1993; for a more detailed discussion of related findings, see Article I).

For example, in an early study, Tallal (1980) found that dyslexics with language problems were poorer than normal readers in deciding the order of two stimuli differing in pitch (100 vs. 305 Hz) presented with fast presentation

rates (with ISIs down to 15 ms). In subsequent studies, Tallal and colleagues have found comparable results with dyslexics without language problems using verbal stimulus contrasts, like a /ba/ - /da/ contrast with a 40 ms transition, but not with a longer 80 ms transition period (Stark & Tallal, 1988). According to Stark and Tallal (1988) these results are explained by a timing deficit in children with language and reading impairments. Tallal and colleagues further suggest that such a temporal processing deficit disrupts the normal processing of speech, which may then delay the development of language.

Tallal and colleagues, as well as the recent review by Farmer and Klein (1995), have recently also been criticised. This issue is discussed more thoroughly in Article I; here a few remarks suffice for the purposes of this study. Studdert-Kennedy and Mody (1995) accuse Tallal and colleagues of using the term 'temporal' rather vaguely and attributing wrongly poor performance on some tasks to the transitional character of the formant transitions, when in their view it is rather a question of brevity. Brevity is undoubtedly a critical factor for example in the above mentioned /ba/ - /da/ contrast (Stark & Tallal, 1988), which was more difficult to detect with a short transition duration (40 ms instead of 80 ms). However, it could also be possible that the transitional character itself contributes to difficulty on the task (cf. e. g. the study by Stefanatos, Green, & Ratcliff, 1989 described in Article I). It is further possible that temporal features, serving as critical speech cues, are affected by the same or closely linked brain mechanisms that are responsible for the detection of fast changes in stimuli. It should also be noticed, that critical discussion around the timing deficit issue is related to a debate about the 'speech vs. nonspeech nature' of processing difficulties linked to dyslexia, which is, however, beyond the focus of this work, because with our data we cannot address the issue (see e. g. Brady et al., 1983).

In any case, the criticism launched against a general lower level timing deficit does not make unimportant findings related to problems either in the processing of short spectral cues or of rapid changes, such as reviewed above. For example, related processing abilities in infancy have been used to predict later language skills both in language impaired and control infants (Benasich & Tallal, 1996). Developmental prospective studies by Benasich and colleagues (Benasich & Spitz, 1998; Benasich, Spitz, & Tallal, 1995), which have investigated the genetic contribution to language impairment by tracking temporal processing abilities (focusing on speech sounds characterised by brief or rapidly changing temporal cues) and language acquisition in the offspring of language impaired individuals, have for example shown, that differences in infant discrimination (from the age of six months) of rapid auditory cues are strongly and reliably related to differences in language comprehension and production in toddler age.

There is also more direct evidence of processing difficulties related to the temporal or durational aspects of speech. Steffens, Eilers, Gross-Glenn, and Jallad (1992), for example, compared the performance of adult subjects with familial dyslexia and that of controls in a behavioural experiment, in which a temporal cue requiring exact timing, a silence gap within a syllable, was systematically varied along the synthetic speech continuum /sta/ - /sa/. With

no silence between the offset of /s/ and the onset of /a/ the syllable sounded /sa/, and with an increase in the duration of the silence period (up to 130 ms in steps of 13 ms) the syllable was perceived, at some point, as /sta/. In an identification task, the dyslexics required a longer silence duration to identify the stimulus as /sta/ than the controls, and thus their crossover point was closer to the /sta/ - end of the dimension than that of the controls.

Comparable phenomenon in the Finnish language context, that affected the choice of the stimuli for this work, is related to the ability to discriminate between various degrees of quantity (duration of speech sounds), which is an essential prerequisite for a child to learn the Finnish language, because differences in speech sounds are critical in cueing semantic differences and oppositions in this language[7]. In Finnish the plosives (stop consonants like /k/, /p/, and /t/) require perception of both rapidly changing auditory information as well as temporal aspects (see e. g. Stark & Tallal, 1979). Exact processing of rapid changes is required when discriminating between the plosives, because the discriminative cue (the interval between the explosive burst of a plosive and the beginning of the following fundamental oscillation) is very short in Finnish due to lack of aspiration (Lehtonen, 1970). The processing of temporal features is required in differentiating between short and long speech sounds. Finnish dyslexic children and adults have been found to have problems in this aspect, for example when reading pseudo-words (Lyytinen et al., 1994; Lyytinen et al., 1995; Richardson, 1998).

Other indices or problems related to auditory processing reported in dyslexics include, for example, abnormal hemispheric dominance/laterality (Hiscock & Kinsbourne, 1995), speech perception and categorisation difficulties (Reed, 1989; Werker & Tees, 1987), and verbal short term memory (STM) problems (McBride-Chang, 1995; Pennington, van Orden, Kirson, & Haith, 1991; Swanson, Ashbaker, & Lee, 1996; Wagner & Torgesen, 1987). Recent research suggests, though, that they may also have a deficit in fast motor-sensory and visual processing (Lovegrove, 1993; Stein & Fowler, 1985; Stein & Walsh, 1997).

Brain electrical activation to auditory stimuli in dyslexics

Several ERP studies suggest that the brain electrical activation generated both by pure tones and speech sounds differs between dyslexics and controls (for a review, see Article I; only a brief summary is provided here).

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7 Differences between single or short and long vowels or consonants, the prosodic feature known as *quantity*, is a highly distinctive feature in Finnish. Quantity may mean subjectively perceived dimension of time as well as acoustically measured objective time. A more precisely definable term is *duration* (for further discussion on duration variations and their meaning in the Finnish language, see Lehtonen, 1970). The perceived change in durational patterns, by itself alone, can contribute to the identification of a word (Lehtonen, 1970). For instance, the word /mato/ (worm) has a different meaning than the word /matto/ (carpet), and strings like /tuli/, /tuuli/, /tulli/ (fire, wind, customs) are typical words with different meanings.

Some group differences have been found already in the exogenous ERPs[8] at the latency range of P1-N1-P2 components (at ca. 50-180 ms), for example, longer latencies in poor spellers compared to normal spellers (Byring & Järvilehto, 1985) and reduced amplitudes in poor readers/spellers (Byring & Järvilehto, 1985; Pinkerton, Watson, & McClelland, 1989). Further, differential N1 hemispheric distribution (Brunswick & Rippon, 1994) and differential P1 component amplitude correlation to phonemic discrimination tasks (Wood et al., 1991) have been reported in dyslexics.

A possible reason for the latency differences between dyslexics and controls could be, that they are related to the earlier described timing deficit. This possibility is supported by the fact that processes reflected by N1 are thought to precede sensory memory processes (reflected in later MMN) and other further executive processes (see e. g. Näätänen, 1990). According to this view, the delay in N1 latency could result from the slowered speed of sensory processing, which may then have an impact on higher level processing, like speech processing. It is of interest, that exogenous component latency delays have been consistently found in children with language disorders (Dawson, Finley, Phillips, & Lewy, 1989; Jirsa & Clontz, 1990; Lincoln, Courchesne, Harms, & Allen, 1995; Neville, Coffey, Holcomb, & Tallal, 1993; Tonnquist-Uhlén, Borg, Persson, & Spens, 1996), suggesting that the above hypothesised linkage may be more robust in them.

Amplitude group differences of exogenous responses could reflect differences in the efficiency (or fine 'tuning') of sensory processing or in the general arousal system (perhaps partly related to attentional factors, as suggested e. g. by Pinkerton et al., 1989). It should also be noted, that the alterations of N1 component, in general, cannot be directly regarded to reflect the impairment or dysfunction of cortical language areas in general (which was suggested e. g. by Dawson et al., 1989). N1, more specifically its supratemporal component, is regarded to reflect sensory processing at the supratemporal plane of the auditory cortex (and, at least partly, in its tonotopically oriented areas; Tiitinen et al., 1993) 'informing' of the arrival of the auditory information (Näätänen, 1988, 1990, 1992), whereas language areas are usually thought to cover larger temporo-parietal areas of the cortex.

Differences between dyslexics and controls have also been found in endogenous ERPs, that occur at late latencies and are dependent on subjective factors, such as the significance of stimuli, task difficulty, attention, and memory (cf. Hillyard, 1985; Näätänen, 1990). The findings reviewed in Article I are in line with early studies on learning disabilities (Dool, Stelmack, & Rourke, 1993; Stelmack, Rourke, & Vlugt, 1995), in which subjects with reading disorders were usually included in experiments with subjects with other learning disabilities. The reduced amplitudes and longer latencies of auditory

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8 Exogenous (or obligatory/sensory) components are the ones occurring before or around 100 ms in adults and their generation is based mainly on the physical features of the stimuli.

P3[9] have typically been reported in dyslexics (amplitudes by Erez & Pratt, 1992; Holcomb, Ackerman, & Dykman, 1986; Lovrich & Stamm, 1983; Mazzotta & Gallai, 1992, and latencies by Mazzotta & Gallai, 1992), with some contradictory findings and failures to find P3 differences in dyslexic children (Duncan et al., 1994; Segalowitz, Wagner, & Menna, 1992).

These P3 results are, however, only of limited significance for the purposes of this work in searching for the basic and low level auditory processing differences between those at-risk for dyslexia and those without such a risk. P3 is modality independent and modifiable by several aspects related to cognitive functions, such as attention and memory or allocation of effort, aspects which are not easily controllable in infant studies. It suffices to mention here that the assumption of attentional problems behind P3 differences between dyslexics and controls is in line with similar P3 findings in dyslexics and individuals with attentional problems; children with hyperactivity also show smaller P3 responses than controls. The well known co-morbidity of attentional and reading disorders (Lyytinen, 1995) may explain these results. The findings of no P3 differences between RD participants and normal readers could also be explained, as suggested for example in the study of Duncan and co-workers (Duncan et al., 1994) by co-morbidity; the clinical P3 features (smaller amplitudes and longer latencies) may be related to attention problems in a sub-group of dyslexics rather than to the core deficit of dyslexia itself.

Laterality differences have also been reported between poor readers and controls (Brunswick & Rippon, 1994; Duncan et al., 1994; Erez & Pratt, 1992; Fried, Tanguay, Boder, Doubleday, & Greensite, 1981; Mazzotta & Gallai, 1992; Rosenthal, Boder, & Callaway, 1982; Shucard, Cummins, & McGee, 1984; also indirectly, cf. Pinkerton et al., 1989; Wood et al., 1991; for a review, see Article I). In controls ERPs generated by speech stimuli are, generally speaking, greater at the left than at the right hemisphere, while those generated by pure tones either lack this asymmetry or are greater at the right hemisphere. This pattern, as a whole, is consistent with a general observation that in most people linguistic material is preferentially processed by the left hemisphere (Carr & Posner, 1995; Lukatela, Carello, Savic, & Turvey, 1986; Neville, Kutas, & Schmidt, 1982; Rugg, Kok, Barret, & Fischler, 1986). In dyslexics, the ERP hemispheric pattern is generally either in the opposite direction compared to controls or the left hemispheric asymmetry is lacking, which implies that there

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9 The P3 component is usually generated at the latency of 300-500 ms and within its latency range several components may overlap both in time and space; for example Sutton and Ruchkin (1984) speak about the late positive complex (for further discussion on the issue, see Sutton & Ruchkin, 1984). However, these 'sub-components' have not often been specified; studies usually only mention that P3 was measured. Sutton and Ruchkin (1984) have listed two to three separate P3 components, that vary as a function of latency and scalp distribution: P3a, that often follows N2b and reflects involuntary attention switch (Squires, Squires, & Hillyard, 1975), P3b related to novelty, and P300E that is earlier and more fronto-central than P3b, that is maximal parietally. In addition, there is still another positive component, called Slow Wave (SW), that seems to be related to further processing or mobilisation of effort required by stimuli. In the studies reviewed here, P3 seems most often to refer to P3b (or as sometimes referred to as P300 according to its latency).

are differences in the hemispheric preponderance of processing involvement as reflected in the ERPs. Several other brain imaging techniques, including EEG (Electroencephalography), and PET (positron emission tomography), have also shown differences in left hemispheric functioning between dyslexics and controls (for a review, see Hynd, Semrud-Clikeman, & Lyytinen, 1991b). For example, Rumsey et al. (1992) found in a PET study, that dyslexic men failed to activate those left temporo-parietal regions that were activated in controls during rhyme detection, but that they did not differ from controls in a nonphonological task.[10] It should be noted, that asymmetries of different ERP components are related to different levels of the cognitive hierarchy and are dependent on task requirements. Thus, generally speaking, asymmetries in the exogenous/sensory ERPs may be regarded to reflect 'perceptual asymmetry' in the initial registration and encoding of a stimulus, and those in the endogenous ERPs (like P3) reflect asymmetries in integrated cognitive functions. In the reviewed ERP studies (Article I) asymmetries exist both in exogenous and endogenous ERP components. It is interesting in this respect, that Wada and Davis (1977) show evidence suggesting that electrophysiological hemispheric asymmetries are generated in young infants by stimuli with no verbal content, interpreted by the authors as an indication that language is only a part of more fundamental asymmetries including auditory and visual processing, and which are expected to develop independently of and even before language.

Neurobiological alterations in dyslexics

Several, though relatively minor alterations at the anatomical and structural level of the brain have been reported, at least in a proportion of dyslexics. For example, the planum temporale differs between dyslexics and controls as reported in postmortem anatomical studies (e. g. Galaburda, 1991; Galaburda, Sherman, Rosen, Aboitiz, & Geschwind, 1985; Humphreys, Kaufmann, & Galaburda, 1990; Rosen, Sherman, & Galaburda, 1993), as well as in MRI (magnetic resonance imaging) studies (Geschwind & Levitsky, 1968; Hynd & Hiemenz, 1997; Hynd, Marshall, & Semrud-Clikeman, 1991a; Hynd, Semrud-Clikeman, Lorys, Novey, & Eliopulos, 1990; Jancke, Schlaug, Huang, & Steinmetz, 1994; Larsen, Höien, Lundberg, & Ödegaard, 1990; Leonard et al., 1993; Schultz et al., 1994; for similar results on the temporal lobe subcortical areas lateral to the insula, see Dalby, Elbro, & Stödkilde-Jörgensen, 1998). The planum temporale is located at the temporal lobe (forming its superior posterior surface), which is a part of Wernicke's area in the left hemisphere thought to be involved in phonological processing (e. g. Pennington, 1991a), which may thus explain the association of the altered planum temporale asymmetry with phonological coding deficits in dyslexics.

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10 There are also failures to demonstrate the left hemispheric predominance deviation in dyslexics. For example, while Hagman et al. (1992) showed significant differences in the medial temporal lobe metabolism in general in a PET study in dyslexics as compared to controls during auditory syllable discrimination, no laterality differences were found between the groups.

Further, differences in anatomy between dyslexics and controls have been found in the symmetry of the medial geniculate nuclei (MGN) of the thalamus, the way station that handles auditory inputs (Galaburda, Menard, & Rosen, 1994). In dyslexics, the left MGN neurons were smaller and they had more small and fewer large neurons than the controls. These findings were linked, analogously, to defects dyslexics are suggested to have in relation to the functioning of the visual magnocellular system dealing with rapidly moving objects and information on the overall organisation of the visual world (e. g. Galaburda & Livingstone, 1993; Livingstone, 1993). Galaburda et al. (1994) suggest that the neurons of the MGN, related to the processing of rapid temporal transitions, form an auditory subsystem corresponding to the neurons of the large-cell division of the lateral geniculate nucleus (LGN) in the visual pathway, and that phonological problems in dyslexics could result from abnormal development of this auditory subsystem. They speculate that their MGN group differences are secondary to the cortical changes, reflecting abnormalities in the target areas for axons arising from the MGN during development. This suggestion is consistent with cortical abnormalities found in dyslexics, including neuronal ectopias and architectonic dysplasias in perisylvian regions (Galaburda et al., 1985; Humphreys et al., 1990; Rosen et al., 1993), which would originate prenatally during the period of neuronal migration and subsequent cortical maturation (see Rosen, Press, Sherman, & Galaburda, 1992). It is interesting in this connection, that studies using animal models of induced neocortical microgyric lesions (like those seen in dyslexic brains) reveal, that rats, when tested behaviourally, show significant auditory temporal-processing deficits similar to those in dyslexics or infants with a positive family history of language impairment, as well as specific anomalies in the MGN of the thalamus (see Benasich & Tallal, 1996; Fitch, Miller, & Tallal, 1997; Fitch, Tallal, Brown, Galaburda, & Rosen, 1994; Herman, Fitch, Galaburda, & Rosen, 1995; Tallal et al., 1993). Taken together, the MGN and cortical abnormality findings would imply that processing deficits seen in dyslexic children may be detectable very early in development.

These differences in brain functions and neurobiology between dyslexics and controls fit well, in general terms, to a notion of auditory/speech processing deficits as one underlying factor that contributes to phonological problems in dyslexia. The variety of findings, on the other hand, suggests that developmental dyslexia is not explained by any single deficit or alterations in some sharply localised brain structure. Furthermore, as is well known, there is a sensitive period for language development in the first five years of life, during which the brain mechanisms/systems responsible for speech perception and language are vulnerable to a variety of environmental influences at many different points in development. However, while acknowledging, that no one single factor is likely to be able to account for dyslexia, it is still useful to pursue to identify what specific features, for example in auditory processing, might be impaired in this disorder. Of crucial relevance is to find constructs, that could provide explanations for the relationship between ERPs measured early in life and later language development.

AIMS OF THE EMPIRICAL STUDIES

The dissertation had two main aims: The first was to investigate the developmental features of brain electrical activity generated in various oddball paradigms by changes in tone pitch and in duration of speech sound elements at birth and at the age of six months. As the review above reveals, only a limited number of studies have compared the brain event-related potentials of newborns to pitch changes and none, to my knowledge, have dealt with the ERPs of young infants in relation to changes in sound duration.

The second major goal was to see, whether electro-cortical activity generated by changes in sound duration would be different in infants who have a high familial/genetic risk for developmental dyslexia in comparison to infants without such a risk, as could be expected to be the case on the basis of the studies above and those reviewed in Article I, which show auditory and speech processing problems as well as neurobiological alterations in dyslexics. In view of the fact, that dyslexics are known to have problems in the processing of various aspects of speech, especially in relation to stimulus features varying in temporal structure and requiring exact timing, the search for group differences was focused on the ERPs to related stimuli varying in vowel and stop-consonant duration. The ability to discriminate between speech sounds with different durations is an essential basis in learning the Finnish language, because differences in this feature are critical in cueing semantic differences. More specific goals concerning each empirical study are presented in the summary section.

METHODS

Participants

Selection of participant families

Families expecting a baby in the years 1993-1996 in the Province of Central Finland were contacted and requested to participate in the Jyväskylä Longitudinal Study of Dyslexia (JLD; Lyytinen, 1997; Lyytinen et al., 1995). They were enrolled according to institutional informed consent procedures. Infants from families with a familial background of dyslexia form the *at-risk group*. Infants from matched control families without any signs of dyslexia belong to the *control group* (see below for a more detailed description of matching the groups).

All the parents in both groups reported that they had normal hearing and that their speech was not deviant[11]. Further, sensoric or neurological abnormalities led to exclusion from either group. The inclusion criteria to the at-risk group (for details see, Leinonen et al., submitted; Lyytinen et al., 1995) were either parent's report of his/her own reading disorder, comparable report concerning at least one close relative and multiple diagnostic test results indicative of dyslexia. In order to be diagnosed with dyslexia the parent had to have a score of at least 1 *SD* below the norm in accuracy or speed in oral text reading or accuracy in written spelling, and in at least two separate accuracy or response latency measures of word recognition. Each parent's IQ had to be 85 or above (assessed with the Raven B, C and D matrices; Raven, Court, & Raven, 1992). Some of the parents who had several relatives with a reading disability, despite a strong background of self-reported school-age and present reading problems, did not score significantly below the norm on all the required measures assessing reading related skills, but because of their strong family

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11 One family was excluded from the analyses due to the mother's dysphasia, developmental language disorder.

history of reading difficulties they were included as compensated dyslexics. It should be noted, that inclusion of the families with compensated dyslexics is a 'conservative' decision, in that their infants could only be expected to differ to a lesser degree than other at-risk infants from control infants, as suggested by our preliminary unpublished results for the stimulation used in the studies of Article V. It is not excluded, though, that phenotype features of the compensated dyslexics could have a somewhat different origin as compared to those of the other dyslexics in our sample, but that is an issue beyond the focus of this work.

To be able to take parental socio-economic status and intelligence (IQ) into consideration as possible factors in explaining the results, a summary of these is presented here for each study, in which the groups were compared. The socio-economic status in the JLD project (for details see, Leinonen et al., submitted; Lyytinen et al., 1995) has been determined on the basis of the length or level of parental education, when both basic (primary and high-school level education) and continued education (such as vocational or university education) were combined.[12] This socio-educational status of the participants was representative of its distribution in the Finnish population. Both the education status and IQ differences between the groups were compared with independent *t*-tests for both the mother and father for each study. These data are presented in Table 1[13] (for a description of different experimental conditions, see below and Table 2).

TABLE 1 Independent *t*-tests for parental education (basic and continued education combined) and IQ differences between the at-risk and control groups

Article	Parental education		Parental IQ	
	Mother	Father	Mother	Father
	t	*t*	*t*	*t*
Article III				
Newborns	-1.26	-1.55	-2.70*	-2.52*
Six-month-olds	-3.61**	-1.15	-2.52*	-3.35**
Article IV				
Newborns	-1.36	0.27	-0.06	-2.38*
Article V				
Six-month-olds				
1. experiment	0.05	-2.65*	-0.99	-1.84
2. experiment	1.65	0.18	-1,88	-2.19*

Note. *$p < 0.05$; **$p < 0.01$. Negative *t*-value indicates smaller average score in the at-risk group.

12 This was considered, in the project, as a sufficient matching criterion for a study in Finnish society, which is relatively homogeneous and has a well developed social policy. This means that socio-economic differences are not very significant in that they would affect, for example, the pre- or peri-natal care of mothers and their young infants.

13 All of the information was not available for all families, resulting in missing cases, which were excluded from the group comparisons. From the at-risk families only the index parent (with a dyslexia diagnosis) was initially tested for IQ. All the parents' IQ will eventually be tested more carefully during the second phase of parent assessment.

From Table 1 it is evident, that socio-educational level was generally lower in the at-risk group than in the control group, though statistically significantly only in two comparisons. The parental IQ was also lower in the at-risk group, this difference being statistically significant more consistently in fathers.

Infant participants

Altogether the data concerning 124 newborn babies, of whom 70 were from the control and 54 from the at-risk group, and data concerning 127 six-month-old infants, of whom 62 were from the control and 65 from the at-risk group (comprising partly the same infants as at birth), are reported in the present work. At the first measurement, the infants' chronological age was between a day and a week, and the gestational age (GA) was at least 38 weeks, except in 12 infants, who had a GA below this and were tested at the conceptional age (CA) of about 40 weeks. Medical birth histories of the infants were collected by an authorised child physician. In addition to a routine medical examination, the infants were also examined by a neurologist. The infants were without central neurological or other major medical complications and were diagnosed as healthy at the time of testing. All the babies had a birth-weight at least of 3000 grams, except 14 infants (8 from the at-risk and 6 from the control group) whose birth-weight varied between 2000 and 2990 gr. The infants did not have any reported hearing problems. They were screened at the hospital shortly after birth for a possible hearing loss with a 100 dB sound. Later reports, during a family guidance center visit[14], were obtained for those, from whom no record existed or for those who, for some other reason, had an ambiguous result at birth. According to these reports from later ages, all these participants had positive indications of reacting to sound tests.

The second series of measurements were carried out when the infants were six months of age (± 2 weeks, corrected to GA as above). The status of otitis media (middle ear infection) was examined at this age by inquiring about it from the parents during the research visit and from the family guidance center visit records. Those with still ongoing otitis media or those who had a medical record of having an effect of longer ongoing otitis media were not accepted for the analyses of this study. To make sure that differences in the number of otitis media occurrences prior the experiments would not be an explaining factor for possible group differences, this number was compared between the groups in relation to each experiment. No differences between the groups were found ($ps > 0.05$). Further, as was carried out for the parents, the participating infants' later IQ, as indexed by the Bayley Scale Mental Indexes and Psychomotor Indexes obtained at the age of 24 months, was compared between the groups for each experiment of this work (for the infants for whom the data were available). No group differences were found ($ps > 0.05$).

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14 In Finland it is a custom for infants and children to visit special family guidance clinics for regular control of development, of which records are kept. The parents were also later asked about any specific examinations of hearing under taken or the need for a hearing aid for their infants.

The distribution of the participants in the different studies was[15]:

Article II:	28 newborns from the control families.
Article III:	73 newborns, 31 from the control , 42 from the at-risk group.
	51 six-month-olds, 23 from the control, 28 from the at-risk group.
Article IV:	23 newborns, 11 from the control, 12 from the at-risk group.
Article V:	76 six-month-olds, 39 from the control, 37 from the at-risk group.

Experimental settings

Stimuli

The stimuli and their crucial parameters are displayed in Table 2. In Article II the stimuli were three pure tones varying in pitch. In Articles III-IV two consonant-vowel (CV) syllables, digitised from natural speech, were used as stimuli with different vowel durations. In Article V the stimuli were three variants of a naturally produced pseudoword with a voiceless stop, a silence gap, in the middle of the speech sound that serves as a cue for the length of the stop consonant (for details, see Richardson, 1998 and Pihko, Leppäsaari, Leppänen, Richardson, & Lyytinen, 1997). Only the data for the pseudowords with the short and longest silence gaps are reported. For all the stimuli varying in their duration, all other acoustical aspects, such as fundamental frequency, intensity, and rise/fall times were held constant.

Procedure

Except for two control experiments (one in Article II and one in Article V), the stimuli were presented in oddball paradigms, in which deviant stimuli were occasionally and pseudo-randomly embedded among repeated frequent standard stimuli (see Table 2). These oddball sequences had 5-10 (Articles II, III, IV) or 3-5 (Article V) standard stimuli between the deviant stimuli to ensure enough repetitions for the formation of neural representation for the standard stimuli. The sequences were presented in short separate blocks of ca. 4-6 min in all studies, expect in Article IV in which they were presented in blocks of ca. 10 min in the experimental condition with the longer ISI.

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15 Twelve infants from the 56 at-risk infants participating in the Article III studies had a compensated dyslexic parent, and similarly 4 of the 12 infants in the Article IV studies and 10 of the 37 infants in the Article V studies (infants participating in the studies of Articles III and IV were partly the same as those participating in the Article V studies).

TABLE 2 Stimulus parameters

Article	Standard stimulus/ probability, %		Stimulus Duration ms	Deviant stimulus/ probability, %		Stimulus Duration ms	dB	ISI[1] ms
Article II[2]								
1. experiment	1000 Hz	88	74	1100 Hz	12	74	75	425
2. experiment[3]				1100 Hz	100	74	75	
3. experiment	1000 Hz	88	74	1300 Hz	12	74	75	425
Article III, IV	/kaa/	88	250	/ka/	12	110	75	425
Article IV	/kaa/	88	250	/ka/	12	110	75	855
Article V								
1. experiment[4]	1./ata/	80	300/95	2./atta/	10	400/195	75	610
				3./atta/	10	460/255		
2. experiment[4]	3./atta/	80	460/255	2./atta/	10	400/195	75	450
				1. /ata/	10	300/95		/610

Note. [1]Offset-to-offset, except in Article II[2], where onset-to-onset ISI was used. [3]The 'deviant' stimulus was presented alone without an intervening standard stimuli, the inter-deviant interval being ca. 2.5 - 4.7 sec. [4]In the stimulus duration column the 1st figure stands for the total duration and the 2nd figure for the silence gap duration. In the 2nd experiment reported in Article V two ISIs were used (see the text).

EEG and ERP-recordings

The ERP-recordings at birth were carried out in the EEG laboratory of the Central Hospital of Central Finland and those at the age of six months in the ERP-laboratory at the Department of Psychology of the University of Jyväskylä. The stimuli were delivered through a loudspeaker, located 60 cm from the estimated head position of newborns (facing it; the angle between the loudspeaker and the infant crib being 41°) and 80 cm above the estimated head position of six-month-olds. The stimulus presentation intensity was 75 dB SPL, calibrated before the experiments using a Brüel & Kjaer precision sound level-meter (type 2235). The newborns were lying in a crib designed for the purpose and the six-month-olds were sitting on their parent's lap.

The reported data on the newborns include only trials measured during quiet sleep. The EEG-epochs were initially classified into four categories according to the sleep/wakefulness states of the infant: wakefulness, active or quiet sleep or indeterminate state. Infants' behaviour during measurement (e. g. eyes open or closed, facial and bodily movements and crying) were observed and coded on-line. Each one-minute period of the measurement was then classified off-line into one of the various states according to behavioural criteria defined by Anders et al. (1971). In addition, eye movements were monitored

from the ongoing EEG at the EOG-channels[16]. The interrater agreement of the on-line-coding of the infant's behaviour between two independent observers was 95 %, and the interrater agreement of the off-line classification of the EEG-epochs into the four states was 92 %. The interrater agreements were calculated from the data of 5 randomly chosen infants and were defined as the percentage of the total number of EEG-epochs that the two raters agreed on (for further details, see Article II). The 6-month-old data reported here were recorded during wakefulness.

The reported ERPs were recorded with Ag-AgCl electrodes attached to the frontal (F3, F4), central (C3, C4) and parietal (P3, P4) scalp sites according to the International 10-20 electrode system (Jasper, 1958). In addition, in Article V the data are also reported on ERPs measured from the temporal (T3, T4) locations. For the newborns, disposable electrodes (Blue sensor, Medicotest, Denmark) were used, and for the 6-month-olds an electro-cap (Electro-cap International, Inc., USA). The eye movements (EOG) were monitored with two electrodes, one slightly above and lateral to the left eye and the other slightly below and lateral to the right eye. The ERP electrodes were referred to the ipsilateral mastoid and the EOG electrodes to the left mastoid. EEG was stored at a sampling rate of 200 Hz. The bandpass was 0.5-35 Hz. AC-filtering was on. In the studies of Articles II-IV, EEG-epochs of 950 ms pre-deviant-stimulus and 950 ms post-deviant-stimulus time were stored during the measurement for later offline analyses. The rather long pre-stimulus time was used to allow the measurement of the response to the standard stimulus preceding the deviant tone. In the experiments of Article V EEG-epochs of -50-840 ms (with a 50 ms pre-stimulus time) were stored.

ERP-averaging

Individual ERP averages were calculated separately for each stimulus type in each condition. Epochs contaminated by eye movements (EOG exceeding ± 150 μV in newborns and ± 200 μV in 6-month-olds) and by muscle activity or other extra cerebral artefacts (EEG exceeding ± 200 μV) during the analysed time windows (see below) were excluded from the averaging. All epochs, in which the first deviant stimulus occurred among the first ten standard stimuli, were similarly disregarded. At least 70 artefact free trials were required for an individual average to be included in further analyses.

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16 Quiet sleep can be distinguished from active sleep on the basis of behavioural quiescence, absence of bodily movements, lack of eye-movements, and regularity of physiological activity (Anders et al., 1971). Online monitoring of ongoing respiration, as measured with the Static Charge Sensitive Bed (SCSB for infants, model BR8-P), and of EOG confirmed that the behavioural criteria provide enough information for reliable classification between quiet and active sleep states. The EEG and polygraphic data, respiration, movements and ballisto-cardiogram (obtained with SCSB) will be used later to study the possibility of using computerised analyses to classify infant sleep states.

SUMMARY OF THE STUDIES

Article II

As all the present experiments were carried out using oddball paradigms with relatively short ISIs, this first empirical study was intended as a methodological 'ground' work for the other studies, especially for the ones with newborn participants. The main goal was to examine how the ERPs of newborns, during quiet sleep, vary in relation to a pitch change in an oddball paradigm in which stimulus events typically elicit MMN in adults. Changes in pitch, the stimulus frequency, were chosen, because in adult studies the characteristics of MMN to pitch change are known best. Three major questions were addressed in the main experiment and two complementary conditions: I. Do ERPs to a rarely occurring and deviating tone differ from ERPs to a frequently presented tone? II. Are the ERPs to this deviant stimulus different from ERPs to a similar stimulus presented alone when no intervening standard tones are presented in between the 'deviant' stimuli? III. How does an increase in the difference between frequent and rare stimuli affect the ERPs?

Methods

Participants were 28 newborns from the control group. Three different stimulus conditions were employed (see Table 2). In the first condition, labelled in Article II as the *1100-Hz-deviant* condition, a sine wave tone of 1000 Hz (with rise and fall times of 24 ms) was used as the standard stimulus and a tone of 1100 Hz as the deviant stimulus. These stimuli were chosen because they had been successfully used in our previous studies indicating a clear MMN both in adults and children (e. g. Leppänen, 1992; Leppänen et al., 1992). The onset-to-onset ISI used in this study was somewhat shorter than that used by Alho et al. (1990a); 425 ms instead of 610 ms. The use of this shorter ISI was justified in view of the

fact that the MMN-response can be recorded even with very short ISIs, and as shown by Näätänen, Paavilainen, Alho, Reinikainen, and Sams (1987) for as short an ISI as 51 ms. Moreover, the rapid presentation rate of the frequent stimulus is thought to lead to a well established memory trace formed by this stimulus (Näätänen, 1992).

In the 2nd condition, labelled as the *1100-Hz-alone* condition, the setting was similar to that of the 1st condition, with the exception that the standard tones were omitted from between the deviant tones. This was done to test the context effect; MMN is thought to reflect a 'comparison' process between the existing memory trace for the standard stimulus and the input generated by the deviant stimulus. When the context, the standard stimuli, is omitted, one typically sees in adults a waveform different from MMN and one that has a higher peak amplitude, an earlier latency, and a more central scalp distribution (Näätänen, Paavilainen, Alho, Reinikainen, & Sams, 1989).

In the 3rd condition, labelled as the *1300-Hz-deviant* condition, the difference between the deviant and standard stimuli was increased from 10% of the 1st condition to 30 % (1300 Hz, 12% vs. 1000 Hz) in order to test the stimulus difference effect and to make sure that possible differences in our study and that of Alho et al. (1990a) would not be due to the smaller stimulus difference used; they used a deviant stimulus of 1200 Hz.

ERPs were averaged from a range of -475-425 ms, including the response window for the pre-deviant standard stimulus (with a 50 ms pre-stimulus baseline), which was used for all the following measures. (1) *Mean amplitudes* were calculated across the periods of 25-125 ms, 125-225 ms, 225-325 ms, and 325-425 ms. (2) A mean *difference score* representing response to change was calculated for each period by subtracting the mean amplitude to the standard from that to the deviant. For peak amplitudes and latencies a difference wave (deviant ERPs - standard ERPs) was also calculated for the whole averaging period. From this difference wave (3) a *negative peak amplitude* was determined as the most negative (or the least positive) deflection within a time window of 150-375 ms (cf. Alho et al., 1990a). (4) Similarly, the most *positive peak amplitude* (or least negative) was also calculated from the same period. In the *1100-Hz-alone* condition these peak amplitudes were calculated from the 1100 Hz stimulus at a corresponding time window. (5) As a *measure of polarity* , the amplitude of the largest deflection from the baseline (regardless of the sign) within a time window of 150-375 ms was used. For statistical analyses MANOVA and ANOVA for repeated measures and univariate *F*-tests were used.

Results

The responses to the 1000 Hz standard tones were very small without any clear peak and did not reach statistical significance (see Figure 1). The most typical response to the 1100 Hz deviant tone was a slow positive deflection, which was wide spread across the fronto-central scalp areas. The mean ERPs to the deviant tones, calculated over the consecutive 100 ms periods, differed from those to the standard tones over a wide range of 125-425 ms, indicating the 'slowness' of the response. At 125-225 ms, the mean difference amplitude was more positive over the right than over the left hemisphere. At the central sites the responses were consistently (across the last three periods) significant only at the right sites. Also, the mean difference response was more positive fronto - centrally than parietally.

The peak analyses confirmed the predominantly positive difference waveform at the fronto-central sites reaching maximum at C4 at the latency of 271 ms (see Figure 2). Some negativity was found at P3. Individual ERP differences were also found. In 14 of 28 (50 %) infants a negative fronto - central difference wave peak was observed, seen most clearly at C3 and at P3. In 10 of these 14 infants (36 % of all subjects) the largest deflection (or the maximum regardless of the sign) of the difference wave had a negative polarity.

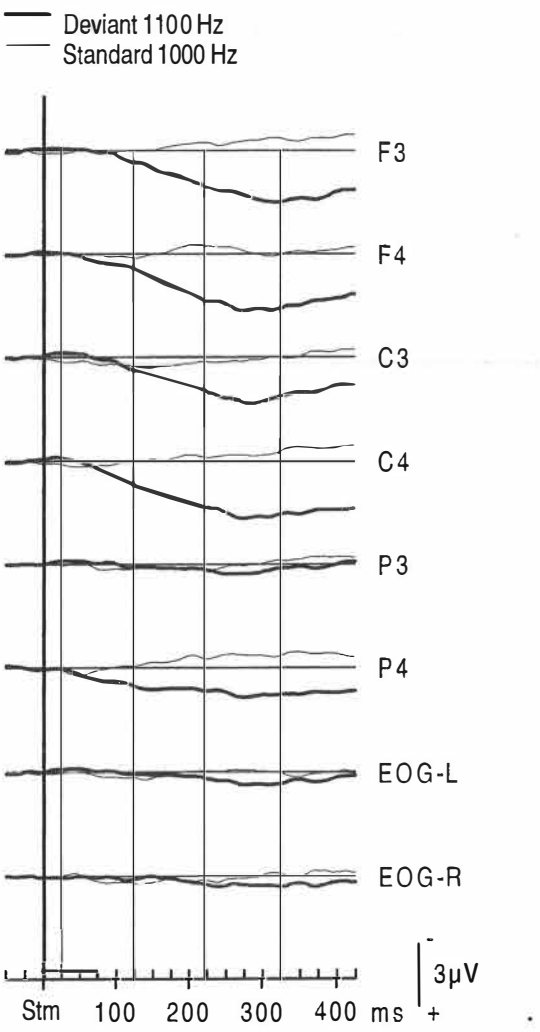

FIGURE 1 ERPs (averaged across 28 participants) to the rare 1100 Hz deviant tone (thick lines) and the frequent 1000 Hz standard tone (thin lines). Vertical lines across channels separate the consecutive 100 ms periods starting from 25 ms. Negativity up.

Peak analyses also revealed maturational effects in relation to the amplitude and polarity of the ERPs: the individually largest deflection of the difference wave was positively correlated to GA and/or CA at F3, F4, and C3, and the deviant response to CA at F3. These correlations indicated that the greater the GA or CA the more positive the amplitude of the largest response.

Within subject comparisons of *1100-Hz-alone* and *1100-Hz-deviant* conditions in a sub-sample of 11 participants revealed that the mean response was more positive at a late range of 325-425 ms in the *1100-Hz-deviant* condition than in the *1100-Hz-alone* condition at C4, indicating that the positive response was longer in duration to the deviant stimulus than to the equivalent stimulus presented alone with long intervals. In the *1100-Hz-alone* condition the response reached significance only in the 225-325 ms period revealing that a response to an auditory stimulus per se is 'narrower' in terms of its latency range or 'faster' than a response to a deviant stimulus among repeated standard stimuli.

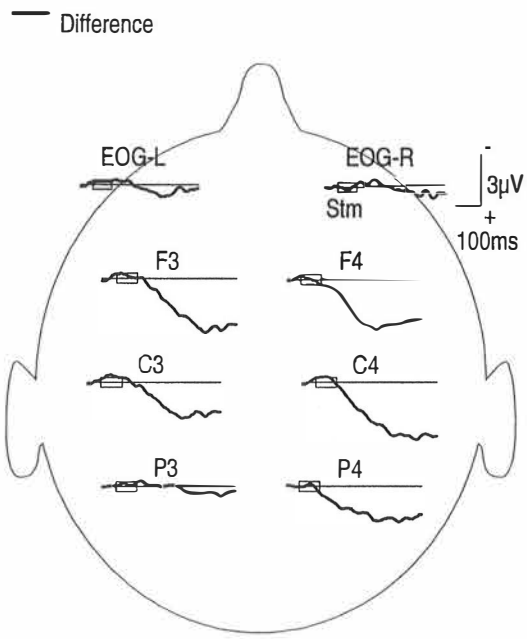

FIGURE 2 Difference waves (based on the averages across the 28 participants) obtained by subtracting the ERPs to the standard 1000 Hz tone from those to the deviant 1100 Hz tone for an epoch of -50 - 425 ms. Negativity up.

Comparisons of *1300-Hz-deviant* and *1100-Hz-deviant* conditions with 9 participants revealed, surprisingly, that the responses to the greater stimulus change in the *1300-Hz-condition* had a tendency to be smaller than those to the smaller change in the first condition (1300 vs. 1000 Hz as opposed to 1100 vs. 1000 Hz, respectively). This is seen in the fact, that the mean difference scores did not differ from the baseline at any 100-ms time period in the *1300-Hz-condition*. The difference wave peak analyses showed that the negative peak amplitudes were greater for the greater stimulus difference, but only at P4. On the other hand, the positive peak amplitude was greater, at P3, for the smaller change (see Figure 3).

Discussion

The small responses to the standard stimuli can be accounted for by the fast presentation rate (1/425 ms) in view of the long refractory periods in newborns (cf. (Kurtzberg et al., 1995; Ohlrich, Barnet, Weiss, & Shanks, 1978).

The predominantly positive response to the deviant stimulus found in full term newborns in this study is in line with some previous infant studies, with somewhat older infants, that have used relatively fast stimulus rates (Alho et al., 1990b; Dehaene-Lambertz & Baillet, 1998; Kurtzberg et al., 1995). Some earlier studies with longer ISIs, typically between 2-3.3 seconds, have also reported waveforms generated by deviant stimuli that are positively displaced in relation to the responses to the standard stimuli (Duclaux et al., 1991; McIsaac & Polich, 1992; Tokioka et al., 1995). Usually these responses occur at longer latencies and have been related to long term memory processes (cf. McIsaac & Polich, 1992). In the current study the positive peak latencies were within the reported infant MMN latency range (cf. e. g. Cheour et al., 1998b). There is thus a discrepancy between this and some other infant MMN studies (cf. Alho et al., 1990a; Cheour et al., 1998a; Cheour-Luhtanen et al., 1995).

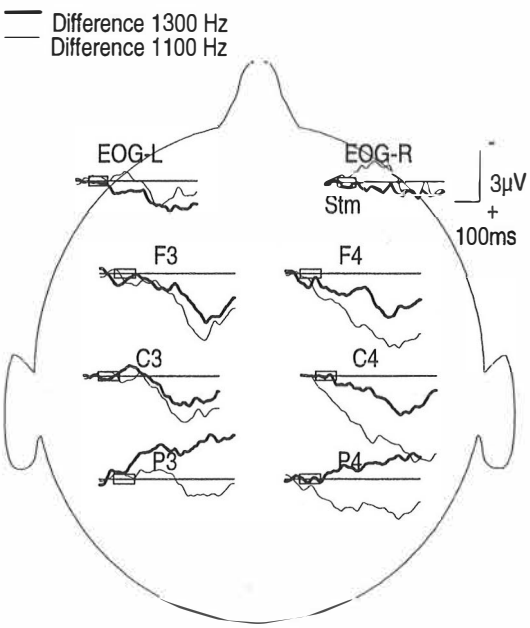

FIGURE 3 Difference waves (averaged across 9 participants) obtained by subtracting the ERPs to the standard tone from those to the deviant tone (for an epoch of -50 - 425 ms) for the 1300 Hz (thick lines) and 1100 Hz deviant stimuli (thin lines). Negativity up.

Considering the fact, that the response to the standard stimulus (1000 Hz) was almost non-existent, the major contribution to the difference wave comes from the response to the deviant stimulus (1100 Hz). That it had a similar waveform as compared to the response to a similar stimulus (1100 Hz, used previously as the deviant stimulus) but presented without the context of repeated standard tones, supports the idea that it partly represents a non-refractory exogenous response to an auditory stimulus per se. In this sense the results are in line with early studies with long ISIs and equal probabilities of the

presented stimuli (cf. Barnet et al., 1975; Ellingson et al., 1974; Graziani et al., 1974; Kurtzberg et al., 1984a; Kurtzberg et al., 1986; Novak et al., 1989; Pasman et al., 1992; Rotteveel et al., 1986; Weitzman & Graziani, 1968). However, the longer positivity to the deviant stimulus as compared to the same stimulus alone, suggests that the presentation context also has an effect.

The individual differences found in the study are likely to be due to maturational differences, as suggested by positive correlations between the individually largest deflections and gestational and/or conceptional age; the greater the GA/CA, the more positive the responses. This is supported by the fact, that in most of the individuals, who displayed a negatively displaced deviant response, the individually largest response was also negative in polarity. This would fit well with the description of negative responses as being more immature at birth (cf. Kurtzberg et al., 1984a; see also Novak et al., 1989). This notion of the relationship between ERP amplitude, its polarity on the one hand and maturational factors on the other hand, receives further support in a recent analysis (unpublished study from our laboratory) using cardiac measures. These measures, Vagal tone (V) and Heart period (HP), are generally known to be associated to maturation during the first year of life (Fracasso, Porges, Lamb, & Rosenberg, 1994; Porges, 1988). For example, when V and HP were entered together with GA in a regression analysis as the explaining variables, significant models were found for the ERPs at F3, F4, and C3 with squared regression coefficients, R^2, ranging between .32 and .51 ($ps<.05$). For HP it ranged between .37 and .42 ($ps<.01$). The relationship between HP and ERPs is demonstrated in Figure 4 that displays the grand average ERPs, when the participants (N=21) were classified into 3 equally sized groups (n = 7) according to HP. It is of interest that the maturational effects were more wide spread over the left hemisphere, whereas there was a right hemispheric preponderance of the stimulus effects, suggesting a differential maturational timetable between the left and right hemispheres.

This is not to say, that negatively displaced responses to deviant stimuli found in other studies could be explained by appealing merely to maturational factors. In fact, some evidence was found for a possible overlap of responses with opposite polarities at the latency of a typical MMN in our study, in the condition with the greater stimulus change. This is supported by the fact that the deviant response in this condition was less positive than that with a smaller stimulus difference; one would have expected the opposite to be the case and, thus, enhanced positive responses to the more distinguishable stimulus change.

Overall, these experiments suggest that more than one separate process related to the monitoring of the auditory environment, based on different neural generators, may be distinguishable in the auditory system already at birth. First, an ERP-component to auditory stimuli was observed, the polarity of which is, at least partly, determined by the individual maturational levels of the ERPs. It seems to reflect a process affected by refractoriness to repetition and/or a process affected by dishabituation to a small change. These two processes cannot be differentiated on the basis of the data from this study. Second, some suggestive evidence was also found for the existence of an overlapping negative

response. This seemed to be enhanced at the parietal sites, suggesting also scalp distribution differences between infant and adult ERP data.

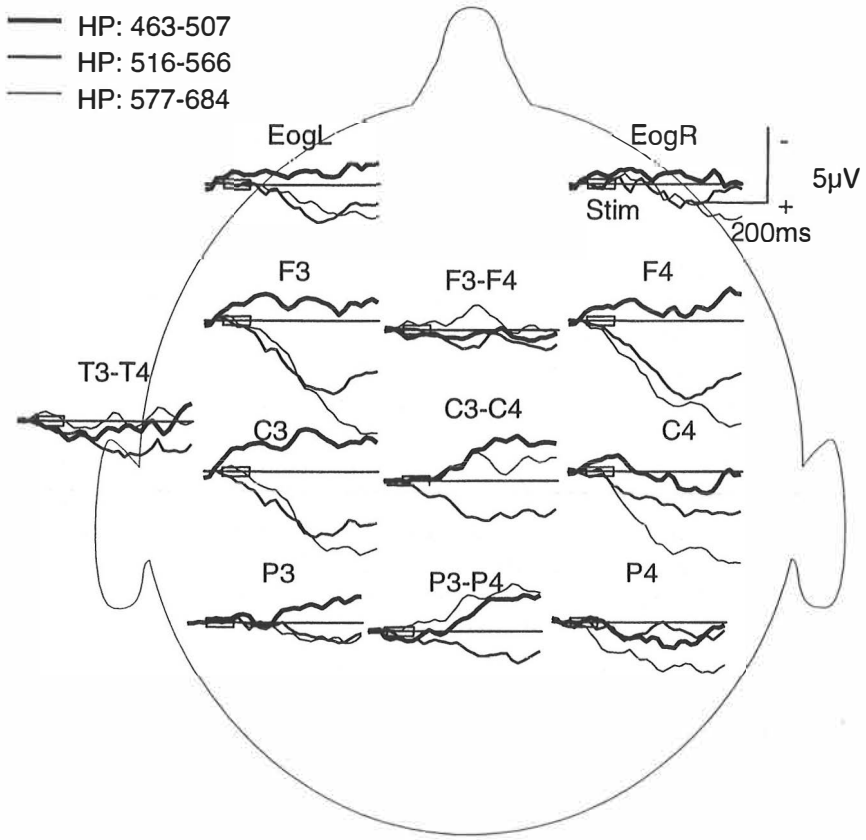

FIGURE 4 Grand average ERPs of 3 equally sized groups (n = 7, each) according to HP. The thickest line represents the ERPs of the hypothetically least mature and the thinnest line the ERPs of the most mature infants. Negativity up.

Article III

The focus of this study was on the duration changes of a vowel in a CV-syllable, /kaa/, variations of which frequently occur in the Finnish language as part of a word (like in the words /kato/ and /kaato/). This second empirical study had two major goals: I. To examine, whether the ERPs to stimuli differing in vowel duration would differ between at-risk and control infants. II. To clarify how the brain's detection of speech sound duration change is reflected in ERPs at birth

and how ERPs change with development. ERPs were obtained from two age groups, newborns and six-month-olds, partly comprising of the same infants.

Methods

Seventy newborns, 31 from the control and 42 from the at-risk group, participated in the first experiments, and 51 infants, 23 from the control and 28 from the at-risk group, at the age of six months. In these experiments stimuli with a change in vowel duration were employed. The CV-syllable /kaa/ was used as a standard and /ka/ as a deviant stimulus. Korpilahti and Lang (1994) have found, for example, a reduced MMN to a stimulus duration change (50 ms, 80 % vs. 500 ms) in language impaired children (diagnosed in early childhood) as compared to control children. The ISI here was the same as in Article II, but now 425 ms between the stimulus offset and the onset of the next stimulus to keep the distance between the stimuli constant. This naturally also affected the rhythm created by the onsets of the stimuli, which was, however, the same for all the stimulus pairs, except for the deviant and the following standard stimulus (the response to the latter has not been analysed in the present work).

The individual ERP averages, separately calculated for the pre-deviant standard stimuli and the deviant stimuli, from a time window of -50 - 535 ms (with a 50 ms pre-stimulus baseline) were used for further analyses. From the individual averages the mean ERPs for consecutive 5-datapoint periods (covering 20 ms) were calculated. The statistical analyses were mainly carried out by comparing each 5-datapoint period between stimulus types and groups with two-tailed *t*-tests starting from the latency of 130 ms. Only the differences across at least two 5-datapoint periods at the level of $p < 0.05$ or one 5-datapoint period at the level of $p < 0.01$ are reported as significant.

Results

A similar slow positive deflection peaking at ca. 300 ms was seen for the stimuli in this study as was seen in the experiments of Article II, but now a clear response was also generated by the long standard /kaa/ stimulus (Figure 5).

No major stimulus or group effects were found at birth. The response to the short deviant /ka/ differed from that to the standard only in the at-risk group and only at F4, being more positive at 280-325 ms. The ERPs of the six-month-old infants had a more mature waveform with a clear negative-positive-negative waveform (Figure 6). At this age the groups differed from each other in their responses to the standard /kaa/ at C4 and P4 at the late latencies (405-525 and 405-450 ms, respectively), the amplitude of the at-risk group being more negative.

In both six-month-old groups, the responses to the deviant /ka/ were clearly positively displaced in relation to those to the standard /kaa/. This effect was pronounced at a range of 200-350 ms, in which the slope from the

positive to negative deflection occurred. The effect was bilateral fronto-centrally in both groups, and in addition, it occurred at the left parietal site in the control group. The deviant and standard ERPs also differed at later latency ranges of 380-535 ms at the fronto-central electrodes in both groups, with the exception that no significant difference was seen at C4 in the control group and at F3 in the at-risk group. A stimulus x hemisphere by group interaction was also found for C3 and C4 between 430-475 ms. At the late latencies the negative deflection generated by the deviant /ka/ appeared to be shorter in duration than that generated by the standard /kaa/.

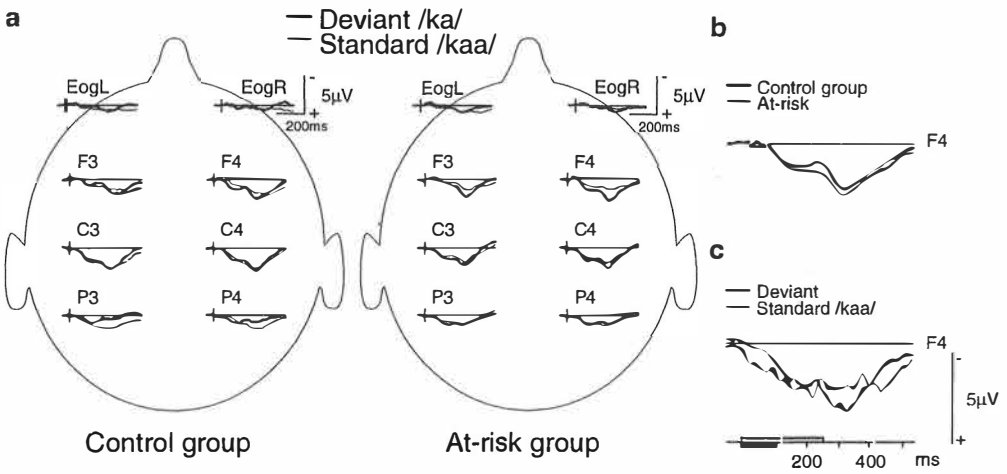

FIGURE 5 **a,** The newborn ERPs (averaged across participants) to the long standard /kaa/ (thin line) and short deviant /ka/ (thick line) in the control (N=31, left) and at-risk (N=42, right) groups. The stimulus onset is marked with the vertical line. **b,** The deviant response at F4 in the control (thick line) and at-risk (thin line) groups plotted over each other. **c,** The ERPs of a separate subgroup of 13 newborns (5 at-risk and 8 control infants, pooled together) in an awake state to the standard (thin line) and deviant stimulus (thick line) at F4. The stimuli are marked with the boxes above (/kaa/) and below (/ka/) the calibration line. Negativity up.

Discussion

The ERP changes in this study, from a slow positive deflection in the newborns to a more differentiated negative-positive-negative waveform in the 6-month-olds show maturational changes in the ERPs and are in line with previous experiments with full-term neonates and young infants (Kurtzberg et al., 1984b; Leppänen et al., 1997; Thomas & Crow, 1994). They also fit well with the increase of myelination throughout the first three to four months after birth and the maturation of synaptic connectivity (Huttenlocher, 1994; Johnson, 1998). These general waveform changes do not seem to be explainable by different arousal states (the data were obtained from newborns during quiet sleep and

from six-month-olds while awake), as can be seen from the ERP data from a smaller sub-sample of 13 newborns (5 at-risk, 8 control babies) obtained in an awake state (Figure 5c).

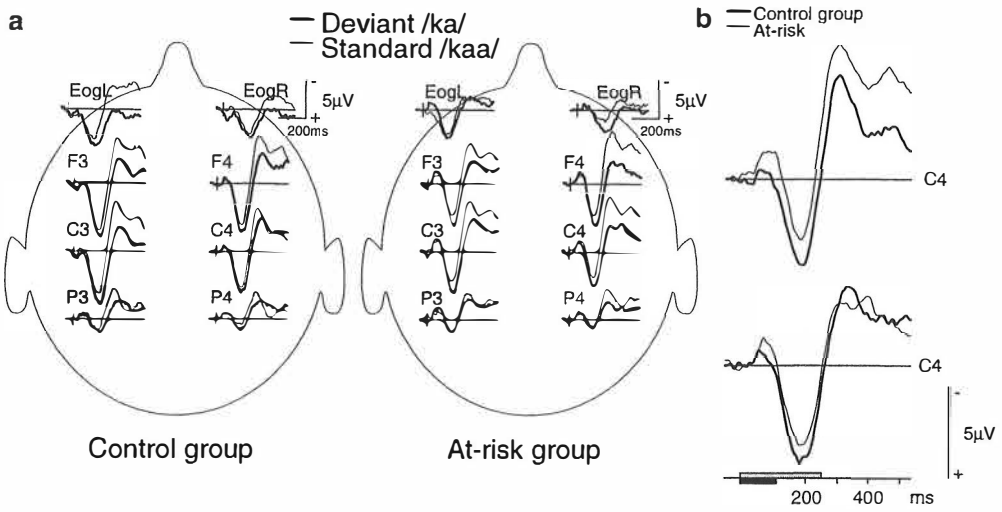

FIGURE 6 **a,** The ERPs of the six-month-olds (averaged across participants) to the standard /kaa/ (thin line) and deviant /ka/ (thick line) in the control (N=23, left) and at-risk (N=28, right) groups. **b,** The standard response (top) and the deviant response (bottom) at C4 in the control (thick line) and at-risk (thin line) groups plotted over each other. Negativity up.

Prominent differences between the responses to standard /kaa/ with a long vowel and deviant /ka/ with a short vowel indicate that the infants' brains processed these durations differently, but only by the age of six months. Either the stimulus difference was too small for newborns or the presentation rate was too fast. The latter option was tested in the experiments of Article IV.

As in the previous study, the ERPs to the deviant stimulus were also positively displaced in relation to those to the standard stimulus in this study. The responses to the standard stimulus can be considered to reflect a 'typical' infant response to auditory/speech stimulation per se. The response to a deviant stimulus in a sound stream may, then, reflect either the processing of stimulus change or of 'new' physical stimulus properties. Here the deviant stimulus was 140 ms shorter than the standard stimulus. It would be difficult to imagine how the positive deflection of the shorter deviant response could be greater and/or 'last longer', if it were just due to the 'new' physical properties of the stimulus. In line with the interpretation of the results of the previous study, this positively displaced deflection to the deviant stimulus can be taken to suggest a discriminative response that is not typically seen at adults in similar latencies.

One tentative explanation for the lack of a clear adult-like MMN, as opposed to the studies of Alho, Cheour and colleagues (cf. Alho et al., 1990a;

Cheour et al., 1998a; Cheour-Luhtanen et al., 1995), could be in the differences in the ISIs used. For example, Cheour-Luhtanen et al. (1995) used an ISI of 700 ms (between stimuli), while in this study it was 425 ms. It is possible, that with longer ISIs the stimulus effects might be clearer, as suggested above (cf. Kurtzberg et al., 1995). In line with this explanation, the lack of group differences and stimulus effects at birth may also be dependent on the short ISI used in the current study. To clarify this issue, the ISI was made longer in the second set of experiments in Article IV.

Only some group differences were observed, but not until the age of six months. That this difference occurred in the response to the standard stimulus, suggests differences in the basic responsiveness rather than in the change detection mechanism. A differential hemispheric pattern, related to this standard response effect, was also seen between the groups. The used vowel difference might have been 'too' easy for both groups for any deviant related group differences to show up. As a whole, the results suggest basic processing differences between groups already at this early age.

Article IV

In the previous study presented in Article III, clear evidence for a reliable detection of duration change of speech sounds was found only by the age of six months. Similarly, group differences were not found until the age of six months. It is possible, that developmental factors, such as the refractoriness of responses related to interstimulus interval variations, affected the results (see e. g. Kurtzberg et al., 1995; Ohlrich et al., 1978), and that a longer ISI than used in the Article III study would, therefore, be necessary for a clearly observable discriminative response. Thus, in Article IV, the research questions were: I. Does a slower presentation rate lead to a more clearly distinguishable brain's response to change in stimulus duration in newborns? II. Does this ISI prolongation also make ERP group differences more marked?

Methods

A separate sub-sample of 23 newborns, 11 from the control and 12 from the at-risk group, participated in these experiments. In this study, two conditions were employed, in the first labelled as the *fast rate condition* the procedures were the same as in Article III. In the 2nd *slow rate condition* the procedures were also otherwise similar, except that the ISI was prolonged to 855 ms. Also, similar statistical analyses were employed.

Results

The ERPs of this sub-sample in the *fast rate condition* were similar in their waveform and polarity to those in Article III, with no stimulus effects in either group in any of the frontal or central channels, replicating the previous results. In the *slow rate condition* the responses were clearly more positive than in the *fast rate condition* (Figure 7); the responses to the deviant /ka/ differed significantly between the two conditions in both groups. The differences were more widely distributed at the left fronto-central hemisphere in the control group, and across all the measured right hemisphere sites in the at-risk group, in which the condition differences were more prominent and more wide spread. The response to the standard /kaa/ differed significantly between the *fast* and *slow rate conditions* only in the control group at F4 at the ranges of 130-225 and 255-400 ms.

In the *slow rate condition* clear differences between the responses to the deviant and standard stimuli were seen in both groups (Figure 8). In the control group these differences were significant only at the left hemisphere, the deviant responses being negatively displaced at F3 at late latencies (430-475 ms) and positively displaced earlier on (155-200) at P3. In the at-risk group the deviant responses were positively displaced at the right hemisphere at C4 and P4 (at 280-350 and 380-425 ms, respectively).

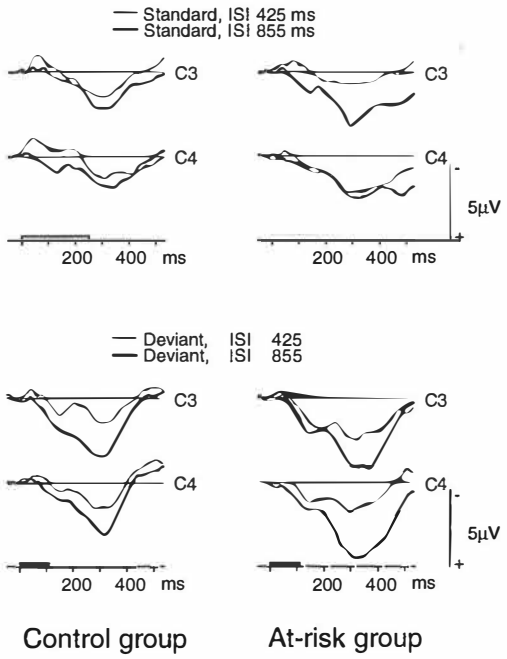

FIGURE 7 The grand-average ERPs of newborns in the *fast rate* (thin line) and *slow rate* (thick line) conditions plotted over each other. The responses to the long standard /kaa/ (top) and short deviant /ka/ stimulus (bottom) in the control (N=11, left) and at-risk (N=12, right) groups. The stimuli are marked with the boxes on the calibration line. Negativity up.

The groups also differed from each other. Some differences were found already in the *fast rate condition*. Both the responses to the deviant (F3, 280-500 ms) and to the standard stimuli (F4, 105-225 and 255-325 ms and P4, 130-200) were significantly more positive in the at-risk than in the control infants. The group differences were, however, more marked in the *slow rate condition*, but were significant only for the ERPs to the deviant /ka/ syllable, being largest at the right frontal and central scalp

areas (see Table 3). The deviant response in the at-risk group had a slow, long lasting positive deflection peaking around 330 ms, while in the control group it did not reach as great a positivity and turned its polarity into a negative direction more quickly.

Discussion

The prolonging of the ISI from 425 to 855 ms (offset-to-onset) resulted in the enhancement of the positive ERPs, in reliable stimulus driven ERP differences in both groups, and ERP group differences between newborn control infants and those at risk for developmental dyslexia, as was expected in Article III.

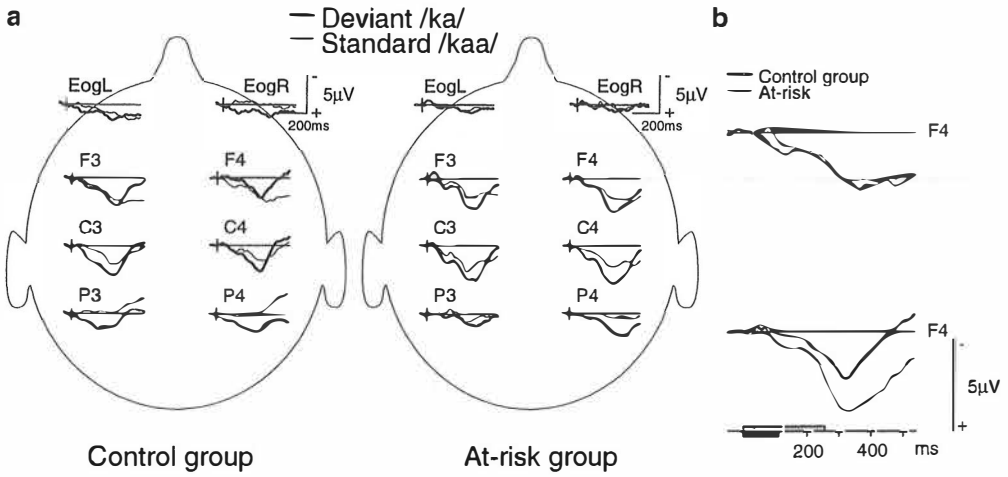

FIGURE 8 **a,** The newborn grand-average ERPs to the standard /kaa/ (thin line) and deviant /ka/ (thick line) in the control (N=11, left) and at-risk (N=12, right) groups. **b,** The standard response (top) and the deviant response (bottom) at F4 in the control (thick line) and at-risk (thin line) groups plotted over each other. Negativity up.

The increases in the amplitude of the positive deflection with the longer ISI can be partly explained by quite long refractory periods in newborns (cf. Kurtzberg et al., 1995); with short ISIs the afferent auditory system remains refractory which is reflected in reduced responses. With the slower stimulus presentation rate the ERPs to the deviant and standard stimuli also differed from each other in both groups. At the central channels, the ERPs of both groups to the deviant stimuli were more positive than those to the standard stimuli repeating the earlier findings in Articles II and III. In addition, in control infants the response to the short deviant /ka/ was negatively displaced at the frontal scalp areas, resembling infant MMN, though at a somewhat later latency than in some other studies (Alho et al., 1990a; Cheour-Luhtanen et al., 1995). However, the late

negativity also resembles a similar looking negativity generated by the same /ka/ stimulus, when presented with equal probability with the long /kaa/ and five other CV-syllables (from our unpublished results from the data of another sub-sample of 49 newborns). Therefore, the frontal negative deflection to the deviant stimulus could just reflect a shorter response to the shorter deviant stimulus. This data does not allow for a decisive conclusion to be made.

The results from the *slow rate condition*, with predominantly positively displaced deflections, show that the lack of an adult-like negative displacement of the deviant response in infant oddball ERPs is not mainly due to a short ISI, and is thus not due to differential refractoriness with different presentation rates. Furthermore, it is striking that the enhancement of the positive deflection was more wide spread and more pronounced for the short deviant /ka/ than for the long standard /kaa/. This phenomenon was more marked in the at-risk group. As was the case with the prolonged positivity to the same deviant /ka/ in the experiments with six-month-olds in Article III, it would be difficult to explain this more enhanced positivity as merely due to a smaller refractory activation of afferent neuronal populations to new physical stimulus features. Rather, the enhancement of the positivity could be related to the processing of change in stimulus duration, i.e., detection either of the 'omission' of the rest of the stimulus or response to the 'earlier' offset of the stimulus. The latter possibility of an offset response is not very likely, however, because the response to the standard stimuli does not seem to commence or peak later than that to the deviant stimulus, as would be expected to be the case for an offset response.

TABLE 3 Time windows of statistically significant differences between control and at-risk groups for responses to the deviant /ka/ stimuli in the *slow rate* condition.

Channel	Time window	*t*-values
F4	330-525 ms	$t > 2.3$*
C4	355-375 ms	$t = 2.41$*
	380-450 ms	$t > 2.8$**
	455-475 ms	$t = 2.19$*
P3	155-225 ms	$t > 2.2$*

The smallest *t*-values (df = 21) within the time windows are given, when more than one 5-datapoint period has been reported.
* = $p < 0.05$, ** = $p < 0.01$.

The groups differed from each other most markedly in the *slow rate condition*, although some differences were also found in the *fast rate condition*, unlike in the previous experiment (Article III), suggesting greater responsiveness in general in at-risk infants. In the *slow rate condition* the positive deflections generated by the deviant stimulus in the at-risk group were greater than those in the control group, most markedly at the right fronto-central sites. This suggests that occasional shortening of the duration of speech sounds leads to a more pronounced right hemispheric brain response in infants at risk. Whether this reflects possible group differences in dishabituation or in a change detection mechanism, presupposing a memory trace for the standard stimulus, is unclear and cannot be determined on the basis of this data.

Significant stimulus and ISI effects occurred more consistently at the left hemisphere in the control group, while in the at-risk group at the right hemisphere. These group differences appear to indicate that infants at high risk for familial and developmental dyslexia process auditory/speech stimulus durations differently from infants without such a risk even from birth. This finding suggests the existence of an early biological factor related to the auditory system, perhaps genetic in nature, which may contribute to the development of speech and phonological processing.

Article V

This article focused on the duration change of a speech cue embedded in a pseudoword /ata/, the silence gap, that signals the length of stop-consonants (see e. g. Lehtonen, 1970). The goal was to see whether the brain's response to changes in this silence gap duration are related to an at-risk status of dyslexia. The research questions examined in two major ERP conditions were: I. Do at-risk and control groups differ in their ERPs to a frequently repeated short /ata/ and an occasionally presented long /atta/ with a prolonged /t/ involving a longer silence gap? II. Does the presentation context affect differently the ERPs of at-risk and control infants? More specifically, do the groups differ in their ERPs to the same short /ata/, but presented as a deviant stimuli among long /atta/s acting as the frequent standard stimuli?

Methods

These experiments involved 76 six-month-olds, 39 from the control and 37 from the at-risk groups. The experiments were carried out using three conditions. In the 1st condition labelled as the */atta/ deviant condition* two deviant stimuli, 400-ms-/atta/ (nr. 2 in Table 2, labelled as the intermediate /atta/ in Article V) and 460-ms-/atta/ (nr. 3 in Table 2, labelled as the long /atta/), were presented occasionally among the repeated short standard /ata/ (nr. 1 in Table 2). Only the data for the short /ata/ and long /atta/ are reported. The ISI was fixed at 610 ms (offset-to-offset) to make the interval between the stimuli sound clearly longer than the standard stimulus. In the 2nd */ata/ deviant condition*, the occurrence probabilities of the short /ata/ and the long /atta/ were reversed, /ata/ being now the second deviant. The sequence remained otherwise similar.[17] For a small sub-sample of 6 of the 39 control participants a further control study of the */ata/ deviant condition* was employed; the short /ata/ and

17 For some subjects an ISI of 450 ms (offset-to-offset) was used. As no statistical difference was found in the control group during the analysed period (see below) between the ERP-measures in the two ISI conditions (450 vs. 610 ms; $p>.05$), the data from these conditions were pooled.

the intermediate /atta/ were presented with an equal probability without the intervening long standard /atta/s, in a similar way as in the *1100-Hz-alone* condition of Article II.

The EEG-epochs of -50-840 ms (with a 50 ms pre-stimulus baseline) were averaged separately for each stimulus type individually. In the */atta/ deviant condition*, the amplitude scores were determined for each participant as the mean amplitude of the 30-ms period centred at each major peak in the waveform. The following time windows were used in searching for these peaks: 60-330 ms for P2, 180-360 ms for N2, 380-580 ms for P3, 450-750 ms for N3, and 580-820 ms for P4 (N2,P3,N3 and P4 reported only for the deviant /atta/; see Figures 9 and 10). The difference wave (the deviant /atta/ - standard /ata/) was also calculated. In the */ata/ deviant condition* the score for the second negative peak was calculated as the mean amplitude from the latency range of 475-675 ms. The statistical analyses were carried out by MANOVA and ANOVA procedures for repeated measures.

Results

Both the short standard /ata/ and the long deviant /atta/ elicited a clear N1-P2-N2-P3 response pattern (Figures 9 and 10). The deviant /atta/ generated, in addition, another major negative peak (N3) reaching maximum at ca. 600 ms followed by a positive deflection (P4; note that the peak labels, shown in Figure 10 are just according to their polarity and appearance order).

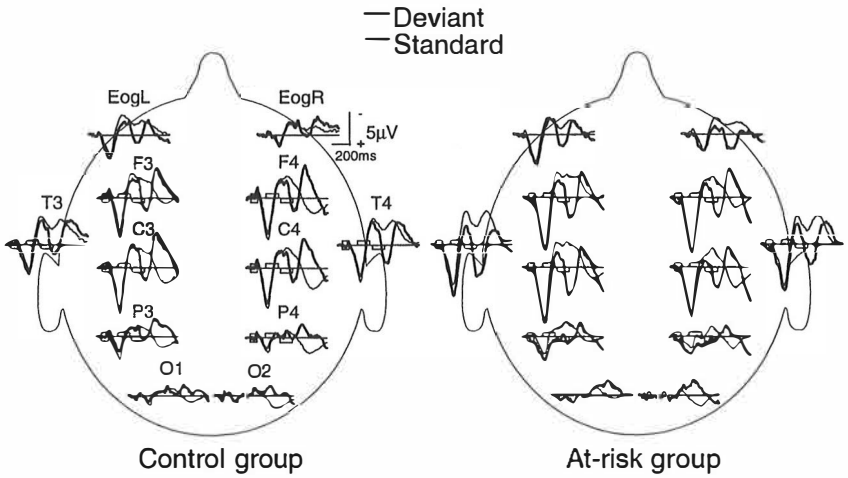

FIGURE 9 The brain electric responses (grand-average ERPs) of 27 control and 25 at-risk infants to the short /ata/ (thin line) and the long /atta/ (thick line). The stimuli are marked with the two boxes, with an empty space in between, above (/ata/) and below (/atta/) the baseline. The standard and deviant response patterns in relation to each other are clearly different between the groups at the left hemisphere, most markedly at C3.

The brain responses differed between the groups already in the early P2 component, which could not have been affected by the stimulus differences. Clear group differences were also found in the late components at the latencies, from which the stimulus differences could be detected. Analyses performed separately for each component and each hemisphere indicated, that P3- and P4-peaks had more positive amplitudes in the at-risk than in the control group, whereas the N3-amplitude was more negative in the control group. These effects were found only at the left hemisphere. The groups also differed in their difference waves (the deviant ERPs - standard ERPs) between 590-625 ms and 715-755 ms at C3 (Figure 10). Use of the amplitude of the P2 component as a covariate, in order to test how the differences in exogenous responsiveness would affect the observed group differences of P3, N3, and P4 components, resulted in the disappearance of the group differences. However, for the N3 component at C3 the group difference remained in a separate ANOVA with the P2-amplitude still as a covariate, indicating that a part of the group differences for the deviant response amplitude at the left hemisphere is due to a differential response pattern to the change in the temporal structure of the stimuli.

To test whether the presentation context affects the responses of the two groups differently the positions of the short /ata/ and long /atta/ were reversed in the 2nd */ata/ deviant condition.* Had the context no effect, the brain's response to the short /ata/ as the deviant stimulus should be similar to it's use as the standard stimulus. However, the short deviant /ata/ generated another negative peak following N2 in the control infants (Figure 11). This additional negative deflection was completely missing in the at-risk group, indicating that the stimulus presentation context has a differential effect on the at-risk and control group's brain responses.

In a discriminant function analysis, used to determine how well brain activation could correctly identify the infants at risk for dyslexia, the ERP measures (P2, P3, N3, P4 of the deviant response at the C3 and T3 sites) in the */atta/ deviant condition* correctly classified 68.0 % of the at-risk infants and 85.2 % of the control infants, suggesting a rather high predictability.

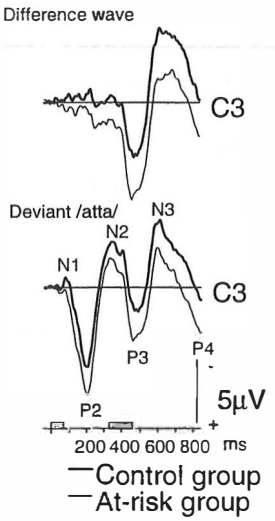

FIGURE 10 The difference wave (deviant - standard response), top, and the deviant /atta/ response, bottom, at C3 in the control (thick line) and at-risk (thin line) groups plotted over each other. Peaks are labelled according to their polarity and appearance order.

Discussion

The groups differed both in their exogenous responsiveness and in their responses to stimulus duration change, presupposing the formation of memory traces for the repeated stimuli preceding the deviant stimuli.

The additional negative deflection at the fronto-central sites at ca. 550 ms in the short */ata/ deviant condition* resembles in the waveform adult MMN and in terms of its latency (ca. 380 ms from the time point at which the change could be detected) it also resembles reported infant MMN (Cheour et al., 1998b). It should be noted, that in this case the whole deviant /ata/ was shorter than the standard /atta/ in terms of the total duration. Thus this difference may also have contributed to the generation of the second negative peak. That the response was also similar to the long /atta/ deviant-response in the */atta/ deviant condition*, could be taken to suggest an alternative explanation for MMN. In this view, the sound environment would affect how subsequent sounds are processed; it could 'tune' the brain's response or make it more sensitive to the physical features of stimulation already present in the sound context. Further evidence would be necessary in order to be able to favour this possibility.

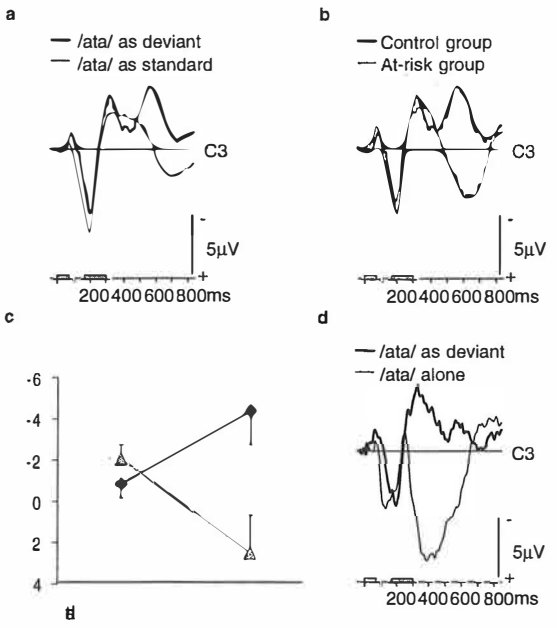

FIGURE 11 The ERPs (averaged across the infants) at C3 (the stimuli marked with boxes on the calibration line). **a,** The control group ERPs to the standard short /ata/ in the */atta/ deviant condition* (thin line, occurrence rate 80%, N=27) and the same /ata/ as the deviant stimulus in the */ata/ deviant condition* (thick line, 10%, N=12). The deviant /ata/ generates an additional negative deflection at ca. 550 ms. **b,** The ERPs to the deviant /ata/ in the */ata/ deviant condition* in the control (blue, N=12) and at-risk (thick line, N=12) groups plotted over each other. **c,** Mean amplitude over the 475-625 ms range for the short /ata/ as the standard and as the deviant stimulus in the control (square) and at-risk group (triangle). Bars indicate s.e.m. **d,** The ERPs to the short deviant /ata/ in the */ata/ deviant condition* (thick line) and the same /ata/ presented with the inter-deviant intervals but without the intervening standard stimuli (thin line). The control and at-risk group data are pooled (n=6).

The second negative peak in the control group is not likely to be due to enhanced afferent element activation because of the prolonged intervals between the deviant /ata/s. This is shown by the fact that no equivalent additional negativity was elicited when the same /ata/ was presented without any intervening standard stimuli (in a further control study with a small sub-sample using 6 of the participants, Figure 11d).

In addition, the present results show that the at-risk infants have, in comparison to the control infants, a more pronounced early positive exogenous response to sounds. A similar kind of larger positive response has been earlier observed by Alho et al. (1990b) in 4-7 month old pre-term infants in comparison to full-term infants for a 1200-Hz deviant tone. Pre-terms also have higher risk than full-terms for language problems. It is possible that a similar kind of auditory processing deficit would result in language related difficulties in both pre-terms and infants at-risk for dyslexia. However, this possible link between the findings can be regarded only as speculative, because pre-terms as a group are not comparable to the at-risk infants of the present study, who were full-terms, and in whom the question is not, supposedly, so much of maturational delay than that of processing differences. The present results also show, that the responses of the at-risk group are more or less similar regardless of whether the same stimulus is a standard or deviant stimulus. On the other hand, the control infants' responses are differently modulated or affected by the ongoing speech sound environment.

Although the present data do not prove that infants at risk for dyslexia would have differences only in temporal processing, the results do support a notion of early problems in processing the temporal structure of speech elements. A possibility exists, that these problems may be caused by similar brain mechanisms, that may underlie the reported deficit in processing rapid information changes or short acoustic cues, which has been suggested to be one potential underlying factor for future problems in learning to manipulate efficiently sublexical units during reading acquisition (Frith & Frith, 1996; Galaburda & Livingstone, 1993; Tallal et al., 1993; for a more elaborate discussion on this issue, see General discussion).

GENERAL DISCUSSION

These present studies reveal developmental effects on the event-related potentials of young infants, and demonstrate, for the first time, that reliable brain responses can be measured to duration changes in speech sounds even at birth. These studies further demonstrate that the brain electrical activation generated by speech sounds varying in their temporal structure differ between newborn and six-month-old infants who have a high genetic risk for dyslexia and infants without such a risk even before they learn to speak.

In this work maturational effects were studied at two developmental stages, at birth and at the age of six months. The ERPs undergo marked developmental changes during this period. The ERPs of fullterm newborns were transformed from a slow and shallow waveform to a wave complex with clearly distinguishable deflections reflecting a typical more mature negative-positive-negative deflection structure. This scheme is in line with a number of developmental ERP studies (Alho et al., 1990b; Cheour, 1998; Cheour et al., 1998a, b; Cheour-Luhtanen et al., 1995; Dehaene-Lambertz & Baillet, 1998; Duclaux et al., 1991; Kurtzberg et al., 1995; McIsaac & Polich, 1992; Tokioka et al., 1995). At birth the most typical waveform was a long lasting positive deflection, which was observed in all stimulus conditions in all cases when a reliable response was observed. It was thus generated equally by rapidly presented pure tone deviant stimuli, pure tones presented with equal probability and with a slow rate, and CV-syllables irrespective of their presentation probability (i.e., whether presented as deviant or standard stimuli). This strongly suggests that this slow positive deflection represents a typical newborn response to any auditory/speech stimulus and is in line with a number of early studies carried out with equal presentation probabilities and slow rates (e. g. Barnet et al., 1975; Ellingson et al., 1974; Graziani et al., 1974; Kurtzberg et al., 1984a; Kurtzberg et al., 1986; Novak et al., 1989; Pasman et al., 1992; Rotteveel et al., 1986; Weitzman & Graziani, 1968).

Developmental changes were also observed in stimulus effects on ERPs. Though the newborns clearly 'detected' pitch change in a stimulus stream with

a fairly rapid rate, duration changes were not detected, despite a somewhat slower presentation rate, until the age of six months, as judged from the ERPs. However, by making the presentation rate more than two times slower, clear ERP differences between short and long speech stimuli were observed also at birth. Thus, both stimulus and ISI effects may have their own independent, though interrelated impact on infant ERPs (for further discussion on these effects, see below).

Group differences were obtained using stimuli that varied in their temporal structure, either in the duration of the vowel in a CV-syllable or in the duration of the silence period within a pseudoword. All the observed ERP group differences were amplitude differences. The latencies were similar in both groups. At birth no group differences were observed in the ERPs to the vowel duration change with an offset-to-offset ISI of 425 ms, but clear group differences occurred with the slower stimulus rate (855 ms ISI). The fact that no stimulus effects were found in either group with the faster stimulus rate, suggests that the lack of group effects in that condition are due to a floor effect in both groups. Thus, provided that reliable ERPs can be measured, at-risk and control infants seem to differ already at birth in their brain activation generated by changes in vowel duration. That only some group effects were found at the age of six months, may partly be related to the earlier discussed ISI effects (cf. also below) or to a possibility that the duration difference was 'too easy' for both groups. More marked group differences were found in the ERPs to the duration change of the silence gap cueing the length of stop consonants. These ERP results suggested that the at-risk infants differ from controls both in their basic responsiveness to auditory stimuli as well as in terms of how the stimulus presentation context (whether presented as a standard or a deviant stimulus) affects the ERPs.

Maturation of infant ERPs

Stimulus effects

Two different stimulus types were used at birth, pure tones and CV-syllables, whereas CV-syllables and pseudowords were used at the age of six months. At birth, the ERPs to the deviant stimuli irrespective of the stimulus type resembled each other in both groups, but the responses to the standard stimuli differed between the stimulus types, being clearly more marked to the CV-syllables. This might be explained, though only partly, by a somewhat longer interval between the stimulus onsets for the CV-syllables. A more probable explanation may be, that because CV-syllables are more complex than pure tones and thus also 'carry more information', they may activate larger neuronal populations, summating temporally, and therefore produce a greater response than the pure tones. This is supported by observations obtained using behavioural methods. For example, Colombo (1985) found that there is a

general linear increase in 4-month-olds' attention to auditory stimuli as a function of the complexity of their spectral structure. Total stimulus duration was also longer in the CV-syllables in these studies, which may have also resulted in greater responses. No such difference was found, however, in the measurements for the six-month-olds between the CV-syllables (Article III) and the pseudowords (Article V), despite the longer total duration and longer offset to offset ISI for the pseudowords. Rather, the standard responses were remarkably reminiscent of each other. However, what determines behavioural, and presumably also electro-cortical responsiveness is not any single stimulus feature but rather a combination and interaction of several features, such as intensity, duration, complexity and presentation rate (Clarkson & Clifton, 1991).

The responses to the deviant stimuli were generally positively displaced in relation to those to the standard stimuli in all experiments with significant differences in the ERPs between the stimuli. This pattern was not, however, observable in the studies using the silence gap duration change (Article V). It should be noted, though, that in the latter experiments a traditional way to use difference waves (subtracting the standard ERPs from the deviant ERPs) is problematic, because in the used pseudowords more than one stimulus element, which can initiate its own summated activation, appear at different latencies and thus the responses to these elements overlap each other. In the other studies (Articles II-IV) the positively displaced deflections, generated by the deviant stimuli, either reached their maximum or extended over a latency range at which MMN has also been reported to occur (cf. Alho et al., 1990a; Cheour et al., 1998a; Cheour-Luhtanen et al., 1995), though for the vowel duration changes these appear relatively early.

As pointed out in discussing each study separately, these either greater (in the case of pitch changes) and/or prolonged (in the case of vowel duration changes) positive responses cannot be explained merely by the non-refractory activation of afferent systems to 'new' physical stimulus elements. Similar kinds of positivities (Alho et al., 1990b; Dehaene-Lambertz & Baillet, 1998; Kurtzberg et al., 1995) have been interpreted, for example by Alho et al. (1990b), to manifest an adult-like P3a response reflecting involuntary attention switch (Novak, Ritter, Vaughan, & Wiznitzer, 1990; Sams et al., 1985a; Snyder & Hillyard, 1976; Squires et al., 1975). In line with this explanation, for example McIsaac and Polich (1992) related comparable positive deflections observed in oddball paradigms (see also Tokioka et al., 1995) to long term memory processes and higher cortical functions. In these latter studies the infants were encouraged to pay attention to the sounds, while in the present studies the infants were either in deep quiet sleep (newborns) or were entertained by interesting toys in order to attract their attention (six-month-olds).

As one possible explanation for a failure to record a clearly observable MMN to pitch change in a number of infants in the present studies (Article II), Alho and Cheour (1997) suggested a low signal-to-noise ratio in infant ERPs. While it is true, that there is more variability in infant ERPs than in adult ERPs, the differences in the polarity of change-driven ERPs in the present studies and for example those of Alho, Cheour and colleagues (e. g. Alho et al., 1990a; Cheour et al., 1998a; Cheour-Luhtanen et al., 1995) cannot be explained by this

factor. In the present studies of Article II the number of acceptable EEG-epochs for ERP averaging for each deviant stimulus type was at least 90 (ranging between 92 and 267, with an average above 100), which is close to the minimum of 100 acceptable epochs used by Cheour and colleagues (cf. Cheour-Luhtanen et al., 1995). Taken together, the positive responses to deviant stimuli seen in the present study seem to reflect, in part, an exogenous brain response to any auditory stimulus, but also in part brain mechanisms related to the processing of stimulus changes in a sound stream, mechanisms that presuppose pre-existing neural traces of the repeated stimuli. Further, taking into account the differences between the infant and adult auditory systems due to early brain developmental factors, it is plausible to expect differences also in the ERPs between these age groups at corresponding latencies.

Some evidence was also found for a negatively displaced response to deviant stimuli and an adult-like MMN (cf. Cheour et al., 1998a). First, an unexpected reduction of the positive deflection to the greater pitch change was observed in the 3rd study of Article II, which was taken to suggest an overlapping negative response at the same latencies. For example, Kurtzberg et al. (1995) have suggested that MMN in infants might be seen as a reduction of the typical positive deflection. The smaller positivity to the greater change was among the strongest evidence found in the present studies for a possible negative change detection response. Second, in the condition with the prolonged ISI reported in Article IV, control infants' response to the deviant /ka/ was negatively displaced at the frontal sites, resembling infant MMN, although at later than typical latencies (cf. Alho et al., 1990a; Cheour-Luhtanen et al., 1995). However, as this late negativity was highly similar to the response generated by the same stimulus presented with an equal probability with other stimuli, the finding does not unambiguously support a MMN interpretation. Third, the most adult-like MMN was observed when comparing control infants' responses to the same /ata/ presented as the deviant and as a standard stimulus in Article V. The response to /ata/ as the deviant stimulus generated an additional negative deflection resembling reported MMN in six-month-olds (Cheour et al., 1998b). Theoretically an option exists, though, that this negative deflection could also be taken to represent the 'tuning' effect of the sound context making the auditory system more sensitive to frequently occurring features. The former alternative is favoured, as there is no clear evidence on the latter. However, the present studies do not allow one to draw final conclusions.

Individual variation in the polarity of newborn ERPs, for example the negatively displaced deviant response observed in Article II, could be partly explained by maturational factors, indexed for example by GA, CA and cardiac measures (see under Discussion for Article II). This notion fits well with the description of five maturational levels through which the ERPs of young infants evolve until the age of three months (cf. Kurtzberg et al., 1984a; see also Novak et al., 1989; Weitzman & Graziani, 1968): the least mature ERPs, like those of pre-terms, show negative polarity at midline and lateral sites, and the most mature ERPs positive polarity at both these sites. These developmental effects suggest that in infant ERP studies individual maturational variation should be taken into consideration in interpreting the results.

ISI effects

The stimulus presentation rate has a substantial effect on infant ERPs, as seen from the studies in Article IV, in which newborn ERPs were compared in two ISI conditions. The greater the ISI, the greater the responses.[18] This phenomenon may be explained, at least partly and as suggested earlier, by long refractory periods in newborns (cf. Kurtzberg et al., 1995; Ohlrich et al., 1978). Refractory periods refer to a brief period when the cell is resistant to re-excitation (one or more ms after an action potential). During the first part, the so called absolute refractory period, the membrane cannot produce an action potential. During the second, the relative refractory period, a stimulus must exceed a threshold to produce an action potential. Throughout the total refractory period, permeability to sodium ions is low, and permeability to potassium ions is higher than normal. The refractory period sets a maximum on the firing frequency of a neuron (Kalat, 1992). However, as EEG is regarded as reflective of the post-synaptic temporal summation of large enough neural populations (Regan, 1989), it is plausible to relate long refractory periods in infancy to immature synaptic functioning. The lack of mature myelination could also be thought to slow down the responsiveness.

Accordingly, one could speculate that in the pitch change paradigm of Article II with the short ISI the response to standard stimuli became refractory, whereas the non-refractory response to deviant stimuli (with rather long inter-deviant intervals), though perhaps overlapping with a possible negative response, remained positive, leaving also the difference between the deviant- and standard-responses positive in most full-term newborns. Correspondingly, in infants with the ERPs reflecting an earlier maturational level, with predominantly negative responses, negativity was enhanced. The matter is complicated by the fact, that the amplitude of MMN is also dependent on the inter-deviant intervals: with very short ISIs, if the probability of the deviants is kept constant, this interval becomes so short that the deviant tones start to form a memory trace of their own resulting in a smaller MMN (Näätänen, 1992). We have earlier observed that, for example, in 9-10-year-olds shortening the ISI from 610 ms to 400 ms results in a much smaller response both to the deviant and standard tones (Laukkonen, Leppänen, & Lyytinen, 1992). However, in the studies reported in Articles II and III the inter-deviant interval (2550 - 4675 ms, 3910-7285 ms, respectively) should have been long enough for a distinguishable MMN. For example, MMN has been shown to be elicited even with an ISI of 101 ms with a rate of one deviant and nine standards (on average) in one second (Näätänen et al., 1987).

Even so, a possible explanation for the lack of a clear adult-like MMN remains: with longer ISIs than used in Article II or III the responses to both standard and deviant stimuli would possibly have become larger, and consequently, the response elicited by the deviant stimuli at the latency of MMN might have become negatively displaced in relation to the response to the standard stimuli. However, the enhanced positivity to the deviant stimuli

18 This issue is also elaborately discussed in Article II.

with the slower stimulus presentation rate in Article IV clearly indicates, that this possibility does not explain the missing adult-like MMN in the present studies, at least not in those dealing with temporal changes (Articles III-IV).

Arousal state effects

The present studies at birth were carried out during quiet sleep and the studies at the age of six months during wakefulness. That the general waveform changes between these ages are not due to arousal states was shown in our preliminary study in which the responses were quite similar in sleep and during wakefulness. Arousal states are known, however, to affect ERPs. For example, ERPs have been reported to be largest in quiet sleep (e. g. Ellingson et al., 1974) and one study (Duclaux et al., 1991) found a difference between responses to deviant and standard tones only during quiet sleep. This is somewhat surprising in view that no or reduced MMN has been reported during sleep in adults (Campbell, Bell, & Bastien, 1991; Paavilainen et al., 1987). On the other hand, a MMN-like deflection has been reported to occur during sleep stage 2 in conjunction with the micro-states of K-complexes (Sallinen et al., 1994). How this is related to the fact, that it is quiet sleep, from which K-complexes also emerge later in infancy (Metcalfe et al., 1971), is unclear.

Cheour (1998) has reported, that in infants, MMN is somewhat reduced during quiet sleep and she suggested that this might be due to greater positive responses observed in quiet sleep. Her suggestion is supported by the fact that the ERPs of wakefulness, the typical state for MMN studies, resemble those of active sleep rather than those of quiet sleep in newborns (e. g. Ellingson et al. 1974). However, the finding by Duclaux et al. (1991) of differences between the deviant- and standard-responses only during quiet sleep speaks against this argument. But as Duclaux et al. (1991) used a rather long ISI (2000 ms) compared to typical MMN studies, their finding cannot necessarily be generalised to MMN. Be as it may, the present studies demonstrate that the major factor contributing to the presence or absence of adult-like MMN in infants is not differences in arousal states. All in all, these differences between adults and infants demonstrate developmental differences in sleep and its nature.

Group differences of the ERPs and their implications

ERPs to change in stimulus duration has earlier been reported to differ between a clinical group, language impaired, and control children. For example, Korpilahti and Lang (1994) have observed reduced MMN to pure tone duration change (50 vs. 500 ms) in 7-13-year-old language impaired children in comparison to control children. However, due to differences in the age,

diagnostic groups and stimulus material, their results are not fully comparable to the results in these studies.

The following major observations related to differences in processing durational changes between infants at risk for developmental dyslexia and control infants were made on the basis of the present studies.

Auditory responsiveness and context effect differences

The brain responses differed between the groups not only to the deviant stimuli varying in duration but also to the standard stimuli: at birth the standard /kaa/ response was more positive at relatively early latencies in the at-risk group than in the control group in the condition with the fast stimulus rate (Article IV), at the age of six months the corresponding response of the at-risk group was more negative at late latencies (Article III). Also at this age, in the experiments relating to consonant duration change the brain responses differed between the groups already in the early P2 component, which could not have been affected by the stimulus differences. Furthermore, in this study the group amplitude differences of the P3 and P4 components for the deviant stimulus were, at least in part, explained by the more positive exogenous response (of P2, when used as a covariate). These results suggest that there are differences between the groups also in the responsiveness to auditory/speech stimuli as such, independent of whether the stimulus involves a change or is repeated as similar. Surprisingly, in all the cases the amplitudes were higher in the at-risk group. One would have expected to see lower amplitudes in the at-risk group, which is a more typical finding in clinical populations (see Article I). What this means, for example, in terms of maturational effects on ERPs, is unclear as yet, as we have not analysed maturational correlates of GA, CA, and cardiac measures separately in each group.

Clearer group differences were found for the deviant stimuli differing both in vowel and consonant duration, at birth to the shorter deviant /ka/ (Article IV) and at the age of six months for the longer deviant /atta/ and shorter /ata/ when used as a deviant stimulus (Article V). The N3 component response to the long /atta/ at the left hemisphere was shown to be due to a differential response pattern to the change in the temporal structure of the stimuli, and not merely a result of a more prominent exogenous response to the second part of the stimulus. Moreover, the response to the short /ata/, when presented as the deviant stimulus generated an additional negative response in the control group; this second peak was completely missing in the at-risk group and the response in them resembled that to the same stimulus as the standard stimulus. Thus, as also pointed out earlier on, the group differences to the deviant stimuli cannot be explained only by differences in general auditory responsiveness.

As a whole, the results from Article V show that the at-risk infants have, in comparison to the control infants, a more pronounced positive exogenous response to sounds and that their responses are more or less similar in their waveform regardless of whether the same stimulus is a standard or deviant

stimulus. On the other hand, the control infants' responses are differently modulated or affected by the ongoing speech sound environment. These findings may tentatively be interpreted to mean that in at-risk infants the brain activation generated by the auditory system is 'too dependent' on physical sound features, in the sense that it is not capable of utilising the contextual information to the same extent as in control infants. It has been suggested, that speech sounds are represented as kinds of prototypes in the brain allowing for, however, some variation around the prototypes, and that these prototypes serve as perceptual 'magnets' for sounds close to prototypes in their physical features (cf. the 'magnet effect' described by Kuhl, 1991; see also Aaltonen, Eerola, Hellström, Uusipaikka, & Lang, 1997). Sensory memory traces could be thought to underlie the usage of contextual information and, thus, formation of the prototypes. It is possible, that failure to use contextual auditory information and high dependence on the physical sound features could disturb in at-risk infants the formation of such flexible prototypes of speech sounds. This phenomenon could, then, be associated with the categorical perception problems that have been related to developmental dyslexia (Werker & Tees, 1987; Steffens et al., 1992). Not only enough precision but also the flexibility to allow some variation in the vicinity of prototypes in speech sound representations can be thought to be a prerequisite for functional categorical perception.

This tentatively suggested interpretation does not, however, fit so well for the data on vowel duration change, for which the ERPs were greater in the at-risk group, though predominantly at the opposite hemisphere compared to the control group. Differences in the complexity of the stimuli might partly explain this phenomenon. The idea of possible group differences in speech prototypes would need, thus, to be further studied and validated in experiments employing several stimulus types (both tones and speech sounds varying in pitch, duration and transitional elements) and with controls for stimulus probabilities (e. g. reversing standard and deviant probabilities and presenting stimuli alone). The linkage to behavioral performance would also be necessary.

Hemispheric differences

In newborns, both condition (425 vs. 855 ISI) and stimulus (/kaa/ vs. /ka/) effects occurred more consistently at the left hemisphere in the control group, whereas in the at-risk group they were more prominent at the right hemisphere (Article IV). This is in line with a similar tendency in six-month-olds with the same stimuli (Article III). Also, at this age, group differences in the ERPs to the long deviant /atta/ occurred at the left hemisphere (Article V).[19] Behavioural

[19] This left hemispheric group effect is not in contradiction with the bilateral group effect for the additional negativity in the condition when the short ata was used as the deviant (*/ata/ deviant condition*), because the additional negative response in that condition was absent altogether in the at-risk infants. In this group the mean amplitude was rather, even more positive than the corresponding mean of the response to the same stimulus when used as the standard (*/atta/ deviant condition*).

studies with the dichotic listening technique have shown a right ear advantage (REA) for stop consonants, indicating predominantly left hemispheric processing (e. g. Dwyer, Blumstein, & Ryalls, 1982). In the present studies, however, the responses to the pseudowords with the stop consonants was bilateral.

Overall, these results suggest that there are hemispheric differences in the early auditory/speech processing between the groups. Although it is too early to state, how these findings are related to abnormal hemispheric dominance/laterality in dyslexics (see e. g. Hiscock & Kinsbourne, 1995; Zurif & Carson, 1970), the results are consistent with brain imaging findings of the differences in left-hemispheric functioning in dyslexics (Hynd et al., 1991b; Salmelin, Service, Kiesilä, Uutela, & Salonen, 1996; see also Hiscock & Kinsbourne, 1995; Article I). To get a final answer one needs to wait until the studied infants reach reading age.

Differences in the processing of the temporal structure of speech elements

The present data thus show that the at-risk infants differ from the control infants in their auditory/speech processing as reflected in brain electrical activation at a very early age. The differences found in this study were measured using speech stimuli that vary in duration. However, because no other speech or stimulus features were utilised, it cannot be concluded that only duration related aspects would be processed differently by the at-risk and control groups, as in fact, the review Article I also demonstrates.

One possibility to explain group differences in the ERPs to changes in the temporal structure of the used stimuli, especially in Article V could be differences in the temporal integration (Tervaniemi, Saarinen, Paavilainen, Danilova, & Näätänen, 1994; Yabe, Tervaniemi, Reinikainen, & Näätänen, 1997) between the groups. If the interval between two parts of a stimulus (or two stimuli) is long enough, the brain seems to process these as separate entities, at least to a certain extent. However, if the interval is short enough the brain processes these two parts as though they formed one entity, resulting in a fusion of their perception. This has been confirmed, for example, in studies that have demonstrated, that MMN is elicited even to a sound omission, like that of the second part of a paired stimulus, if the two parts of the standard stimuli appear close enough in time (Tervaniemi et al., 1994). In line with this idea, the at-risk infants could have a longer temporal integration window than controls, possibly due to a lower processing speed, resulting in a more 'merged' or integrated sensory event with longer within-pair intervals. One peaked negative deflection in the waveform to the deviant short /ata/ could be interpreted to reflect this phenomenon (Article V).

The temporal integration interpretation is in line with the finding of McCroskey and Kidder (1980) in their study of auditory fusion with dyslexic children. The time-point for fusion was defined on the basis of both ascending and descending series of paired stimuli. For example in an ascending series of paired stimuli with increasingly longer intervals between the paired stimuli, the

fusion point was defined as the last interval at which the stimulus was still perceived as a single event before the perception of two consecutive dual events occurred. The authors found that normally reading school-age children experience auditory fusion at shorter time intervals between tone pairs than reading disabled children, who thus require longer within-pair intervals to perceive two distinct stimulus events. Recently, Richardson (1998) using the same speech feature as in the present studies, and partly with the same infants, found that six-month-old Finnish infants at risk for familial dyslexia require a longer consonant duration than control infants to respond to a long consonant in a categorical fashion in a behavioral study employing a conditioned head-turn paradigm. This result could also be explained with the notion of temporal integration differences between the groups.

It is, though, somewhat puzzling that no very apparent latency differences were seen between the groups, which would have been further support for the notion of a lower processing speed in the at risk group. On the other hand, general latency decreases of ERPs during development have been related to the development of myelination (Casaer, 1993; Creutzfeldt, 1995), and thus, we would not expect any differences in myelination between the groups. However, other factors, not necessarily reflected in ERP latencies in infancy, may also affect processing speed or temporal integration. Casaer (1993) interestingly suggests, that it is not myelination as such which is important for effective processing, but rather that interacting brain centres are provided with fast signal-conducting pathways. At the speculative level an option is that possible differences in temporal integration might be affected by developmental differences in auditory pathways from the medial geniculate nuclei (MGN) of the thalamus to the auditory cortex (see below, cf. also Galaburda et al., 1994). Speculatively, the observed group differences could also be related to differences in the 'clock rate' (see e. g. Hari & Kiesilä, 1996) between individuals with dyslexia and without it. This phenomenon could also explain temporal integration differences. A slower processing rate would lead to imprecise representations of duration related information, which could be reflected in ERP differences generated by stimuli, in which the crucial element is not any spectral feature but one related to the flow of time, as is the case both in changes of the vowel and gap durations in the present study. However, not enough is known about how the brain encodes time and other temporally related information.

On explaining observed ERP group differences

The most obvious interpretation for the observed ERP differences between the group of infants at risk for dyslexia and the control group would be, of course, differences in the familiality of dyslexia in their families and close relatives, and thus likely in their genetic background. However, before one makes such a conclusion, one needs to consider whether other participant

related factors than the common familial background could account for the group differences.

Of these, pre-and perinatal factors could be excluded on the grounds that none of the participating infants could be diagnosed as a very low birth weight pre-term (and the number of few infants small for their GA was roughly the same in both groups) and that the infants in neither group had any abnormalities or neurological problems. Possible hearing status differences between the groups is more difficult to judge, because measures that were available for hearing assessment for the participating infants, were relatively robust. However, according to these and records available from their family guidance clinic visit, the infants had no hearing problems. Neither had the infants in either group an ongoing otitis media, nor were there any differences between the groups in the prevalence of its occurrence prior to the measurements. That the early exogenous response was larger in the at-risk group than in the control group, speaks against possible hearing status effects, because clear ERP responses can be regarded to presuppose a synchronous and summated activity of post-synaptic potentials (Regan, 1989); thus larger responses could hardly reflect a reduced hearing level.

Second, there are parent-related factors other than dyslexia, which could thought to be indirectly related to dyslexia. Of such possible factors other diagnoses co-occurring with dyslexia can be excluded, because the families were carefully screened and questioned for any possible other diagnoses, such as sensory or neurologic deficits. A more complex issue is IQ as an affecting factor. The fathers' IQ was lower in the at-risk group than in the control group on two occasions in relation to major ERP group differences. But in none of the cases did the mother's IQ differ between the groups. Thus, the burden of proof would be on the side of those trying to explain group differences with the parental IQs. In the ERP-literature there is evidence that IQ and ERPs are related. Otsuka, Sunaga, Nagashima, & Kuroume (1993) found, for example, that the P300 component latency had a significant negative correlation with verbal IQ, full scale IQ, and performance IQ (when using WISC-R). The authors concluded that the P300 latency reflects the stable aspects of intelligence. It is possible that both IQ and ERP-latencies reflect a common factor affecting both. However, to my knowledge no evidence exists for a connection between parental IQ and the ERPs of infants, an interesting research topic, but which is beyond the focus of this study. It is noteworthy that in this study the infants' IQ, when measured later at the age of 24 months, did not differ between the groups. Further, it should be also noted, that a criterion for a dyslexia diagnosis and the inclusion of a parent with dyslexia in the study was an IQ within normal range, that is, at least or above 85. A difference in socio-economic status between the fathers found on one occasion cannot be taken to explain even as much as the parental IQ and can thus be safely excluded as a possible explaining factor. In conclusion, the explaining power of IQ for ERP group differences remains at best very 'thin' in this study.

Yet another parent-related factor, which may be partly also interwoven with the previously discussed IQ-issue, is related to the speech input infants receive from their parents. According to this view, it would not be so much

genetic factors (if not indirectly via speed-related factors of IQ), which play a major role in the development of early auditory/speech processing, but rather the environment of infants. It is known, for example, that a variety of sounds are available to the fetus within the uterus during the prenatal period (see e. g. DeCasper & Spence, 1991) and that newborns are more responsive to speech passages that had been recited aloud during their prenatal period than to novel passages, suggesting that the fetuses had learned and remembered something about the environmental acoustic cues (DeCasper & Spence, 1988). Infants have also a preference for the parental language very soon after birth (see Eimas, 1996). In this study, this line of explanation for group differences in ERPs would presuppose, that parents in the at-risk group do speak to their infants in such a way as to lead to differential responding to speech sounds that vary, perhaps among other features, in their duration.[20] While this explanation is plausible, the fact however that the at-risk group differed from the control group already in their exogenous ERPs, suggests more fundamental processing differences than just differences in some feature specific speech representations. This issue needs further clarification and cannot be fully resolved on the basis of the data obtained in this study.

An alternative, and not exclusive explanation in relation to the former, could be that the found ERP group differences might result from abnormal development of the auditory subsystem(s). Some differences in anatomy between dyslexics and controls have been found in the symmetry of the medial geniculate nuclei (MGN) of the thalamus, the relay/way station that handles auditory inputs (Galaburda et al., 1994). It has been suggested that the MGN group differences are secondary to the cortical changes, reflecting abnormalities in the target areas for axons arising from the MGN during development (Galaburda et al., 1994). As pointed out in the introduction, this suggestion would fit with some cortical abnormalities found in dyslexics, including neuronal ectopias and architectonic dysplasias in the perisylvian regions (Galaburda et al., 1985; Humphreys et al., 1990; Rosen et al., 1993), and these could originate prenatally during the period of neuronal migration and subsequent cortical maturation (Rosen et al., 1992). If this were the case, the genetic basis for the early auditory/speech processing group differences, reflected in ERPs, would be favored.

Recently, evidence of difficulties in processing briefly presented or rapidly changing auditory information has been reported, and these difficulties have been suggested as one of potential underlying factors contributing to future developmental dyslexia (Hari & Kiesilä, 1996; Reed, 1989; Stark & Tallal, 1988; Tallal, 1980; Tallal et al., 1985a; for reviews, see Farmer & Klein, 1995; Galaburda & Livingstone, 1993; Tallal & Curtiss, 1990; Tallal et al., 1993; see also Frith & Frith, 1996). Problems with fast processing have also been suggested to occur in the motor-sensory and visual domain (Galaburda & Livingstone, 1993; Livingstone, 1993; Lovegrove, 1993; Stein & Fowler, 1985; Stein & Walsh, 1997). For example, Livingstone (1993), suggests that a subset of dyslexics have defects

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20 Unfortunately, no data of infant-directed parents' speech has been available to me in order to be able to solve this issue empirically.

in the fast visual magnocellular system dealing with moving objects and the information of the overall organisation of the visual world (in contrast to the parvocellular system related to detailed visual analysis).

A recent study by Eden et al. (1996) supports this suggestion showing that adults with developmental dyslexia exhibited striking differences in the activity of the brain area responsible for visual motion (V5, at the junction of the occipital and temporal lobes). These differences may be taken as evidence for a deficit in the magnocellular subsystem of the brain in dyslexics. This finding was linked, for example, by Frith and Frith (1996) to the reported auditory deficit in sensitivity to rapid changes in auditory information in dyslexics (see above). These authors suggested, as a possibility, that the differences in visual motion perception represent a marker of a more general cognitive deficit in timing affecting all brain modalities. They state that "in order to hear the differences between consonants, we need to be able to distinguish between very rapid changes in frequency" (p. 20). Salmelin et al. (1996) have also recently demonstrated, that while in normal readers the left inferior temporo-occipital region (specific to word responding) was sharply activated (at about 180 ms in a magnetoencephalography, MEG, study) in viewing single words, in dyslexics this region remained 'silent' or showed a slowly increasing late response.

On the other hand, Bishop, Bishop, Bright, and James (1999) have very recently reported on evidence in a twin study suggesting, that temporal processing problems may be differently transmitted in comparison to phonological processing problems. They found that, while language impaired participants performed worse both on a temporal task (Tallal's Auditory Repetition Test, ART) and on a phonological short-term memory task, there was no evidence of a heritable influence on the temporal task scores; correlations between twins and their co-twins were high for both monozygotic and dizygotic twins. This suggested, according to the authors, an influence due to a shared environment rather than genetic factors. On the other hand, the phonological nonword repetition test produced high estimates of heritability. This seems to suggest, at first sight, and provided that the language impaired and dyslexics can be regarded to have the same underlying problems, that 'temporal processing problems' found also in dyslexics, such as measured with pure tone stimuli (as is done in ART), are influenced more by the environment than genes. However, could such an influence take place via the parental speech input? One should note however, as the authors also point out, that the ART test was not well suited for identifying rate-processing limitations, but measured rather how well children could discriminate and remember nonverbal auditory information. Also, they point out that performance on the ART task is also influenced by learning and attentional strategies. It may well be, that these are related and, thus perhaps at least partly, mediating skills are influenced more by the environment than by genes. If this is the case, one should be cautious about drawing direct conclusions from this study to the present study, where differences between the at-risk and control infants were found already at birth, at which stage attentional and learning related factors could hardly account for ERP group differences. It should also be noted, that in the present studies speech stimuli were used in group comparisons instead of

pure tones as in the study of Bishop et al. (1999). It is possible, that early speech processing – such as indexed by ERPs here – is more directly related to later phonological skills than the processing of pure tone stimuli. Overall, the present results favor an interpretation of a fundamental processing difference between at-risk and control infants, which could not be solely explained by the environmental input. However, further research of the critical issues, as identified out in the previous discussions, is needed, before a firmer conclusion can be reached.

Finally, it should also be noted, that it has not been the intention of the present work to address the widely debated issue of whether poor language skills and dyslexia are caused by a deficient speech module or by an auditory problem at the level of simple tone processing. In the present work only speech sounds were used in group comparisons, not pure tone stimuli, which makes significant claims on behalf of either side impossible. However, while stating this, the present data, taken together, suggest that the temporal processing demands involved in differentiating speech duration changes tap some critical aspect of an early auditory/speech processing deficiency related to dyslexia. Furthermore, as Bishop et al. (1999) point out, it is possible that slowly maturing – to which I would add, differently maturing – auditory perceptual system might leave a lasting legacy of language problems, even if discrimination skills improve later on.

Concluding remarks

Overall, the present results reveal developmental changes in the brain electrical activity related to sound changes. They further indicate that the brains of infants who are at a genetic risk for developmental dyslexia due to a familial background of reading problems respond to auditory temporal information of speech sounds differently from infants without such a risk already at a very early age. The results support the notion, that those affected by dyslexia may also have a very early speech perceptual problem contributing in turn to difficulties in phonological processing (cf. e. g. McBride-Chang, 1995). To what extent early processing differences could be utilised in the early identification of the disorder in young infants, and particularly in a population at high risk, remains a matter for future studies. Further, direct evidence that deviations in brain activation measured early in development could predict later dyslexia or other language related disorders has yet to be found.

It is noteworthy, that on the basis of the literature, one would expect that only about one half of the infants in the at-risk group actually carry the genetic basis for dyslexia (Pennington, 1995), when the risk is based on the dyslexia of the father and/or mother and one or more of his/her close relative(s). It is possible, though, that even if there is a genetic basis for dyslexia, it will not be manifested as a phenotype in all individuals, which would also suggest a strong environmental influence on the development of dyslexia. In any event, the

present results, indicating clear group differences at birth and at six months of age, are of significant interest, because it is well known that a considerable percentage of infants from families with dyslexic members will most probably not become dyslexic when they reach reading age.

YHTEENVETO

Aivovasteet ääni- ja puheärsykkeiden muutoksiin vauvoilla, joilla on ja vauvoilla, joilla ei ole riskiä suvussa esiintyvään dysleksiaan

Kehityksellistä dysleksiaa, lukemaan oppimisen erityisvaikeutta, pidetään yleisesti periytyvänä häiriönä, mutta toistaiseksi tiedetään vasta vähän sen varhaisista ennusmerkeistä. Tässä väitöskirjatyössä tutkittiin aivojen sähköisiä reaktioita auditorisiin muutoksiin äänivirrassa sekä vastasyntyneiltä että puolen vuoden ikäisiltä sellaisilta vauvoilta, jotka ovat perheistä, joiden suvussa on esiintynyt dysleksiaa (riskiryhmä) ja vauvoilta joiden perheissä ei esiintynyt lukemisvaikeuksia (kontrolliryhmä). Tutkimuksen kohteena olivat sekä riski- ja kontrolliryhmien väliset erot että aivojen herätevasteiden (event-related potentials, ERPs) kehitykselliset piirteet. Päähuomio oli äänivirrassa tapahtuvissa muutoksissa, jotka liittyivät ärsykkeiden temporaaliseen rakenteeseen eli muutoksiin puheäänen elementtien kestoissa. Kestomuutosten vaikutusta herätevasteisiin tutkittiin vaihtelemalla joko vokaalin kestoa (/kaa/ vs. /ka/) tai vaihtelemalla hiljaisuuden kestoa, joka heijastuu havaittuna erona konsonantin kestossa (/ata/ vs. /atta/). Ärsykkeet esitettiin äänisarjoissa, joissa lyhyin välein toistuva ärsyke silloin tällöin korvattiin yhdellä tai kahdella (/ata/-/atta/-kokeissa) keston suhteen poikkeavalla ärsykkeellä.

Tutkimus osoitti, että vauvoilta on mahdollista mitata luotettavasti aivojen sähköisiä vasteita puheäänen keston muutoksiin jo heti syntymän jälkeen. Tuloksista voidaan päätellä, että kummassakin ryhmässä aivot prosessoivat äänen kestossa tapahtuvia muutoksia. Nämä tulokset osoittavat lisäksi, että aivojen aktivaatio, joka syntyy kun toistuvien puheäänten sarjassa esitetään kestoltaan poikkeava ärsyke, eroaa riski- ja kontrolliryhmien välillä varhaisessa iässä jo ennen tuottavaa puhetta.

ERP:n kehityksellisten piirteiden tarkastelussa selvisi, että ne muuttuvat merkittävästi syntymästä puoleen vuoteen mennessä. Hidas ja laaja aaltomuoto muuttuu kompleksiseksi rakenteeksi, josta on selvästi erotettavissa ERP:lle tyypillinen negatiivinen-positiivinen-negatiivinen aaltomuoto eli signaalirakenne. Heti syntymän jälkeen tyypillisin aaltomuoto on pitkään kestävä positiivinen jänniteheilahdus. Tämä voitiin havaita kaikissa koetilanteissa riippumatta käytetystä ärsyketyypistä, olipa sitten kyseessä äänenkorkeuden, vokaalin keston muutos tai konsonanttien keston havaitsemiseen liittyen muutos puheäänen keskellä olevassa hiljaisessa jaksossa. Eikä positiivisella aaltomuodolla ollut yleisesti ottaen yhteyttä ärsykkeen esiintymistodennäköisyyteen (usein toistuva vs. harvoin esiintyvä poikkeava ärsyke). Hidas positiivinen vaste näyttää siis olevan vastasyntyneiden vauvojen tyypillinen aivojen herätevaste mihin tahansa auditoriseen ärsykkeeseen, mikä löydös on samansuuntainen aiemmin raportoitujen ERP-tutkimusten kanssa.

Kehityksellisiä muutoksia ERP:ssä havaittiin myös suhteessa ärsyketyyppiin että niiden esiintymistodennäköisyyteen. Vaikka vastasyntyneillä nopeassa

tempossa esitetyt eri taajuiset sini-äänet synnyttivät erilaisen vasteen, tavuissa esiintyviin vokaalin kestomuutoksiin ei eroa selkeästi syntynyt siitäkin huolimatta, että tavuja esitettiin hitaammalla tempolla. Vokaalin kestomuutoksen synnyttämiä eroja herätevasteissa esiintyi vasta puolen vuoden ikäisillä. Tavuärsykkeiden esiintymistempon hidastaminen yli puolella, eli kasvattamalla ärsykkeiden väliä 425 ms:sta 855 ms:iin, toi vastaavat erot näkyviin jo vastasyntyneillä. Siten sekä ärsykkeiden väliset erot, esittämistempo että kehityksellinen ikä vaikuttavat herätevasteisiin, näiden vaikutusten kuitenkin liittyen lähes erottamattomasti toisiinsa.

Tutkimukset tehtiin käyttäen koeasetelmaa, jossa harvoin esiintyvät samoista usein toistetuista ärsykkeistä poikkeavat ärsykkeet synnyttävät aikuisilla ns. poikkeavuusnegatiivisuus-vasteen, MMN (mismatch negativity), joka on suurimmillaan n. 200 ms kuluttua ärsykkeen esittämisen alusta mitattuna aivojen etu- ja keskialueiden päältä. Myös vauvoilta on raportoitu samantapaisia negatiivisia vasteita suunnilleen samalta aikajaksolta tai vähän myöhemmin. Toisin kuin aiemmin, kaikissa niissä koetilanteissa, joissa syntyi merkitseviä ERP-eroja ärsykkeiden välillä, poikkeavat ärsykkeet synnyttivät vauvoilla ERP:n, joka oli positiivinen polariteetiltaan usein toistettujen ärsykkeiden vasteisiin nähden.[21] Vokaalin keston muutoksia koskevaa koeasetelmaa lukuun ottamatta positiiviset jänniteheilahdukset saavuttivat maksimikohtansa tai jatkuivat yli latenssikohdan, jolla MMN:n on raportoitu esiintyvän vauvaikäisillä.

Näitä joko suurempia (taajuuden muutoksen synnyttämiä) tai pitempään kestäviä (vokaalin keston muutoksen synnyttämiä) positiivisia vasteita ei voitane selittää pelkästään afferenttien hermojärjestelmien aktivaatiolla, joka syntyy uusiin fysikaalisiin ärsykepiirteisiin. Käytetyissä koeasetelmissa havaitut positiiviset vasteet oletettavasti liittyvät pikemminkin ärsykkeiden muutoksen prosessointiin. Tällainen muutoksen prosessointi edellyttää toistettujen äänten synnyttämiä muistijälkiä. Tutkimuksessa löytyi myös jossain määrin viitteitä traditionaalisemman MMN-tulkinnan puolesta. Selvin viite tuli esille vastasyntyneiden taajuuserottelua mittaavassa kontrollikoeasetelmassa, jossa pääkokeeseen verrattuna käytettiin suurempaa ärsykkeiden välistä taajuuseroa (Artikkeli II). Yllättävää oli, että suurempaan ärsyke-eroon syntyikin pienempi positiivinen heilahdus ja 'kuoppa' n. 200 ms kohdalla. Tavallisesti suurempi ärsyke-ero synnyttää selkeämmän vasteen[22]. Tämä vasteen pieneneminen voi olla selitettävissä positiivisen vasteen kanssa päällekkäistyvällä negatiivisella vasteella, joka tulee paremmin esille käytettäessä suurempaa ärsyke-eroa. Eniten aikuisten MMN:ta muistuttava vaste syntyi koetilanteessa, jossa pääkokeessa esitetty lyhyt standardiärsyke /ata/ esitettiinkin poikkeavana ärsykkeenä (Artikkeli V). Poikkeava /ata/ synnytti puolen vuoden ikäisillä kontrolliryhmän

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21 Poikkeuksen muodosti koeasetelma, jossa mitattiin vasteita hiljaisuuden keston muutokseen. Tässä tapauksessa on kuitenkin huomioitava, että tuloksia ei voi rinnastaa tyypillisiin MMN-asetelmiin, koska käyttämissämme pseudosanoissa oli mukana useampia elementtejä, jotka saattoivat tuottaa päällekkäistyviä vasteita.

22 Joissakin tapauksissa pienempi ärsyke-ero voi tosin synnyttää suuremman vasteen, jos kyse on suurempaa kognitiivista ponnistusta vaativasta tehtävästä. Näissä tutkimuksissa vauvat olivat kuitenkin unessa tutkimuksen aikana.

vauvoilla toisen negatiivisen heilahduksen, jota ei esiintynyt kun sama ärsyke esiintyi usein toistettuna ärsykkeenä.

Vauvojen aivojen herätevasteissa esiintyi selkeitä eroja riski- ja kontrolliryhmään kuuluvien vauvojen välillä. Vastasyntyneiden ERP:ssä tavuihin, jotka vaihtelivat vokaalin kestoltaan, nähtiin eroja ryhmien välillä vasta kun ärsykkeiden esittämisväliä, ISI:ä (interstimulus interval) kasvatettiin 425 ms:sta 855 ms:iin. Ryhmäerojen puuttuminen lyhyemmällä ISI:llä selittyy todennäköisimmin ns. lattiaefektillä. Puolen vuoden iässäkin havaittiin vain vähäisiä ryhmäeroja esitettäessä ärsykkeitä nopealla tempolla. Selkeimmät ryhmäerot havaittiin käytettäessä ärsykkeinä pseudosanoja, joiden keskellä olevaa hiljaisen tauon kestoa vaihdeltiin (/ata/ vs. /atta/). Harvoin esiintyvän /atta/-sanan synnyttämät vasteet erosivat ryhmien välillä siten, että vasemmalla aivopuoliskolla riskiryhmässä positiiviset vasteet olivat suurempia ja näitä seuraava negatiivisuus pienempi kuin kontrolliryhmässä. Kun puolestaan /ata/-sanaa käytettiin koeasetelmassa poikkeavana ärsykkeenä pitkien /atta/-standardien joukossa kontrolliryhmällä näkyi selkeästi kontekstista riippuva, 'ylimääräinen' negatiivinen aalto. Tämä toinen jänniteheilahdus puuttui riskivauvoilta kokonaan. Nämä tulokset viittaavat siihen, että riskiryhmän vauvat eroavat kontrolliryhmästä sekä auditiivisten ärsykkeiden fysikaalisten piirteiden synnyttämän aivojen aktivaation että ärsykekontekstin mukaan vaihtelevan aivojen prosessoinnin suhteen.

Havaittuja ryhmäeroja voidaan alustavasti tulkita siten, että riskiryhmän vauvojen auditorinen järjestelmä on herkkä aktivoitumaan selkeästi havaittaville ärsyke-eroille ja, jossain mielessä, jopa liiankin riippuvainen ärsykkeiden fysikaalisista piirteistä. Kontrolliryhmän vauvojen auditorinen järjestelmä on puolestaan adaptiivisempi aktivoitumaan ääniympäristön mukaan. On esitetty, että puheäänille syntyisi aivoihin prototyypin kaltainen edustus, mutta siten, että havaintojärjestelmä 'sallii' jonkun verran variaatiota eri puheäänten prototyyppien ympärillä ja että tällaiset prototyypit toimisivat eräänlaisina 'havaintomagneetteina' äänille, jotka muistuttavat läheisesti näitä prototyyppejä. Sensorisen muistin voidaan ajatella olevan yhteydessä tällaiseen kontekstuaalisen informaation käyttöön ja siten protyyppien muodostumiseen. Siten voisi olla mahdollista, että heikompi kyky käyttää kontekstuaalista auditiivista informaatiota ja suurempi riippuvuus äänten fysikaalisista piirteistä saattaisi 'häiritä' riskivauvoilla joustavien prototyyppien syntymistä. Toimivien prototyyppien on myös ajateltu olevan perusta hyvälle kategoriselle havainnoinnille. Tämä ilmiö saattaisi siten puolestaan liittyä kategorisen havainnon pulmiin, jotka on myös liitetty kehitykselliseen dysleksiaan. Tämän mahdollisen tulkinnan vahvistamiseksi vaaditaan kuitenkin paljon jatkotutkimuksia.

Ryhmäeroja koetilanteessa, jossa vaihdeltiin hiljaisuuden kestoa, voitaisiin selittää, ainakin osittain, ryhmien välisillä eroilla ns. temporaalisessa integraatiossa. On mahdollista, että riskiryhmällä on pitempi temporaalisen integraation aikaikkuna, mikä voi johtua esimerkiksi hitaammasta prosessointinopeudesta. Tällainen pitempi aikaikkuna johtaisi sellaistenkin ärsykeosien fuusioitumiseen, jotka muutoin prosessoitaisiin erillisinä. Toisen kontekstisidonnaisen negatiivisen heilahduksen puuttuminen koetilanteessa, jossa ly-

hyttä /ata/-pseudosanaa esitettiin poikkeavana ärsykkeenä (Artikkeli V), sopisi tähän tulkintaan.

Vaikka tämän tutkimuksen tulokset eivät osoitakaan, että riskivauvoilla olisi pelkästään äänen temporaalisiin piirteisiin liittyviä eroja aivojen sähköisessä aktivaatiossa, niin ryhmäerot sekä vokaalin että hiljaisuuden kestomuutosten synnyttämissä ERP:ssä tukevat ajatusta, että kestojen erottelun asettamat temporaalisen prosessoinnin vaatimukset heijastuvat jossakin kriittisessä varhaisen auditorisen toiminnan aspektissa, joka puolestaan liittyy dysleksian syntyyn. Aiemmissa tutkimuksissa sekä lapsilla että aikuisilla, joilla on dysleksiaa, on havaittu olevan pulmia prosessoida esimerkiksi nopeasti vaihtuvia puheen osia. Myös nopeasti vaihtuvan visuaalisen informaation prosessoinnin on havaittu olevan heikompaa dyslektikoilla, mikä on liitetty neuraalisella tasolla puutteelliseen magnosolujen toimintaan. Tutkimuksessa havaittiin myös johdonmukaisia ryhmäeroja kestomuutosten synnyttämien herätevasteiden hemisfäärijakaumissa. Sekä ärsyke- että kotilannemuutosten aiheuttamat erot vastasyntyneillä kontrolliryhmän vauvoilla olivat johdonmukaisempia vasemmalla aivopuoliskolla, kun taas vastaavat ERP-erot olivat johdonmukaisemmin oikealla hemisfäärillä koeryhmässä. Puolen vuoden iässä ryhmät erosivat toisistaan vasemman aivopuoliskon vasteissa poikkeavan hiljaisuuden keston sisältämään ärsykkeeseen. Nämä tulokset viittaavat aivopuoliskojen toiminnallisiin eroihin ryhmien välillä jo varhaisessa kehityksen vaiheessa. Missä määrin tulokset liittyvät havaittuihin aivopuoliskoeroihin dyslektikoiden ja tavallisesti lukevien välillä, on vielä epäselvää. Lopullista vastausta täytyy odottaa tutkimuslasten lukuikään asti.

Yleisesti ottaen nämä tutkimukset osoittavat, että vauvoilla, joilla on geneettinen riski kehitykselliseen dysleksiaan – arvioituna suvussa esiintyvien pulmien perusteella – on eroja auditiivisen temporaalisen informaation synnyttämässä aivojen sähkötoiminnan aktivaatiossa jo varhain sellaisiin vauvoihin nähden, joilla ei suvun rasitetta esiinny. Tuloksissa huomioarvoista on se, että ryhmäeroja löytyi, vaikka dysleksian perimää koskevien tutkimusten mukaan on oletettavaa, että lukivaikeuksia ilmaantuu lopultakin vain osalle riskilapsia siinä vaiheessa, kun he saavuttavat lukemisiän.

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I

AUDITORY EVENT-RELATED POTENTIALS IN THE STUDY OF DEVELOPMENTAL LANGUAGE-RELATED DISORDERS

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II

EVENT-RELATED BRAIN POTENTIALS TO CHANGE IN RAPIDLY PRESENTED ACOUSTIC STIMULI IN NEWBORNS

By

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Event-Related Brain Potentials to Change in Rapidly Presented Acoustic Stimuli in Newborns

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Event-related brain potentials of 28 newborns to pitch change were studied during quiet sleep under stimulus conditions that typically elicit mismatch negativity in adults. Rarely occurring deviant tones of 1100 Hz (probability 12%) were embedded among repeated standard tones of 1000 Hz in an oddball-sequence with an interstimulus interval of 425 ms. Two control conditions were also employed: In the first, the 1100-Hz stimulus was presented alone without the intervening standard stimuli, and in the second the deviant stimulus had a pitch of 1300 Hz. In all conditions the infrequent stimulus elicited in most newborns a slow positive deflection peaking at a latency of 250–350 ms. The response to the standard tone was very small. These results indicate passive detection of even a small pitch change based either on refractoriness to repetition or dishabituation to change, or both. Some evidence was also found for a mismatch negativity-like response overlapping with the positive response and appearing as a reduction of this positive deflection at a latency of a typical mismatch negativity.

Event-related potentials (ERPs) have been successfully applied in studying the brain's processing of change in auditory information. In adults ERPs to stimulus change are usually studied using a so-called oddball paradigm, in which a rarely occurring deviating stimulus embedded among a repeated frequent stimulus typically generates an ERP-component called mismatch negativity (MMN; Näätänen, Gaillard, & Mäntysalo, 1978; for reviews, see Näätänen, 1990, 1992, and Näätänen & Alho, 1995). This component has been widely studied in adults, and it has

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recently received attention from researchers of infant ERPs in their attempts to find an objective measure of basic auditory processing capabilities of young infants. This interest has been facilitated by occurrence of the response to almost any kind of deviating feature of auditory stimuli in adults and even when no attention is paid to the stimuli (Alho, Woods, & Algazi, 1992; Lyytinen, Blomberg, & Näätänen, 1992; Näätänen, 1992; Näätänen, Paavilainen, Tiitinen, Jiang, & Alho, 1993; Paavilainen, Tiitinen, Alho, & Näätänen, 1993; Sams, Paavilainen, Alho, & Näätänen, 1985).

The MMN component is thought to reflect the functioning of the sensory memory upon which the detection of auditory change is dependent. According to a theory proposed by Näätänen (1984, 1992), a frequently repeated tone in a series of tones forms a memory trace or neural model of the acoustic features of this tone in the sensory memory. This trace can last up to about 8–10 sec (Böttcher-Gandor & Ullsperger, 1992; Mäntysalo & Näätänen, 1987). The sensory input generated by a deviating tone does not fit with the existing model or memory trace, thereby resulting in a mismatch process reflected in a negative deflection reaching its maximum over the frontal and central areas of the scalp (Giard, Perrin, Pernier, & Bouchet, 1990; Näätänen, 1990, 1992; Paavilainen, Alho, Reinikainen, Sams, & Näätänen, 1991). The major source for this response is shown to reside in the supratemporal auditory cortex (Giard et al., 1990; Hari et al., 1984; Kaukoranta, Sams, Hari, Hämäläinen, & Näätänen, 1989; Sams, Hämäläinen, et al., 1985). This mismatch process may then also initiate brain processes leading to some higher executive cognitive functions related to attention, long-term memory, and other mechanisms under voluntary control, for example, conscious discrimination of change in auditory information (Näätänen, 1988, 1991, 1992; Öhman, 1979; Paavilainen et al., 1991; Sams, Paavilainen, et al., 1985). Because an ERP wave may reflect a summation of many simultaneous brain processes (Näätänen & Picton, 1987), a so-called difference wave obtained by subtracting the response to a frequently presented standard stimulus from the response to an infrequent deviant stimulus is thought to best represent the MMN response (Näätänen, 1990).

MMN is thought to indicate a discriminative response to a change in a stimulus sequence, not to a specific stimulus per se. Many infant studies have shown that the ERPs of young infants respond differentially to a number of various features of auditory stimuli (see, e.g., Kurtzberg, Hilpert, Kreuzer, & Vaughan, 1984; Kurtzberg, Stone, & Vaughan, 1986; Molfese & Betz, 1988; Molfese, Burger-Judisch, & Hans, 1991; Molfese & Molfese, 1985, 1986; Novak, Kurtzberg, Kreuzer, & Vaughan, 1989). Studies of child and infant MMN are, however, relatively few and recent. MMN has been observed both in nonclinical children (Csepe, 1995; Kraus et al., 1993; Kraus, McGee, Sharma, Carrell, & Nicol, 1992; Kurtzberg, Vaughan, Kreuzer, & Flieger, 1995; Leppänen, Laukkonen, & Lyytinen, 1992; Lyytinen & Lorys-Vernon, 1989) and clinical groups of children (Korpilahti & Lang, 1994; Winsberg, Javitt, Silipo, & Doneshka, 1993). In school-age children the MMN response resembles a typical adult MMN with approximately an equal

latency, peak amplitude of the difference wave, and a fronto-central scalp distribution. However, some differences also exist between child and adult ERPs measured in conditions under which MMN is elicited in adults; for example, unlike in adults, a fairly large response to a frequently presented standard stimulus has been observed in children (e.g., Korpilahti & Lang, 1994; Leppänen et al., 1992).

Alho, Sainio, Sajaniemi, Reinikainen, and Näätänen (1990) reported that in newborn infants an MMN-like response occurs in response to a pitch change in a stimulus sequence during quiet sleep. The response to the deviant tone of 1200 Hz (with a probability of 10%) was negatively displaced in relation to the response to the standard tone of 1000 Hz. This effect was seen in 6 of 8 participants. The mean peak latency of deviant negativity was 296 ms at Fz and 270 ms at Cz (frontal and central midline sites, respectively) and, thus, somewhat later than the corresponding typical adult peak latency, which is usually 200 ms or shorter. The midline distribution of the negativity, however, resembled that of a typical adult. The response to the standard tone was very small, and the authors hypothesized that this was due to the fast stimulus rate (fixed onset-to-onset interstimulus interval [ISI], of 610 ms).

In their review article, Kurtzberg et al. (1995) reported an MMN in 14 of 25 newborns (57%) to 1200-Hz tone (probability 15%) embedded among 1000-Hz standard tones using ISIs of 750 and 1,000 ms. The MMN was defined as any negative deflection of the difference wave (deviant minus standard response) greater than 0.75 μV occurring between 150–450 ms at Fz (p. 107). In another 5 participants (18%) a negative shift to the deviant stimulus or any negatively displaced deviant response in relation to the standard response was observed. Defined in this way, some indication of negativity was found in 19 participants (75%). The peak latencies of negativity were 241 and 298 ms for the 750 and 1,000 ms ISIs, respectively.

Recently, an MMN-like response in ERPs of newborns has also been reported to a change in phonetic elements, a deviant vowel /i/, the end point of the Finnish (Klatt-synthesized) /i/-/y/ continuum, when presented among frequently occurring /y/-vowel tokens during quiet sleep (Cheour-Luhtanen et al., 1995). These vowel tokens were presented with a fixed ISI of 800 ms. The negativity of the difference wave peaked at 200–250 ms and reached its maximum over the frontal and central scalp areas. It was also observed that the MMN-like negativity was smaller when the deviant was a boundary /y/i/ stimulus, that is, when the difference between the deviating and standard stimuli was rather small or not so clear.

This latter finding is consistent with the results (obtained using adult participants) showing that the amplitude of MMN is enhanced when the difference between deviating and standard stimuli is increased (e.g., Sams, Paavilainen, et al., 1985). However, it should be noted that Cheour-Luhtanen et al. (1995) used speech sounds, the properties of which in relation to MMN have not, even in adults, been examined as widely as the properties of pure tones. Thus, the relation of stimulus difference magnitude to auditory ERPs is far from established in newborns and young infants.

These reviewed results (except those by Kurtzberg et al., 1995) indicating an MMN-like negativity in newborns are based on measurements carried out during quiet sleep periods (for a categorizing of newborn sleep, see Anders, Embde, & Parmelee, 1971; and Lombroso, 1985, for a review). It has been known for a long time that the ERPs of newborns are affected by sleep states (e.g., Ellingson, Danahy, Nelson, & Lathrop, 1974). Ellingson et al. (1974) observed, for example, that auditory evoked potentials recorded to 1000-Hz pure tones (presented with irregular intervals of not less than 8 sec) were generally clearest and of highest amplitude during quiet sleep, which is characterized by behavioral quiescence, regularity of physiological activity, and lack of eye movements (Anders et al., 1971). In a recent study, Duclaux, Challamel, Collet, Roullet-Solignac, and Revol (1991) reported, for example, that response amplitudes to a 2000-Hz deviant stimulus (with a probability of 20% among 1000-Hz standard tones having a presentation rate of 1 tone/2 sec) measured in 6-week-olds were larger in quiet sleep than in active sleep. In addition, the response to the deviant tone differed from that to the standard tone only during quiet sleep. Recently, enhancement of responses during quiet sleep has also been reported for neuromagnetic responses to pure tones and pseudowords in a 3-month-old infant (Paetau, Ahonen, Salonen, & Sams, 1995). Thus, if an MMN-like response is expected to be present during sleep in newborns, it is not unreasonable to expect it to occur during this state. In adults an MMN-like deflection has been reported to occur during the Sleep Stage 2 in conjunction with K-complexes (Sallinen, Kaartinen, & Lyytinen, 1994; cf. Paavilainen et al., 1987, who failed to find MMN in sleep; they classified sleep only into various global stages without looking for a response in specific microstates, like the one characterized by the occurrence of K-complexes).

However, even when the sleep states are carefully controlled, information processing during sleep in newborns is not directly comparable to that in adults. This is because of changes that take place in sleep organization in early life of young infants (e.g., Becker & Thoman, 1983; Coons & Guilleminault, 1984; Thoman & Whitney, 1989). The waveform of ERPs in young infants and the refractoriness of responses to stimuli in terms of sensitivity to ISI variations also differ a great deal from those in adults (e.g., Kurtzberg et al., 1995; Ohlrich, Barnet, Weiss, & Shanks, 1978; Shucard, Shucard, & Thomas, 1987). Because developmental changes in these aspects occur during early postnatal weeks and months (e.g., Barnet, Ohlrich, Weiss, & Shanks, 1975; Kurtzberg et al., 1984; Kurtzberg et al., 1986; Novak et al., 1989; see for a review, Thomas & Crow, 1994), it could be expected that the ERPs of newborns to change, when measured under conditions used for adults, would differ from the adult MMN response (cf. Kurtzberg et al. 1995). For instance, the polarity of ERPs changes from predominantly negative to positive polarity with early maturation (e.g., Kurtzberg et al., 1984; Novak et al., 1989).

Our main goal was to examine how the ERPs of newborns, during quiet sleep, vary in relation to a pitch change in an oddball paradigm in which stimulus events

typically elicit MMN in adults. Pitch change in the presented stimulus sequence was used, because in adult studies the characteristics of the MMN to pitch change are known best. Another reason for using a pitch deviation was to increase the comparability of our results with those reported by Alho, Sainio, et al. (1990) and perhaps to extend their findings. However, the ISI used in this study was somewhat shorter than that used by Alho, Sainio, et al. (1990); 425 ms instead of 610 ms. The use of this shorter ISI is justified because the MMN response is typically larger to a change in a shorter ISI context down to a certain limit that is not exceeded here (see DISCUSSION). Recently, Kurtzberg et al. (1995) also suggested that a reliable MMN in newborns might be obtained with as high stimulus rates as three to four stimuli per second.

In order to specify this main aim, three major questions are addressed in the main experiment and two complementary conditions: First, do ERPs to a rarely occurring and deviating tone differ from ERPs to a frequently presented tone? Second, are the ERPs to this deviant stimulus different from ERPs to a similar stimulus presented alone? A response to a similar tone as a deviant tone in an oddball paradigm, but presented without any intervening standard tones (and with the same ISI as deviants in an oddball paradigm), typically has in adults a higher peak amplitude, an earlier latency, and more central scalp distribution than a response to a deviant tone among standard tones (Näätänen, Paavilainen, Alho, Reinikainen, & Sams, 1989; see also Näätänen & Alho, 1995). Third, what effect does an increase of the stimulus difference between frequent and rare stimuli have on ERPs? A greater stimulus change should result in a larger and earlier MMN (Näätänen, 1992; Sams, Paavilainen, et al., 1985).

METHODS

Participants

The main experiment. Twenty-eight healthy newborn participants (16 males, 12 females) are included in this study. Originally, the ERPs of 49 newborns were recorded, but data from 21 participants were excluded because either no data or not enough artefact-free data (see following) were obtained during quiet sleep. The remaining 28 participants had a mean gestational age (GA) of 40.1 weeks (*SD* = 1.44, range: 37–42 weeks) and a mean birth weight of 3,742.5 g (*SD* = 461.1). One-min and 5-min Apgar scores averaged 8.71 and 8.96, respectively (*SD*s = 0.53 and 0.19, respectively). The infants were tested within 34–157 hr (1–6 days) from birth, except for 3 participants, whose GA was below 38 weeks. They were tested at about 40 weeks postconceptional age (and thus within 14–23 days from birth). Thus, the mean conceptional age (CA) at the time of measurement was 40.8 weeks (*SD* = 1.10, range: 38.6–42.7 weeks). All these infants participated in the 1100-Hz-deviant condition of the main experiment (see following).

Control conditions. Thirteen of these 28 infants participated, in addition to the main experiment, in two control conditions. In the 1100-Hz-alone condition (see following) enough artefact-free data during quiet sleep were obtained for 11 of these 13 participants. They had a mean GA of 40.2 weeks (*SD* = 1.24, range: 38–41.9 weeks) and a mean CA of 40.7 weeks (*SD* = 1.26, range: 38.6–42.7 weeks). In the 1300-Hz-deviant condition enough artefact-free data during quiet sleep were obtained for 9 of those 13 participants. Their corresponding characteristics included a mean GA of 40.0 weeks (*SD* = 1.26, range: 38–41.4 weeks) and a mean CA of 40.4 weeks (*SD* = 1.21, range: 38.6–41.9 weeks). No significant differences were found in any of these characteristics in an independent two-tailed *t* test between the infants who participated in these additional control conditions and the rest of the 28 participants (GA, CA, birthweight, 1- and 5-min Apgar scores, $p > .05$).

Stimuli and Procedure

Main experiment: 1100-Hz-deviant condition. The stimuli were sine-wave pure tones. In the 1100-Hz-deviant condition these were presented in an oddball-sequence, in which an infrequent deviant stimulus of 1100 Hz (probability 12%) was embedded among a repeated frequent standard stimulus of 1000 Hz (88%). The duration of the stimuli was 74 ms (rise and fall times of 24 ms each) and the intensity was 75 dB SPL, calibrated before the experiments using Brüel and Kjaer precision sound level-meter (Type 2235). Four different pseudorandom oddball-sequences were created. Each had at least 5–10 standard tones between any two subsequent deviant stimuli. This was done in order to ensure enough repetition of the same stimulus for the formation of neural representation. All four sequences consisted of 65 deviant stimuli. The constant ISI (onset-to-onset) for all stimuli was 425 ms. These sequences were delivered in a random order, but so that two same sequences were never presented in succession.

These blocks of the 1100-Hz-deviant condition alternated with syllable-duration condition blocks in which two consonant–vowel syllables varied in duration (the standard /kaa/ stimulus having a duration of 250 ms and the deviant /ka/ 110 ms; the fixed offset-to-onset ISI was 425 ms). The presentation order of the blocks was counterbalanced between participants. Only the data from the 1100-Hz-deviant condition are reported here. For those infants who participated in the control conditions the syllable-duration condition blocks were replaced with two control condition blocks. The presentation order of the blocks was counterbalanced between participants also in these conditions.

First control condition: 1100-Hz-alone. In the 1100-Hz-alone condition the blocks were similar to the 1100-Hz-deviant condition blocks with the exception

that the standard tones were omitted. The ISI in this condition was, thus, similar to the "interdeviant interval" of the 1100-Hz-deviant condition (i.e., varying between 2,550–4,675 ms).

Second control condition: 1300-Hz-deviant. The 1300-Hz-deviant condition was similar to the 1100-Hz-deviant condition with the exception that in this condition the deviant was 1300 Hz instead of 1100 Hz, and thus the stimulus change was 30% instead of 10%.

All blocks in all these conditions took about 4 min to deliver. During the electrode attachment one of each block type was presented to the infant in order to reduce novelty or orientation effect during the actual test sessions (in two cases one block type was not delivered because the infant had to be temporarily moved from the crib, e.g., due to feeding).

The experiments took place at the neurophysiologic laboratory of the Central Hospital of Central Finland in Jyväskylä. The test times were mostly limited to afternoons, when regular clinical examinations were over for that day. The parents were invited to observe the experiments if they wished. The experiments were conducted in a dimly lit laboratory room. The electroencephalogram (EEG) was measured while the infant was lying in a slightly reclined position ($\angle$ 5.3°) in a small crib designed for these purposes. The auditory stimuli were delivered through a loudspeaker located at the foot of the crib 39 cm above the bed level and 60 cm from the estimated head position of the infant (facing it; the angle between the loudspeaker–head line and the bed level was 41°). The recording was suspended when the infant was either crying or moving excessively.

EEG Recording

The EEG was recorded using disposable Ag/AgCl-electrodes (Blue sensor, Medicotest, Denmark) attached to the frontal (F3, F4), temporal (T3, T4), central (C3, C4), and parietal (P3, P4) scalp sites, according to the International 10–20 electrode system. These electrodes were referred to the ipsilateral mastoid, with the exception of T3 and T4. Each EEG electrode was also referred to the corresponding electrode over the opposite hemisphere. However, only the data from monopolar recordings are reported here. The electrooculogram (EOG) was recorded with two electrodes, one slightly above and lateral to the left eye and the other in the same position below the right eye. Both of the EOG channels were referred to the left mastoid. A ground electrode was placed on the forehead. As an electrolyte, ECI Electro-Gel (Electro-Cap International, Inc., Eaton, USA) was used.

The EEG recorder and signal amplifier was Nihon Kohden Neurofax EEG–5414K. The time constant was set to 0.3 and the high frequency filter to 35

Hz. AC-filtering was on. EEG-epochs of 950-ms predeviant stimulus time and 950-ms postdeviant stimulus time were stored at a sampling rate of 200 Hz. The rather long prestimulus time was used to allow the measurement of the response to the standard stimulus preceding the deviant tone.

Analysis of the ERP Data

Classification of sleep states. The EEG-epochs were classified into four categories according to sleep states of the infant: wakefulness, active sleep, quiet sleep, or indeterminate state. These states were defined according to behavioral criteria in the sleep-state scoring manual by Anders et al. (1971). In addition, eye movements were monitored from the ongoing EEG at the EOG-channels. Each 1-min period of the measurement was classified as one of the states. The behavior of the infant was observed and coded on line during the experiment for the classification of the various states, which was done off line after the measurement. The interrater agreement of the online-coding of the infant's behavior (eyes open or closed, facial or body movements, crying, etc.) between two independent observers was 95%. This was calculated from the data of 5 randomly chosen infants and was defined as the percentage of the total number of EEG-epochs that the two observers agreed about. Comparable interrater agreement of the classification of the EEG-epochs into the four sleep states was 92%. Only the data classified into quiet sleep are reported in this study.

ERP-averaging. The time window of EEG-epochs used for ERP-averaging included 475 ms prior to the onset of the deviant stimulus (the response window for the standard stimulus with a 50-ms prestimulus time) and 425 ms after it. Epochs contaminated by excessive eye movements, defined as the EOG deflections exceeding ± 150 μV, and muscle activity or other extra cerebral artifacts, defined as the EEG deflections exceeding ± 200 μV, during the analyzed time window were excluded from averaging. All epochs, in which the first deviant stimulus occurred among the first 10 standard stimuli, were similarly disregarded. Further, at least 90 acceptable EEG epochs for each stimulus type were required for an average to be included in further analysis (the number of the accepted epochs ranged between 92 and 267). The percentages of the epochs rejected were 5.0%, 2.2%, and 3.2% in the 1100-Hz-deviant, 1100-Hz-alone, and 1300-Hz-deviant conditions, respectively.

Dependent variables. In order to estimate stimulus effects on ERPs, the following measures were taken from the average of each participant from all

channels with a monopolar derivation (i.e., at F3, F4, C3, C4, P3, and P4). *Mean amplitudes* were calculated over the data points of the consecutive 100 ms periods beginning from 25 ms after the stimulus onset in relation to the 50 ms prestimulus baseline (i.e., over 25–125 ms, 125–225 ms, 225–325 ms, and 325–425 ms periods). This was done separately for the responses to the predeviant standard and deviant tones. In the 1100-Hz-alone condition mean amplitudes were calculated only for the ERPs to the 1100-Hz stimulus. A *mean difference score* representing response to change was also calculated for each period by subtracting the mean amplitude to the standard from that to the deviant.

For peak amplitudes and latencies a difference wave was calculated by subtracting the ERPs to the predeviant standard tone from the ERPs to the deviant stimulus within the window of 50 ms before and 425 ms after the stimulus onset. From this difference wave a *negative peak amplitude* was calculated, in reference to the 50 ms prestimulus baseline, at the latency of the most negative (or the least positive) deflection within a time window of 150–375 ms (cf. Alho, Sainio, et al., 1990, who measured the peak latencies approximately within this time window). Similarly, a *positive peak amplitude* was also calculated at the latency of the most positive (or least negative) deflection. In the 1100-Hz-alone condition these peak amplitudes were calculated from the 1100-Hz stimulus response itself. For within-subject comparisons the peak amplitude scores were also calculated from the deviant-response in the 1100-Hz-deviant condition.

In order to estimate a possible relation of the polarity of the ERPs and maturation (a relation suggested by Kurtzberg et al., 1984) a *measure of polarity* was defined as the amplitude of the largest deflection from the baseline (regardless of the sign) within a time window of 150–375 ms.

Statistical analysis. An alpha level of .05 was used for statistical tests. In reporting the significance of separate univariate F-test results the alpha level is adjusted (unless stated otherwise) according to the Bonferroni procedure (the alpha level divided by the number of multiple univariate tests) to protect against Type I error. Two-tailed observed power at the alpha level of .05 was calculated for each statistical test on ERP-measures with a significant result. In the main experiment ($N = 28$) the power averaged .85 (range: .51–1.0). For tests with smaller power than .85 the value is reported separately. In the comparisons of ERPs in the 1100-Hz-alone and 1100-Hz-deviant conditions ($n = 11$) and in the 1300-Hz-deviant and 1100-Hz-deviant conditions ($n = 9$) the power averaged .71 (range: .57–.83). Only such univariate F tests that showed significant results according to the adjusted alpha level were included in this average. For tests with smaller power than .75 the value is reported separately.

RESULTS

Main Experiment: 1100-Hz-Deviant Condition

ERPs to standard tones. The response to the 1000-Hz standard tones was very small without any clear peak as seen in Figure 1. The mean standard response amplitudes over the consecutive 100 ms epochs did not differ from the baseline at any single electrode site in any of the four time periods ($ps > .05$).

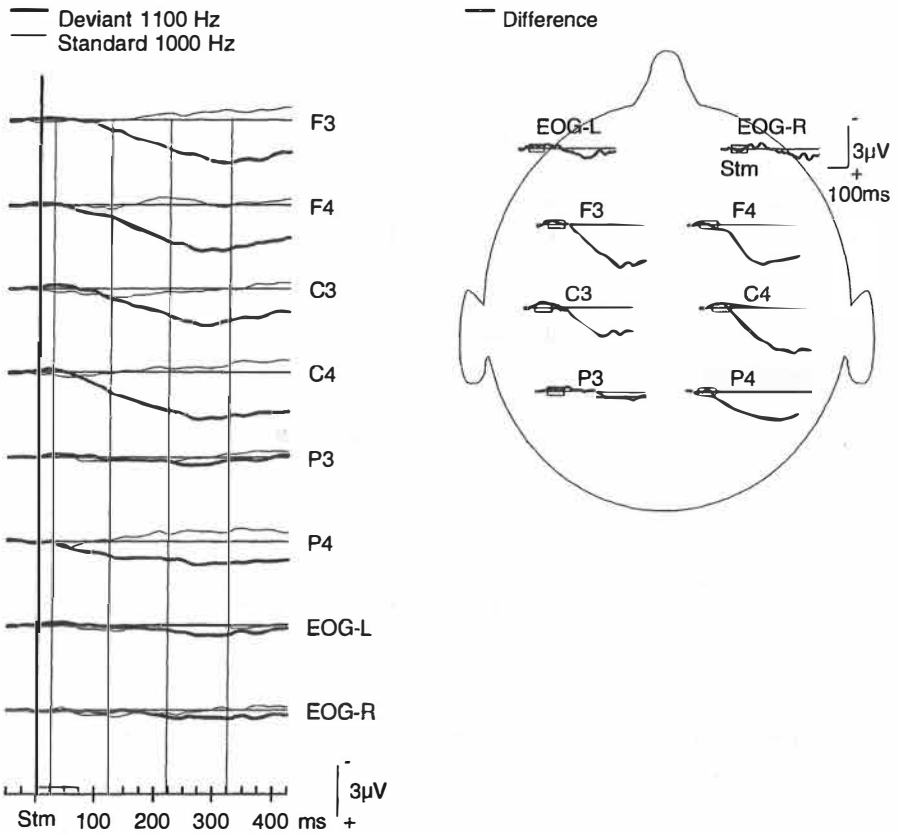

FIGURE 1 On the left panel: Event-related potentials (ERPs; averaged across 28 participants) to the rare 1100-Hz deviant tone (thick lines) and the frequent 1000-Hz standard tone (thin lines). Vertical lines across channels separate the consecutive 100 ms periods starting from 25 ms. On the right panel: Difference waves (based on the averages across the same 28 participants) obtained by subtracting the ERPs to the standard tone from those to the deviant tone for the epoch of –50 – 425 ms; Stm denotes the stimulus onset and length. Negativity up.

Mean response amplitudes over consecutive 100-ms periods. The most typical response to the 1100-Hz deviant tone was a slow positive deflection (Figure 1). The mean amplitude scores over the four consecutive 100 ms periods were analyzed by a Stimulus (deviant or standard response) × Time Period (four 100 ms epochs) × Electrode (six sites) multivariate analysis of variance (MANOVA) for repeated measures. There was a significant main effect for stimulus, $F(1, 27) = 10.88$, $p < .003$, indicating that the ERPs to the deviant tones differed significantly from those to the standard tones over the four time periods and six electrode sites (F3, F4, C3, C4, P3, and P4). Significant Stimulus × Time Period and Stimulus × Electrode interactions were also found, $F(3, 25) = 10.66$, $p < .0001$, $\Lambda = .439$ and $F(5, 23) = 2.84$, $p < .04$, L = .619, respectively (the power for the latter test was .74).

Hemisphere (left or right) × Anterior–Posterior (frontal or central or parietal) MANOVAs for repeated measures were performed for the mean difference scores in each consecutive 100-ms time period separately. The supposed fronto-central distribution of response to change (e.g., Paavilainen et al., 1991, see preceding) was tested with a special contrast comparing combined responses at the frontal and central channels (F3, F4, C3, and C4) to those at the parietal sites (P3 and P4).

In the 25–125 ms period there were no significant effects ($ps > .05$). In each of the three last time periods (125–225 ms, 225–325 ms, 325–425 ms) the mean difference amplitude differed significantly from the baseline in the overall test for the six electrode sites, $Fs(1, 27) = 9.13, 17.21, 10.95$, respectively, $ps < .006$ (the power for the first of these tests was .83). This indicated that the mean deviant response was different and more positive in amplitude than the mean standard response during these time windows. In addition, in the second period (125–225 ms) a hemisphere effect for the mean difference amplitude was found, $F(1, 27) = 5.44$, $p < .03$ (power = .61), indicating that the mean difference shift was more positive over the right than over the left hemisphere. In the third period (225–325 ms) no hemisphere or anterior–posterior effects were found. In the fourth period (325–425 ms) a Hemisphere × Anterior–Posterior interaction was found, $F(2, 26) = 3.81$, $p < .04$, $\Lambda = .774$ (power = .64), indicating that the anterior–posterior differences in the response were different between the hemispheres. According to the contrast comparing combined responses at the frontal and central sites to those at the parietal sites, the mean difference response was greater fronto-centrally in all last three periods, $Fs(1, 27) = 4.84, 6.09$, and 4.26, respectively, $ps < .05$ (power = .56, .66, and .51, respectively).

The univariate F-test results, separate for each electrode site in each time period, are shown in Table 1. They revealed that the positive response in the 125–225 ms period was mainly due to the frontally and centrally measured responses over the right hemisphere. The univariate F-test results further showed that there was a shift at the frontal sites from a significant right-hemisphere response (in the 125–225 ms period), via a significant bilateral response (in the 225–325 ms period), to a

TABLE 1
Univariate *F* Tests for Mean Difference Amplitudes Over Consecutive 100-msec Periods in Main Experiment

		F			
Electrode Site	*df*	*25–125 msec*	*125–225 msec*	*225–325 msec*	*325–425 msec*
F3	27			12.62*	11.85*
F4	27		12.22*	15.30*	
C3	27				
C4	27		14.45*	20.55*	13.58*
P3	27				
P4	27				

Note. $N = 28$.

*$p < .002$. Mean difference amplitudes (mean deviant minus mean standard response) with * differ significantly from the baseline (the alpha level adjusted, 01/6).

significant left-hemisphere response (in the 325–425 ms period). At the central sites the responses were consistently significant only at the right sites in all last three periods.

Peak amplitudes and latencies. The grand average difference wave reached its most negative amplitude at the P3 electrode site (–1.8 μV) at a latency of 255 ms and its most positive amplitude at C4 (4.8 μV) at a latency of 271 ms. Table 2 summarizes the statistical values of the peak amplitudes and latencies of the difference wave. The peak amplitudes and latencies were separately analyzed with a Hemisphere × Anterior–Posterior MANOVA for repeated measures. In general, the results of these analyses confirmed the findings for the mean difference amplitude comparisons over the consecutive 100 ms periods. No significant effects were found for the negative (or least positive) peak amplitude or any significant main effects for the negative peak latency. However, as can be seen from Table 2, the small negativity at P3 reached statistical significance in separate univariate *F* tests. In contrast, the positive (or least negative) peak amplitude differed significantly from the baseline according to the overall test for all six electrode sites, $F(1, 27) = 57.76$, $p < .0001$. Separate univariate *F* tests indicated that this effect was significant at all six electrode sites (see Table 2). No significant hemisphere effects were found. However, a similar contrast was found between the combined frontal and central positive peak amplitudes compared to the parietal peak amplitudes as previously noted over 100 ms periods, $F(1, 27) = 5.66$, $p < .03$ (power = .63). For the positive peak latency no significant hemisphere or anterior–posterior effects were found.

TABLE 2
Mean Negative and Positive Peak Amplitudes and Latencies With Standard Deviations of Difference Wave in Main Experiment

	Negative Peak in all Participants[a]		*Negative Peak in 14 Participants*[b]		*Positive Peak in all Participants*[a]	
Electrode Site	*M*	*SD*	*M*	*SD*	*M*	*SD*
Amplitude (μV)						
F3	0.1	3.5	−2.3	3.2	4.4	4.0**
F4	0.1	3.1	−1.9	2.4	4.4	4.2**
C3	−0.7	3.8	−3.4	3.3*	3.8	3.8**
C4	0.3	3.0	−1.2	2.4	4.8	3.9**
P3	−1.8	2.9*	−2.7	2.9*	2.4	2.7**
P4	−0.4	3.5	−1.0	4.0	3.5	3.4**
Latency (msec)						
F3	208.4	70.3	216.1	68.5	278.9	76.7
F4	255.7	93.8	276.1	96.8	272.3	65.3
C3	249.5	87.4	245.7	79.2	275.4	74.4
C4	259.3	95.7	261.4	102.4	271.1	78.2
P3	254.6	83.2	247.5	88.8	276.3	77.9
P4	226.3	83.5	226.8	94.7	268.4	83.0

[a]$N = 28$. [b]Participants with some negativity in the difference wave at any two frontal or central channels, $n = 14$ (see the text).

*$p < .008$. **$p < .0002$; $df = 1, 27$. Amplitudes with *, or ** differ significantly from the baseline (the alpha level adjusted, .05/6, or .001/6, respectively). Note that *p*-values are displayed only for the peak amplitudes.

Negativity in individual participants. In a proportion of the participants, 14 of 28 (50%), a negative fronto-central peak was observed in the individual difference waves (some negativity at any two frontal or central channels). In these participants the negatively displaced deviant-response in relation to the standard response was most clearly seen at C3 and at P3 (see Table 2). However, in 10 of these 14 participants (36% of all participants) the largest deflection (or the maximum regardless of the sign) of the difference wave had a negative polarity. In these 10 participants the positive mean peak amplitude ranged at different electrode sites between only −0.1 μV (at C3) and 3.1 μV (at C4), being considerably smaller than between 2.4 μV (at P3) and 4.8 μV (at C4) in all 28 participants. In the remaining 4 participants the positive mean peak amplitude ranged, on the other hand, between 3.8 μV (at P3) and 8.3 μV (at F3) indicating that a predominantly positive deflection contributed most to the waveform of these participants. In these participants the negative (or least positive) mean peak amplitude was, in turn, positive only at F3; at the other electrode sites it ranged between −0.2 μV (at F4) and −1.1 μV (at P3).

Polarity of ERPs in relation to GA and CA. Pearson correlations between the largest deflection of the difference wave and GA and CA, as well as between the deviant response and the latter two, were calculated in order to find out whether the polarity of the ERPs would be more positive in infants with a greater GA or CA. A significant correlation between the peak amplitude of the difference wave and both GA and CA was found for the ERPs at F3, $r = .43$, one-tailed $p < .02$, and $r = .42$, one-tailed $p < .02$, respectively, and at F4, $r = .53$, one-tailed $p < .003$, and $r = .47$, one-tailed $p < .006$, respectively. A significant correlation was also found between CA and the difference wave amplitude at C3, $r = .34$, one-tailed $p < .04$, and between CA and the deviant response amplitude at F3, $r = .33$, one-tailed $p < .05$. This indicated that the greater the GA or CA the more positive the amplitude of the largest response at these electrode sites. Figure 2 characterizes this relation at the F4 channel.

Comparison of 1100-Hz-Alone Control and 1100-Hz-Deviant Conditions

Mean response amplitudes over consecutive 100-ms time periods. Eleven infants also participated in the 1100-Hz-alone condition. In this condition the stimulus elicited initially a small negative deflection peaking at about 100 ms followed by a positive response almost of equal amplitude at the frontal and central channels (see Figure 3).

Repeated measures Hemisphere x Frontal–Central MANOVAs were performed for the mean scores representing each consecutive 100-ms time period. These analyses were carried out only for the responses at the frontal (F3 and F4) and central electrode sites (C3 and C4), because it was in these sites where the clearest effects were observed in the main experiment (see Table 1). The only significant effect for the mean response amplitude in the 1100-Hz-alone condition was in the overall test for the four electrode sites in the 225–325-ms period showing that the mean amplitude for this period (with positive polarity) differed significantly from the baseline, $F(1, 10) = 8.59$, $p < .02$. Separate univariate F-test results for each electrode site are shown in Table 3.

In these 11 participants the results of corresponding analyses for the 1100-Hz deviant tone presented among standard tones were in line with the results for the mean difference amplitudes obtained in the 28 participants. The mean amplitude of the deviant response differed from the baseline in the overall test for the four electrode sites in the 225–325 and 325–425-ms periods, $F(1, 10) = 9.41$, $p < .02$, and $F(1, 10) = 6.92$, $p < .03$, respectively (power in the latter was .66). The means indicated that the response to the deviant tone was also positive in polarity (see also Figure 3). See Table 3 for univariate F-test results for each electrode site. No

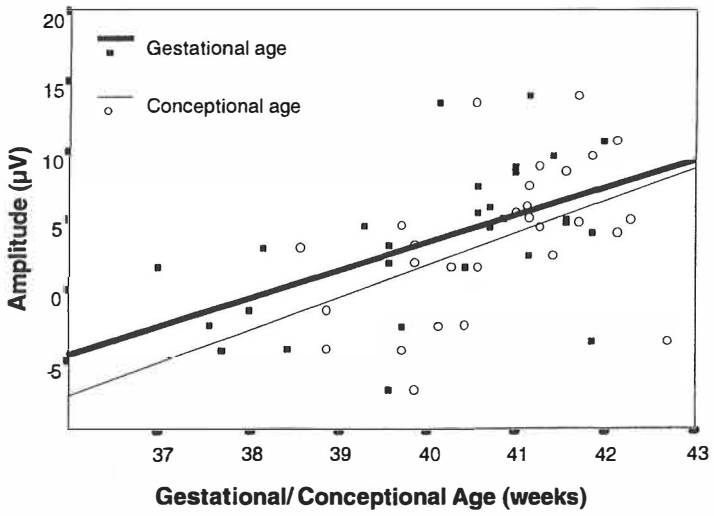

FIGURE 2 Amplitude of the individually largest deflection of the difference wave (of the event-related potentials to the 1000-Hz standard tone subtracted from those to the 1100-Hz deviant tone) at F4 as a function of gestational age (GA) and conceptual age (CA) in the main experiment ($N = 28$; see the text). Squares and circles represent individual averaged amplitude values in relation to GA and CA, respectively. Note that those born before the GA of 38 weeks were measured at the CA of 40 weeks or somewhat later. Lines represent linear regression lines fitted to the scatter plot. Correlations between the F4 amplitude and GA and CA are .53 and .47, respectively. Both correlations are statistically significant ($p < .003$).

hemisphere or frontal–central main effects were found in the omnibus MANOVAs in any of the time periods.

The scores from the electrode sites and time periods with significant differences from the baseline in either condition were used in the analysis of variance (ANOVA) for repeated measures between the two conditions. It was found that the mean response amplitude was more positive in the 1100-Hz-deviant condition than in the 1100-Hz-alone condition at C4 in the 325–425 ms period, $F(1, 10) = 5.97$, $p < .04$ (power = .60). This indicated that the positive response was longer in duration to the deviant stimulus than to the equivalent stimulus presented alone.

Peak amplitudes and latencies. In the 1100-Hz-alone condition the amplitude of the deviant response was, on average, most negative at the P4 electrode site (–0.6 μV) at a latency of 208 ms and most positive at C3 (4.1 μV) at a latency of 271 ms. The peak amplitudes were tested with a repeated measures Condition (1100-Hz-alone or 1100-Hz-deviant) × Hemisphere × Anterior–Posterior MANOVA. All six electrode sites were included in this analysis. There were no significant effects for the negative peak amplitude. Neither did the negative peak amplitude differ from baseline at any single electrode in separate univariate F tests.

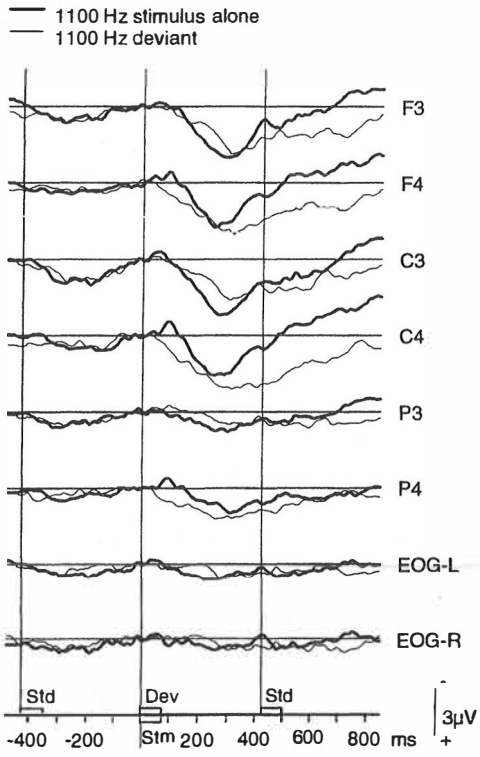

FIGURE 3 Event-related potentials (averaged across 11 participants) to the 1100-Hz tone presented alone (thick lines) and to the 1100-Hz deviant tone (thin lines). Vertical lines mark the beginning of the predeviant standard, deviant, and postdeviant standard stimuli in the condition with the deviant tone (the labels above time-scale) and the equivalent periods in the condition with the same stimulus alone (the label below time-scale). Negativity up.

The positive peak amplitude, on the other hand, differed significantly from the baseline in the overall test for the six electrode sites over both conditions, $F(1, 10) = 25.1$, $p < .0006$. Separate univariate F tests revealed that the positive peak amplitude differed from the baseline at F3, F4, C3, and C4, $Fs(1, 10) > 16.5$, $ps < .003$, in the 1100-Hz-alone condition, and at F3, F4, C4, and P4, $Fs(1, 10) > 14.1$, $ps < .004$, in the 1100-Hz-deviant condition. But no significant condition main effect or any Condition × Hemisphere or Condition × Anterior–Posterior interactions were found in the omnibus MANOVA, indicating that no significant differences existed between the two conditions for the positive peak amplitude. The latencies of both the negative and positive peak amplitudes were tested with similar repeated measures Condition × Hemisphere × Anterior–Posterior MANOVAs. These analyses did not reveal any differences between the conditions.

Comparison of 1300-Hz-Deviant Control and 1100-Hz-Deviant Conditions

Mean response amplitudes over consecutive 100-ms time periods. Nine infants also participated in the 1300-Hz-deviant condition (with a higher stimulus contrast,

TABLE 3
Univariate *F* Tests for Mean Deviant Amplitudes Over Consecutive 100-msec Periods in 1100-Hz-Alone and 1100-Hz-Deviant Conditions[a]

	F					
	1100-Hz-Alone			*1100-Hz-Deviant*		
Electrode Site	*125–225 msec*	*225–325 msec*	*325–425 msec*	*125–225 msec*	*225–325 msec*	*325–425 msec*
F3		6.79*			6.75*	5.57*
F4		8.26*		6.47*	10.63**	8.30*
C3		9.32*				
C4		7.21*		7.36*	9.21*	7.93*

[a]$N = 11$. *F* values in the 1100-Hz-deviant condition are here from those same individuals who participated in the 1100-Hz-alone control condition.

*$p < .05$. **$p < .01$; $df = 1, 10$. Mean deviant amplitudes with * or ** differ significantly from the baseline (using a liberal alpha level not adjusted according to the Bonferroni procedure, power range = .57–.84).

1000 vs. 1300 Hz as opposed to 1000 Hz vs. 1100 Hz). In this condition, too, a positive deflection was elicited by the deviant tone. However, as can be seen from Figure 4, this positivity was somewhat smaller in the 1300-Hz-deviant than in the 1100-Hz-deviant condition.

Similar statistical tests as performed for comparisons in the 1100-Hz-alone and 1100-Hz-deviant conditions (see previous section) were carried out in the 1300-Hz-deviant and the 1100-Hz-deviant conditions. In the 1300-Hz-deviant condition no significant effects were found in repeated measures Hemisphere × Frontal–Central MANOVAs for the mean difference scores in any of the consecutive 100-ms time periods. However, the results of the corresponding analyses in the 1100-Hz-deviant condition for these 9 participants were in line with the findings in the main group of the 28 participants. The mean difference amplitude differed from the baseline in the overall test for the four electrode sites (F3, F4, C3, and C4) in the 225–325-ms period, $F(1, 8) = 5.9$, $p < .05$ (power = .57). According to univariate *F* tests, this effect was observed, using a liberal alpha level of .05, at F3, F4, and C4, Fs$(1, 8) > 5.35$, ps $< .05$ (power > .53). No hemisphere or frontal–central main effects were found in the omnibus MANOVAs in any of the time periods. No significant differences were found in separate ANOVAs for repeated measures between the conditions at these electrode sites.

Peak amplitudes and latencies. In the 1300-Hz-deviant condition the negative peak amplitude of the difference wave was, on average, largest at P3 (–3.8 μV) at a latency of 237 ms, and the positive peak largest at F4 (3.7 μV) at a latency of 270 ms. In a Condition (1300-Hz-deviant or 1100-Hz-deviant) × Hemisphere ×

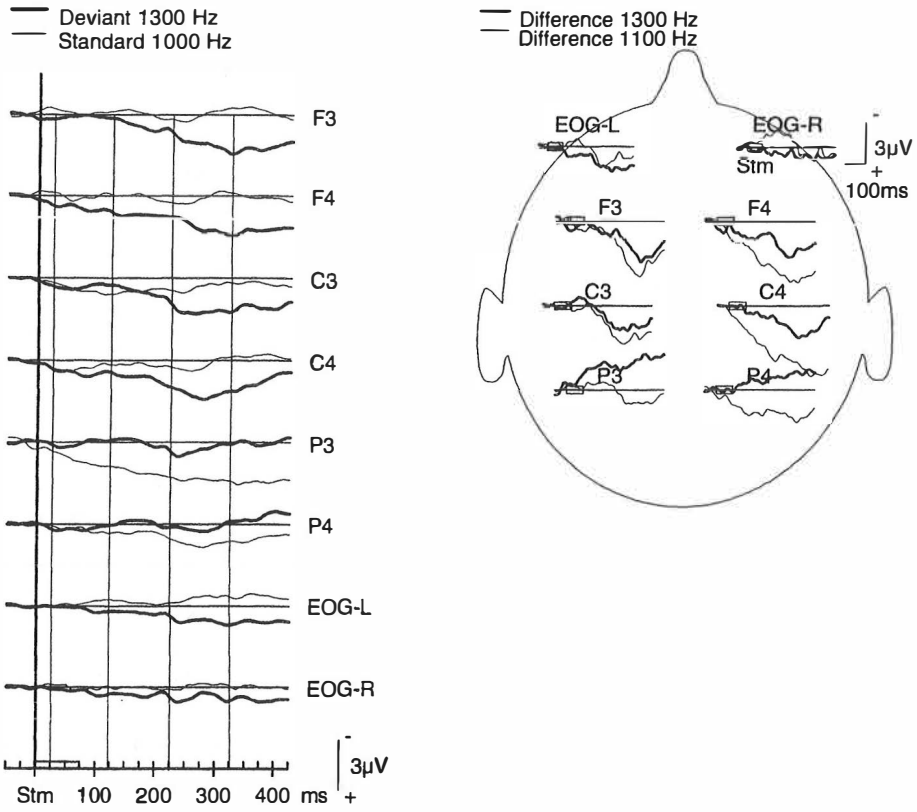

FIGURE 4 On the left panel: Event-related potentials (ERPs; averaged across 9 participants) to the rare 1300-Hz deviant tone (thick lines) and the frequent 1000-Hz standard tone (thin lines). Vertical lines across channels separate the consecutive 100-ms periods starting from 25 ms. On the right panel: Difference waves (based on the averages across the same 9 participants, obtained by subtracting the ERPs to the standard tone from those to the deviant tone for the epoch of –50 – 425 ms) to the 1300-Hz (thick lines) and 1100-Hz deviant stimuli (thin lines); Stm denotes the stimulus onset and length. Negativity up.

Anterior–Posterior MANOVA for repeated measures only anterior–posterior main effect was found for the negative peak amplitude, $F(2, 7) = 21.18$, $p < .01$, $\Lambda = .142$. Separate univariate F tests in each condition, shown in Table 4, revealed that this effect was mainly due to the negative deflection at P3 and P4 in the 1300-Hz-deviant condition. However, according to two-way ANOVAs for repeated measures the negative peak amplitude was larger in the 1300-Hz-deviant condition than in the 1100-Hz-deviant condition only at P4, $F(1, 8) = 6.55$, $p < .04$ (power = .61). Similarly, in the corresponding test for the positive peak amplitude only anterior–posterior main effect was found, $F(2, 7) = 47.13$, $p < .0001$, $\Lambda = .069$, resulting

from a larger positive peak amplitude fronto-centrally than parietally, $F(1, 8) = 49.35$, $p < .0001$. Separate univariate F tests for each electrode site are shown in Table 4. In two-way ANOVAs for repeated measures the positive peak amplitude differed significantly between the conditions only at P3, $F(1, 8) = 6.77$, $p < .04$ (power = .63), indicating that it was smaller in the 1300-Hz-deviant condition than in the 1100-Hz-deviant condition. No significant latency differences were found between the conditions ($ps > .05$).

DISCUSSION

This study shows that early after birth auditory brain ERPs reflect passive discrimination between frequently and rarely occurring tones that differ in pitch. Our results suggest that a typical ERP to auditory stimuli in newborns is a positive response, that, in a case of stimulus change, may be overlapped by a MMN-like response related to the functioning of the sensory memory.

ERPs in Main Experiment

The prominent slow positive deflection that occurred in most participants to the rare 1100-Hz deviant tone, embedded among the frequently presented 1000-Hz standard tones, peaked at about 280 ms latency. This is consistent with previously reported positive responses at similar latencies to deviant tones presented among repeated standard tones in newborns (Kurtzberg et al., 1995), in 6-week-olds (Duclaux et al., 1991), and in 4 to 7-month-old infants (Alho, Sajaniemi, Niitty-vuopio, Sainio, & Näätänen, 1990).

The deviant tone elicited, in relation to the standard tone, only a small negativity that occurred, on average, at a latency range of 225–255 ms. This negativity reached the statistical significance only at the left parietal site. Using the criteria defined by Kurtzberg et al. (1995, with the exception that instead of only Fz any two frontal or central channels were accepted for inspection) a negative deflection greater than 0.75 μV in the difference wave (deviant minus standard) was present in 12 of 28 participants (43%). If the response only to the deviant tone is considered, some negativity (> 0 μV) was found in 13 of 28 participants (46%). With the same criteria some negativity was observed in the difference wave (the deviant response negatively displaced in relation to the standard response) in 14 of 28 participants (50%), which is less than found by Kurtzberg et al. (75%). The small negative shift is not, though, observable in the grand average waves (see Figure 1). The negativity may represent, in some participants, an overlapping MMN-like response (see Maturational effects section).

The response to the standard tones, on the other hand, was only very small, a finding in newborns also reported by Alho, Sainio, et al. (1990). This small standard response can be explained by a long refractory period in newborns (cf. Kurtzberg et al., 1995). Thus, the major contribution to the difference wave seems to come from the response

TABLE 4
Mean Negative and Positive Peak Amplitudes With Standard Deviations of Difference Wave in 1300-Hz-Deviant and 1100-Hz-Deviant Conditions[a]

	Negative Peak				*Positive Peak*			
	1300-Hz-Deviant		*1100-Hz-Deviant*		*1300-Hz-Deviant*		*1100-Hz-Deviant*	
Electrode Site	*M*	*SD*	*M*	*SD*	*M*	*SD*	*M*	*SD*
Amplitude (μV)								
F3	−0.4	2.9	−0.4	4.2	3.4	4.0*	5.0	4.5*
F4	−0.6	3.1	0.7	4.3	3.7	3.1**	6.2	5.5*
C3	−1.0	2.5	−0.6	4.1	3.0	2.2**	3.9	4.5*
C4	−0.7	4.7	1.1	4.0	3.6	6.0	6.4	5.4**
P3	−3.8	3.0**	−1.4	3.6	0.2	2.5	2.4	2.7*
P4	−3.4	3.5*	−0.2	3.9	1.4	4.4	3.2	3.6*

[a]$N = 9$. Peak amplitude values in the 1100-Hz-deviant condition are here from those same individuals who participated in the 1300-Hz-deviant control condition.

*$p < .05$. **$p < .01$; $df = 1, 8$. Amplitudes with * or ** differ significantly from the baseline (using a liberal alpha level not adjusted according to Bonferroni procedure, power range = .61–.94).

to the deviant stimulus. The peak amplitudes show, however, a considerable interindividual variation. Similar individual variability was also observed in the peak latencies. Further, there are individual differences also in the polarity of the dominant deflection.

Positive Deflection: A Typical Response in Newborns to Auditory Stimuli

A control like our first control condition with the 1100-Hz tones (equivalent to the infrequent deviant tone) presented at intervals similar to the ones of the deviant tones but without intervening standard tones is thought to be an appropriate control to differentiate a response to a stimulus or some stimulus feature per se from the MMN response to change (Näätänen et al., 1989; see also Näätänen & Alho, 1995). In our stimulus-alone-condition no clear negative response was observed at the latency of a typical MMN; rather a prominent positive response was observed as in the main experiment to the equivalent deviant tone. A comparable positivity was also evident in the second control condition (with a greater stimulus difference).

These findings clearly indicate that at least part of the positive response occurring to a deviation in a stimulus sequence is comparable to a response that also occurs to a stimulus presented alone. As the small standard response can be accounted for by refractoriness (see previous section), the relatively large positive deflection

represents a response that is elicited by an auditory stimulus presented with an ISI of sufficient length or by a stimulus change, that is, a nonrefractory response to auditory stimulation. The afferent auditory system becomes refractory to the repetition of the standard tone pitch and may remain responsive to the pitch of the deviant tone. On the other hand, the auditory system also seems to be strongly affected by a change (deviation) in a stimulus sequence, meaning that after the sensory system becomes refractory or habituated to the repeated standard tone, even a small stimulus change leads to release from refractoriness or to dishabituation, or both.

The greater positive response to the deviant than to the standard stimulus had a specific scalp distribution in the main experiment. At the time window from 125 ms to 425 ms the mean responses were greater over the fronto-central areas than at the parietal sites. Peak amplitude comparisons confirmed this fronto-central distribution. At the frontal sites in the early portion of the positive deflection (at the latency of 125–225 ms) the mean responses were significant only over the right hemisphere, whereas in the middle portion (225–325 ms) the responses were significant bilaterally. In the last period (at 325–425 ms latency) significance was reached only in the responses over the left hemisphere. At the central sites the mean responses were significant only over the right hemisphere in all aforementioned time periods. These findings suggest that refractoriness or dishabituation is reflected in different scalp areas during the time course of the response as signal processing proceeds. However, the scalp distribution of the positive response to the deviant tone may be partly explained by an overlapping mismatch response (see section on Reduction of Positivity).

A noticeable difference between the stimulus-alone and the oddball conditions was that the positive response to the 1100-Hz deviant stimulus presented among standard stimuli was longer in duration than the response to the 1100-Hz stimulus presented alone. This result suggests that the positive deviant response measured in the oddball paradigm could reflect also a response to a change and not merely a response to novelty or some stimulus per se (cf. Näätänen et al., 1989). This and the fronto-central scalp distribution, which resembles that of an MMN response, means that this positive deviant response fulfills the procedural criteria for the elicitation of MMN. However, at least two observations speak against a mismatch response as a possible explanation for the longer response duration in our study. Although Alho, Sainio, et al. (1990) observed a similar longer duration of the response to an infrequent deviant stimulus in an equivalent control experiment, in their study the ERPs to the deviant tone had a negative polarity in most participants. Second, in our study there was a reduction in the amplitude of the positive response, rather than an enhancement, when there was a greater change in the stimulus sequence (for further discussion on this issue see the following).

The difference in the duration of the positive response may be explained, more naturally, by the onset of a late negative shift that overlaps the positive deflection

in the stimulus alone condition (see Figure 3). Similar late negative deflection has been reported in newborn infants at a latency of 800 ms to sounds presented with a fixed ISI of 2.7 sec (Novak et al., 1989). A possibility also exists that the longer duration of positivity to the deviant tone in the oddball condition would represent, at least partly, an adult-like fronto-central P3a component (occurring somewhat earlier, usually at a latency of ca. 300 ms, than the parietally maximal P300), which is thought to reflect involuntary orienting of attention to changes in unattended auditory stimuli if stimulus change is great enough (e.g., Novak, Ritter, Vaughan, & Witznitzer, 1990; Sams, Paavilainen, et al., 1985; Snyder & Hillyard, 1976; Squires, Squires, & Hillyard, 1975). This was an explanation suggested by Alho, Sajaniemi, et. al. (1990) for a positive, rather than a negative, response in preterm and full-term infants at the age of 4–7 months to similar deviant tones that they had used earlier for newborns (Alho, Sainio, et al., 1990). It should be noted, however, that both latter two explanations may be partially tenable: In newborns the positive response may reflect the same orienting-related process in both the stimulus-alone- and oddball conditions, and the shorter duration in the stimulus-alone-condition may be only due to the onset of the late negative shift.

Maturational effects. As stated, the ERPs with a positive polarity observed in this study most likely represent a typical or normative response in full-term newborns to auditory stimuli. Such positive responses have earlier been reported to auditory stimuli presented with rather long ISIs (e.g., Barnet et al., 1975). Moreover, the ERPs of full-terms, when measured within few days from birth, are predominantly positive in polarity according to studies that have described maturational changes in basic waveform and morphology in infant ERPs up to the age of 3 months (e.g., Kurtzberg et al., 1984, 1986; see also Graziani, Katz, Cracco, Cracco, & Weitzman, 1974; Novak et al., 1989; Thomas & Crow, 1994). Kurtzberg et al. (1984) have actually described five maturational levels of ERPs: The least mature ERPs show negative polarity at midline and lateral sites, and the most mature ERPs positive polarity at both these sites. The ERPs of full-terms show positive polarity at midline electrode locations and negative at temporal locations.

These described maturational changes might also explain the negativity in most of those 14 participants in whom a frontal or central negative peak amplitude was observed in the main experiment. This is supported by the observed positive correlation between the amplitude of the individually largest deflection at the frontal and central sites and the GA or CA, indicating that the greater the GA the more positive the dominant deflection. Further support comes from the occurrence of only a relatively small positive response in 10 of those 14 participants. In addition, in these 10 participants the dominant deflection had a negative polarity, and, therefore, the negative deflection of the difference wave may not represent a mismatch response, but rather a less mature nonrefractory ERP. There is a possibility, though, that MMN overlaps with this negative response, but the differentia-

tion between these two responses in these infants is difficult. On the other hand, in 4 of those, in whom a small frontal or central negative peak was observed, a considerable positive deflection was also found, suggesting that at least in these participants a genuine MMN response may have been elicited.

Mismatch Response Reflected in Reduction of Positivity. Some evidence was found for a possibility that the positive response would be overlapped by a smaller negative component reflecting a mismatch process, which requires discriminable difference between tones, and that strong enough neural representation of one of these tones is developed (Cowan, Winkler, Teder, & Näätänen, 1993). MMN is, then, elicited by a deviation or a change of a stimulus in relation to this neural representation. We suggest that such a mismatch process is reflected in a small negative peak of the difference wave in few participants (see previous paragraph) and possibly in a reduction of the positive amplitude in most participants.

The scalp distribution differences in the first control experiment between the responses to the 1100-Hz tone presented alone and the similar deviant stimulus give tentative support for the existence of the suggested overlapping MMN response. The positive response to the 1100-Hz stimulus alone was bilateral, whereas the response to the similar deviant tone was more prominent and consistent over the right than over the left hemisphere, where no significant responses were observed at the C3 electrode site in either the mean score or peak amplitude measures. A possible overlapping MMN response to the deviant stimulus could explain this reduction of the positive deflection over the left hemisphere. However, it should be noted that the typical requirements for a demonstration of an adult MMN in this kind of control experiment, namely an earlier latency and more central scalp distribution of the negative response to an infrequent stimulus presented alone (Näätänen, 1992; Näätänen et al., 1989), were not fulfilled.

The data from the second control condition with the greater stimulus difference (1300 Hz vs. 1000 Hz as opposed to 1100 Hz vs. 1000 Hz in the main experiment) provide the clearest evidence for a possible MMN overlapping the positive response. Thus, the differences in our study and that of Alho, Sainio, et al. (1990) could be partly explained by the smaller difference between deviant and standard stimuli (10%) used by us in the main experiment compared to a greater difference used in their study (20%). The effect of the greater stimulus difference in our study can be seen in a reduction of the positive amplitude of the deviant response to the 30% change (1300 Hz vs. 1000 Hz) in comparison to the 10% change. In fact, Kurtzberg et al. (1995) suggested that the MMN to the deviant stimulus would make its appearance in newborns as a reduction in the amplitude of a series of positive deflections.

The reduction of positivity to the 1300-Hz deviant tone is seen best in Figure 4 and as a lack of any significant differences from the baseline in the mean difference scores over the 100 ms periods, when, in fact, greater responses than to the 1100-Hz

tone would have been expected. According to Figure 4 this reduction occurs at the latency of the MMN-like response reported earlier by Alho, Sainio, et al. (1990), suggesting a possible overlapping negative component at this latency. Our results are thus in line with the finding of Cheour-Luhtanen et. al. (1995), in which the MMN-like negativity was smaller, when the deviation was of a smaller magnitude. Thus, in this view the MMN response of newborns would be enhanced with the increase of stimulus difference, which is, clearly, the case in adults (Sams, Hämäläinen, et al., 1985). At the first sight, it may thus seem that a greater stimulus difference (30%) is required for the MMN response than for the positive response (10%). However, a possible MMN may just be more clearly identifiable from the overlapping positive deflection occurring with a greater stimulus difference.

Effect of ISI. The response to a deviation as great as 30% (1300 Hz vs. 1000 Hz) still shows no clear negative peak over the expected fronto-central scalp areas, which, at the first sight, seems to challenge our suggestion of the MMN-like response. Negative peak amplitude was enhanced, though, at the parietal sites (at P3 and P4). The lack of a clear negative response fronto-centrally could be explained in turn, at least partly, by the shorter 425 ms ISI used by us as compared to 610 ms used by Alho, Sainio, et al. (1990). Reduction of an ISI may not only affect the response to the standard but also the response to the deviant stimulus. We have, namely, observed that with 9- to 10-year-old children shortening the ISI from 610 ms to 400 ms resulted in a much smaller response to the deviating tone (Laukkonen, Leppänen, & Lyytinen, 1992).

Therefore, it seems that with short ISIs the response to standard stimuli becomes refractory, and the nonrefractory response to deviant stimuli (with rather long interdeviant intervals), though overlapped by a possible MMN response, remains positive, leaving also the difference between the deviant and standard responses positive in most full-term newborns. However, in infants with the ERPs reflecting earlier maturational level with predominantly negative responses (in our case most likely in 10 of 28 participants, 36%) negativity is enhanced. Therefore, a possibility exists that with longer ISIs than used by us the responses to both standard and deviant stimuli may also be larger, and consequently, the enhanced negative deflection elicited by the deviant tone at the latency of MMN might be negatively displaced in relation to the enhanced positivity to the standard tone even in infants with more mature ERPs. This interpretation is supported by the study of Cheour-Luhtanen et al. (1995), in which the response to the standard stimulus presented with an ISI of 800 ms is clearly positive in polarity at a latency of the reported MMN-like deflection (see their Figure 1).

However, if this line of reasoning concerning the effect of ISI on MMN in newborns is tenable, it follows that a simple subtraction of the standard response from the deviant-response cannot be considered to reflect as such the MMN response, not at

least without first considering the ISI effect on refractoriness. Our previous discussion implicitly suggests that the problem may not be as great with long ISIs. However, if separate nonrefractory responses occur to deviant and standard stimuli, as might be the case with large enough stimulus differences (see e.g., Javitt, Doneshka, Zylberman, Ritter, & Vaughan, 1993), the difference wave reflects contribution of both MMN and the nonrefractory response to the deviant stimulus, and their differentiation from each other is difficult. On the other hand, the use of short ISIs typically results in the enhancement of MMN in adults (Näätänen, 1992), and it has been suggested that the same is also true about newborns (see e.g., Kurtzberg et al., 1995). Rapid presentation of a frequent stimulus is, namely, thought to strengthen the memory trace formed by the frequent stimulus (Näätänen, 1992). However, at least two relevant factors should be considered.

First, the amplitude of MMN is also dependent on the interdeviant intervals: With very short ISIs, if the probability of the deviants is kept constant, this interval becomes so short that the deviant tones start to form a memory trace of their own, resulting in a smaller MMN (Näätänen, 1992). In our study the interdeviant interval (2,550–4,675 ms) should have been long enough for a distinguishable MMN. For example, MMN has been shown to be elicited even with an ISI of 101 ms with a rate of one deviant and nine standards (on average) in 1 sec (cf. Näätänen, 1992). However, there may be developmental factors, such as long refractory periods and lack of myelination in newborns, that would require even longer interdeviant intervals for MMN to be clearly observable.

Second, using short ISIs could result in a distinguishable MMN response even in newborns, provided that the overlap of MMN and the nonrefractory deviant response could be avoided. A possibility would be to use even a smaller stimulus difference than the 10% used by us so that no separate nonrefractory deviant tone response (from the standard tone response) would be generated. This suggestion presupposes a speculative functional analogy between the processes reflected in the positive response in newborns and N1 (an exogenous response occuring at ca. 100 ms) in adults. According to Näätänen (1992) the supratemporal N1 probably based on tonotopically organized afferent neuronal population, is not, namely, as stimulus specific as the MMN response based on the sensory memory neuronal population. Further, it has been suggested that with a small enough stimulus difference between the deviant and the standard stimulus no differential N1 refractoriness would occur (see e.g., Javitt et al., 1993). This suggestion of a smaller stimulus difference is, of course, tenable only if the mechanism underlying MMN would be specific enough in newborns.

Effect of Sleep States

In previous studies ERPs have been reported to be largest in quiet sleep (e.g., Ellingson et al., 1974), and Duclaux et al. (1991) found a difference between

responses to deviant and standard tones only during quiet sleep. However, contrary to what we expected on the basis of these earlier studies (see the introduction), our results have led us to suspect that MMN could be more distinguishable during active sleep than during quiet sleep. Auditory evoked potentials of wakefulness, the typical state for MMN studies, resemble those of active sleep rather than those of quiet sleep in newborns (e.g., Ellingson et al., 1974). Moreover, it could be argued that if the previously suggested hypothesis of reduction of positivity is true, a possibility is that MMN cannot be differentiated so easily from overlapping great positive deflections in quiet sleep as from reported smaller deflections occurring during active sleep (e.g., Duclaux et al., 1991). That Duclaux et al. found a difference between the deviant and standard responses only during quiet sleep speaks against this argument. However, because Duclaux et al. used a rather long ISI (2,000 ms) compared to typical MMN studies (Näätänen, 1992) their finding cannot necessarily be generalized to MMN. Further studies are needed to clarify the effect of sleep states on MMN.

Concluding Remarks

In this study a typical oddball paradigm used in MMN studies in adults was applied to newborns. Our results indicate that the MMN response in very young infants may not be measurable without problems under conditions used in adult studies. In addition, the enhanced negative parietal responses to the greater stimulus difference may indicate differences in the scalp distribution of the MMN itself between newborns and adults, in whom MMN is more prominent fronto-centrally. This enhanced parietal activity needs to be confirmed in future studies.

On the whole, our data suggest that two or three separate processes related to the monitoring of auditory environment, based on different neural generators, may be differentiated in the auditory system already at birth. First, an ERP component to auditory stimuli, the polarity of which is, at least partly, determined by individual maturational levels of ERPs. It seems to reflect a process affected by refractoriness to repetition or a process affected by dishabituation to a small change, or both. These two processes cannot be differentiated on the basis of the data from this study. Second, some evidence was also found for the existence of a mismatch process, overlapping the typically positive response, between the existing sensory memory trace for the standard stimulus and a sensory input generated by an incoming different stimulus.

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III

CORTICAL RESPONSES OF INFANTS WITH AND WITHOUT A GENETIC RISK FOR DYSLEXIA: I. AGE EFFECTS

By

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IV

CORTICAL RESPONSES OF INFANTS WITH AND WITHOUT A GENETIC RISK FOR DYSLEXIA: II. GROUP EFFECTS

By

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V

BRAIN RESPONSES REVEAL TEMPORAL PROCESSING DIFFERENCES IN INFANTS AT RISK FOR DYSLEXIA

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