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Tomi K. Guttorm

Newborn Brain Responses Measuring Feature and Change Detection and Predicting Later Language Development in Children with and without Familial Risk for Dyslexia

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ABSTRACT

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Yhteenveto: Vastasyntyneiden aivovasteet puheäänteiden ja niiden muutosten havaitsemisessa sekä myöhemmän kielen kehityksen ennustamisessa dysleksia-riskilapsilla
Diss.

Event-related potentials (ERPs) measuring feature and change detection were studied from newborns with and without familial risk for dyslexia. The possibility of using newborn ERPs to predict later language development was also investigated. Results from a feature detection paradigm (/ba/, /da/, /ga/; presented equiprobably with interstimulus interval, ISI, of 4–7 seconds) showed hemispheric group differences at 540–630 ms (latency identified by principal component analysis, PCA), where the responses to /ga/ were clearly more positive and prolonged in the right hemisphere of the at-risk group. This response pattern in the right hemisphere at birth was related to significantly poorer receptive language skills across both groups at the age of 2.5 years. Similar ERP pattern in the left hemisphere was associated with poorer verbal memory skills at the age of 5 years. In the change detection paradigm (standard /kaa/ and deviant /ka/; presented in an oddball paradigm with 425 ms ISI), the ERPs at 290–320 ms (latency identified by PCA) predicted later skills only in the at-risk group. Larger positive responses to the deviant stimuli (change detection) in the left hemisphere predicted better receptive language skills at 2.5 years and verbal memory skills at 3.5 years, whereas a similar pattern in the right hemisphere was associated with poorer verbal memory skills at 5 years. Larger positive responses to the standard stimuli (general responsiveness) in the left hemisphere were associated with poorer receptive language skills at 2.5 and 3.5 years and verbal memory skills at 5 years. These results indicate that ERPs can be used to predict later language development in children with and without familial risk for dyslexia.

Keywords: event-related potentials, feature detection, change detection, newborns, familial risk for dyslexia, prediction, language development

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Jyväskylä Longitudinal
Study of Dyslexia (JLD)

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Jyväskylä, October 2003 Tomi Guttorm

LIST OF ORIGINAL PUBLICATIONS

This doctoral dissertation is based on the following articles, which are referred to in the text by their Roman numerals (I–IV):

I Guttorm, T. K., Leppänen, P. H. T., Richardson, U., & Lyytinen, H. (2001). Event-related potentials and consonant differentiation in newborns with familial risk for dyslexia. *Journal of Learning Disabilities, 34 (6),* 534-544.

II Guttorm, T. K., Leppänen, P. H. T., Tolvanen, A., & Lyytinen, H. (2003). Event-related potentials in newborns with and without familial risk for dyslexia: Principal component analysis reveals differences between the groups. *Journal of Neural Transmission, 110 (9),* 1059-1074.

III Guttorm, T. K., Leppänen, P. H. T., Poikkeus, A-M., Eklund, K. M., Lyytinen, P., & Lyytinen, H. (in press). Brain event-related potentials (ERPs) measured at birth predict later language development in children with and without familial risk for dyslexia. *Cortex*.

IV Guttorm, T. K., Leppänen, P. H. T., Eklund, K. M., Poikkeus, A-M., Lyytinen, P., & Lyytinen, H. (2003). Brain responses to changes in vowel duration measured at birth predict later language skills in children with familial risk for dyslexia. Manuscript submitted for publication.

CONTENTS

ABBREVIATIONS

AS	Active sleep
CNS	Central nervous system
CV	Consonant-vowel
EEG	Electroencephalography
EMG	Electromyography
EOG	Electro-oculogram
ERPs	Event-related potentials
fMRI	Functional magnetic resonance imaging
GA	Gestational age
HP	Heart period
ISI	Interstimulus interval
JLD	Jyväskylä Longitudinal Study of Dyslexia
MEG	Magnetoencephalography
MGN	Medial geniculate nucleus
MMN	Mismatch negativity
MRI	Magnetic resonance imaging
PCA	Principal component analysis
QS	Quiet sleep
V	Vagal tone

INTRODUCTION

One of the possible causes of dyslexia, or difficulties in the acquisition of fluent reading, is a deficit in phonological processing (Bradley, 1992; Bradley & Bryant, 1978, 1983; Lundberg, Olofsson, & Wall, 1980; Wagner & Torgesen, 1987; Wagner, Torgesen, & Rashotte, 1994). These deficits may, in turn, result from underlying auditory and/or speech processing deviations, such as altered perceptual or discrimination processes. Results from neurocognitive brain research in children and adults with dyslexia seem to support this assumption of lower processing level involvement.

There is strong evidence that dyslexia is genetically transmitted (for a review, see Wood & Grigorenko, 2001). Consequently, infants born to families with an affected parent or parents (and close relatives) are at elevated risk for the disorder. In the Jyväskylä Longitudinal Study of Dyslexia (JLD; see Lyytinen, 1997; Lyytinen et al., 2001; Lyytinen, Leinonen, Nikula, Aro, & Leiwo, 1995), one of the goals has been to trace early precursors or markers of dyslexia by following children with and without familial risk for dyslexia from birth to school-age. The study of children shortly after birth allows for the differentiation, for example, between factors present already at birth, from those that result from complex gene-environmental interaction later on in the development.

There are practical limitations regarding the application of behavioral methods in the study of those developmentally early perceptual and discrimination processes which could underlie the phenotypic deficits in dyslexia. Event-related potentials (ERPs), however, are suited to the detection of these early processing deviations because the ERP technique does not require behavioral responses from the subjects. In the earlier ERP results from the JLD project (Leppänen, Eklund, & Lyytinen, 1997; Leppänen et al., 2002; Leppänen, Pihko, Eklund, & Lyytinen, 1999; Pihko et al., 1999), the main focus concerned the investigation of the brain activation differences reflected in the ERPs between at-risk and control infants. These results showed that newborns and 6-

month-olds at familial risk for dyslexia processed temporal elements of speech differently as compared to the infants without such risk. These elements are crucial to the learning of the Finnish language, as discrimination between sounds with different durations is critical to the cueing of semantic differences.

In the present doctoral dissertation, the first publication focuses on the study of the possible group differences in the ERPs that also reflect other features of speech perception (Article I; Guttorm, Leppänen, Richardson, & Lyytinen, 2001). The second study comprises a methodological comparison of different analysis procedures of newborn ERP data (Article II; Guttorm, Leppänen, Tolvanen, & Lyytinen, 2003). The third and fourth studies focus on the predictive value of newborn ERPs as early markers of language development (Article III; Guttorm, Leppänen, Poikkeus, Eklund, Lyytinen, & Lyytinen, in press, and Article IV: Guttorm, Leppänen, Eklund, Poikkeus, Lyytinen, & Lyytinen, 2003).

Development of speech processing

Development of the auditory system

In the measurement of auditory processing in newborns by ERPs, it is assumed that the human auditory system is sufficiently mature at birth to differentiate between various acoustic and speech elements.

The auditory system matures centripetally, i.e. from the periphery towards the central parts (Ponton, Moore, & Eggermont, 1996). There is evidence from anatomical studies that the onset of cochlear function in the fetus occurs around the 18th week of gestational age (GA), and the maturation of the cochlea is complete about 10 weeks later (Lavigne-Rebillard & Pujol, 1990). Structures in the brainstem auditory pathway undergo myelination between the 26th and 29th fetal weeks, and the definitive myelination is present in all auditory pathways by the 29th week (Moore, Perazzo, & Braun, 1995). In the process of myelination, neuronal pathways become increasingly surrounded by the fatty stealth consisting of glial cell membranes which increases the efficiency of information transmission (Casaer, 1993; Johnson, 1998). The development of the thalamic pathways is relatively complete by birth, but the myelination of the projection fibers to the cortex continues (Spreen, Risser, & Edgell, 1995). By the age of 6 months, the thalamo-olivary tract, the majority of thalamic nuclei, and the auditory projection fibers to the primary auditory cortex, are relatively well myelinated (Dekaban, 1970).

The auditory cortex also follows a centripetal maturation sequence, and according to Novak, Kurtzberg, Kreuzer, and Vaughan (1989), myelination and

synaptogenesis are more advanced in primary than in secondary auditory areas at term. The development of the auditory cortex involves the growth of axons, dendrites, and synaptic circuits (Huttenlocher, 1994). There are rapid bursts of an increase in synaptic density (overproduction) that reaches its maximum near three months of postnatal age (Huttenlocher, 1994; Huttenlocher & Dabholkar, 1997). This phase is followed at around one year of age by synaptic elimination, both by axon withdrawal and the pruning of axon collaterals (Creutzfeldt, 1995; Huttenlocher, 1994). According to Moore (2002), myelinated axons surface only marginal layer of the auditory cortex during the perinatal period (3rd trimester to 4th postnatal month). These axons drive the structural and functional development of cells in the deeper cortical layers, but do not carry sufficient information regarding external auditory stimuli. Moore (2002) states that the maturing thalamocortical afferents to the deeper cortical layers appear to be the first source of input from the lower levels of the auditory system to the auditory cortex in early childhood (6 months to 5 years).

Based on the evidence provided from the aforementioned studies, it can be summarized that subcortical structure of the human auditory system is, albeit in a developing state, functional at birth. According to Moore (2002), the auditory cortex, however, is not fully involved in the processing of auditory or speech stimuli, as cortico-thalamical and cortical pathways appear to be immature at birth.

Development of speech processing measured by behavioral methods

Behavioral studies that assess speech processing usually require some kind of indication that subjects have, for example, noticed a difference between auditory stimuli, or identified certain target stimuli. For this reason, the behavioral methods have usually been applied to older infants.

Behavioral studies that assess infant auditory or speech detection, discrimination, categorization, and preference, have used different methods. These include motor responses, visual fixation responses, high-amplitude sucking measures, and conditioning paradigms such as head-turning procedures (Aslin, Jusczyk, & Pisoni, 1998; Aslin, Pisoni, & Jusczyk, 1983; Eimas, 1996; Madell, 1998; Morrongiello 1988, Morrongiello, Kulig, & Clifton, 1984; Werker & Polka, 1993). In this section, the description of behavioral results focuses on infants' perception of place of articulation cues in stop consonants and the differentiation of temporal elements of speech stimuli, which are also studied in the present dissertation.

The place of articulation cues in stop consonants (the distinction of, for example, /ba/ versus /da/ and /da/ versus /ga/) include the frequency position of the burst in relation to the vowel and the formant transition (for example, the

second formant, F_2, in the stimuli heard as /ba/ have most sharply rising transitions, /da/ less sharp or falling transitions, and /ga/ falling transitions in the transition continuum), and the frequency of the noise components (Borden & Harris, 1981). According to some authors, the place of articulation for a syllable-initial stop consonant can be identified independently of the vowel context, i.e., on the basis of the gross shape of the spectrum sampled at the consonantal release (Blumstein & Stevens; 1979; Stevens & Blumstein, 1978). According to Stevens and Blumstein (1978), the characteristics of this onset spectrum are determined, both by the burst of acoustic energy at the release, and by the initial portions of the formant transitions at the voicing onset. In a review of infants' perception of the place of articulation cues, Aslin et al. (1983) described that infants are capable of discriminating place differences on the basis of burst cues, formant transition cues, or some combination of the two, and that at least one of these cues, namely formant transitions, is categorical. Furthermore, such differences have been found in infants' responsiveness to what appears to be the same acoustic information in both a speech and a non-speech context (Aslin et al., 1983).

In the behavioral studies of perception of durational features, results suggest that 10-week-olds' are sensitive to temporal-order information (Morrongiello, 1988) and 5–11-month-old infants can discriminate between speech-like stimuli that differ only in vowel duration (Eilers, Bull, Oller, & Lewis, 1984). A behavioral study that employed a conditioned head-turn paradigm with 6-month-old infants participating in the JLD project (Richardson, Leppänen, Leiwo, & Lyytinen, 2003), showed that infants with familial risk for dyslexia required a longer consonant duration than control infants in order to respond to a longer consonant in a categorical fashion (/ata/ versus /atta/, for corresponding ERP results, see section ERP studies with oddball paradigms).

Due to the methodological problems of using behavioral measures in the study of auditory processing in infants (see e.g., Aslin et al., 1998; Morse, 1974; Schneider & Trehub, 1992), the majority of behavioral measures provide reliable results, only in infants older than 4–5 months of age (Benasich & Tallal, 1996). When studying auditory processing in younger infants and newborns, psychophysiological measures such as ERPs are more suited to these purposes as they do not require infants' overt response.

ERPs in studying speech processing in newborns

The methodological difficulties encountered when using behavioral measures in the assessment of auditory processing in infants can be avoided by using ERPs[1]. Because the procedure does not necessarily require the subjects' conscious attention (see e.g., Lyytinen, Blomberg, & Näätänen, 1992; Näätänen, 1992; Alho, Woods, Algazi, Näätänen, 1992), recordings can be performed, for example, while subjects are asleep, as is the case usually with newborns. It has recently been shown that ERPs can even be used to trace the effects of training in sleeping newborns (Cheour et al., 2002).

ERPs are measured with the usual EEG techniques. By averaging multiple EEG-epochs, it is possible to obtain a synchronized ERP pattern that is time-locked to a certain stimulus event (Donchin, Ritter, & McCallum, 1978). Averaging cancels spontaneous and random EEG activity in relation to the stimulus, and thereby brings out the waveform that is invariant across the stimulus presentations (Coles, Gratton, & Fabiani, 1990). The series of positive and negative deflections in the ERPs, reflecting changes in amplitude and latency, are thought to result from the volume-conducted electrical activity generated in various brain regions. This activity mainly reflects the postsynaptic potentials of the large neuronal populations (Kurtzberg et al., 1984).

The ERPs can be categorized into exogenous and endogenous components according to their relations to extrinsic and intrinsic stimuli to the nervous system (Näätänen, 1992). The characteristics of the exogenous components depend on the physical parameters of the eliciting stimulus and they change only in relation to stimulus features. The endogenous components, however, are "invoked" by the psychological demands of the situation rather than merely by the stimulus parameters, and thus indexing stimulus-related cognitive processes.

The ERP components can also be defined by their underlying neuronal generators which can be identified by their scalp distribution (Näätänen & Picton, 1987; Sams, Alho, & Näätänen, 1984), their polarity, their amplitude, and their latency (Donchin et al., 1978). However, as noted, for example, by Donchin et al. (1978), the definition of the components must also be based on the function of the ERPs, that is, in terms of their relation with experimentally induced variations in determining the subprocesses (see also van der Molen & Molenaar, 1994). With ERPs, it is possible to follow the course of brain activity over time to a precision level of tens of milliseconds, and to obtain knowledge,

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[1] Auditory brainstem responses and middle latency responses are not discussed in the present dissertation.

both from the end product of the processing, as well as from the sequence, timing, and stages of the specific processes (see e.g., Garnsey, 1993).

Developmental features of the ERPs

When studying newborns, it is important to consider the maturational and developmental aspects of the ERPs. The newborn ERPs are typically characterized by a rather shallow waveform, with a predominantly positive deflection with a maximum at about 300 ms. This is often followed by a later negativity, peaking after about 500 ms (Barnet, Ohlrich, Weiss, & Shanks, 1975; Ellingson, Danahy, Nelson, & Lathrop, 1974; Kurtzberg, Hilpert, Kreuzer, & Vaughan, 1984; Kurtzberg, Stone, & Vaughan, 1986; Kurztberg, Vaughan, et al., 1984; Leppänen et al., 1997; Novak et al., 1989; Weitzman & Graziani, 1968). Some studies have shown a discontinuity (a minor negative peak around 200 ms) in this major positive deflection (Novak et al., 1989). The positive-polarity ERP morphology seems to be typical to newborns despite differences in the used stimuli, interstimulus intervals, and arousal states (for a review, see e.g., Thomas & Crow, 1994). With regard to the effect of arousal states, newborn ERPs seem to be similar in both the active sleep and awake states (Kurtzberg et al., 1984; Novak et al., 1989), but the responses recorded from quiet sleep differ from these former two arousal states (Duclaux, Challamel, Collet, Roullet-Solignac, & Revol, 1991; Ellingson et al., 1974).

The developmental trends in ERPs can be seen, for example, in the systematic progression from a predominantly negative polarity at the midline and lateral electrode sites (pre-terms), to a predominantly positive polarity at these sites (3 months) during early infancy (Kurtzberg et al., 1984; Novak et al., 1989). The temporal response changes from negative to positive from 1 to 2 months after birth, thus displaying a maturational delay, as compared to the responses from the midline sites (Kurtzberg et al., 1984). According to Kurtzberg et al. (1984), the developmental changes in brain potentials reflect altered distribution of synaptic contacts (morphological changes in location, type, and geometrical relationships of pre- and post-synaptic elements) and patterns of synaptic activation (changes in the effectiveness of synaptic transmission). The developmental changes in the ERP components, from infants to those measured from older children and adults, include increased morphological complexity, increased amplitude, and decreased component latency (Thomas & Crow, 1994, see also Shucard, Shucard, & Thomas, 1987, 1988). It should be noted, however, that comparisons between the ERPs of different age groups may be difficult to interpret. This is because ERP components have complex maturational timetables and differ from each other in terms of age of emergence, ERP waveform, latency, amplitude, and task

conditions that generate these components (Courchesne, 1983, 1990). Furthermore, knowledge concerning the developmental stage of one ERP component may not accurately predict the stage of development of another, and the exact rate of development may vary from infant to infant (Anthony & Friedman, 1991; Courchesne, 1990; Friedman, 1991; Thomas et al., 1997). Age-related changes may reflect cognitive growth, brain maturation, or the developmental time course of their interaction (van der Molen & Molenaar, 1994).

ERPs to equiprobably presented stimuli with slow rates

The ERPs measured in paradigms using equiprobably presented stimuli with long interstimulus intervals (ranging from about two seconds to more than eight seconds, see e.g., Barnet et al., 1975; Ellingson et al., 1974; Kurtzberg et al., 1984; 1986; Leppänen et al., 1997; Novak et al., 1989; Weitzman & Graziani, 1968), are thought to reflect the basic or obligatory auditory responses to auditory stimulus features per se (feature detection), or stimulus driven general responsiveness of the auditory system.

Newborn ERPs to equiprobably presented stimuli with slow rates have been studied extensively by Molfese and colleagues. They investigated, for example, functional hemispheric differences in responses to speech stimuli prior to the onset of language acquisition and speech development (Molfese, Freeman, & Palermo, 1975; Molfese, Nunez, Seibert, & Ramanaiah, 1976) and also studied the stimulus characteristics that elicit these lateralized responses (Molfese and Molfese, 1979a, 1979b, 1980). Molfese and colleagues have also studied the possibility of using newborn ERPs to predict later language development (Molfese; 2001; Molfese and Molfese, 1985, 1997; Molfese, Molfese, & Modglin, 2001; Molfese & Searock, 1986).

By using principal component analysis (PCA)-analysis of variance (ANOVA)-procedure (see later), Molfese and Molfese (1985) were able to identify specific ERP components in newborns which discriminated between groups of children with high and low language skills at the age of three years. The responses to consonant-vowel syllables (/bi/, /ba/, /bu/; /gi/, /ga/, /gu/, and the non-speech counterparts) were recorded from the left and right temporal lobes (T3 and T4) while newborns were in a quiet awake state. At three years of age, the infants were grouped into the high (above 50, mean = 77.25, SD = 15.5, N = 8) and low (below 50, mean = 20.5, SD = 12.6, N = 8) groups according to their performance on the verbal subtest of the McCarthy Scales of Children's Abilities (McCarthy, 1972). Newborn ERP waveforms between 88 and 240 ms at the left hemisphere (T3) of the high performance group differentiated between the consonants /b/ and /g/. The peak was smaller for the /b/ initial syllables than

for the /g/ initial syllables. No such differentiation between consonants was found in the ERPs of the low performance group. Furthermore, a later component with a peak latency of 664 ms reflected bilateral discrimination of these consonant sounds (depending on the following vowels) in the high performance group. The discrimination between the consonants in the high performance group shown by the lateralized and bilateral ERP responses was in line with the findings of Molfese and Molfese (1979a) and Molfese, Burger-Judisch, and Hans (1991).

Molfese and Molfese (1997) extended the language performance prediction from newborn ERPs to five years of age. Newborn ERPs were measured to consonant-vowel syllables composed of three consonants (/b/, /d/, and /g/) and three vowels (/a/, /i/, and /u/) from the three electrode sites (frontal, temporal, and parietal) from each hemisphere. The ERP components between 70–140 ms and 170–320 ms (matching the latency of the components identified in 1985) were used in discriminant function analyses to distinguish children on the basis of their scores (high performance group = above 100, N = 61; low performance group = below 100, N = 9) on the Stanford-Binet Verbal Reasoning subtest (Thorndike, Hagen, & Sattler, 1986). The accuracy of classification ranged from 78.9 % to 95.8 %, depending on how many variables were used in the discriminant analysis procedures. In general, the ERP amplitude, positive in polarity, was larger in the high performance group.

By using ERP baseline-to-peak amplitude and latency measures, Molfese (2000) identified three newborn ERP components (initial negative peak around 174 ms, positive peak around 310 ms, and a second large negative peak around 460 ms) which discriminated (Wide Range Achievement Test 3, WRAT; Jastak & Wilkinson, 1984) amongst children with dyslexia (mean WRAT = 80.6, N = 17), poor readers (mean WRAT = 85.4, N = 7), and control children (mean WRAT = 103.75, N = 24) at the age of eight years. The ERP responses to consonant-vowel syllables /bi/ and /gi/, both at the left and right hemisphere, contributed to the classification accuracy of the group membership. One of the discriminating features was the latency shift in the N1 component which was suggested to be related to the brain's ability to detect, react to, and process information more quickly.

These results demonstrated that newborn ERPs can be used to predict later language development. Molfese and colleagues suggest that more precise discrimination ability, as manifested in the clearer differences in the ERPs, could also be utilized to better detect and discriminate between patterns of sounds in the natural language environment, and in the extensive process of language acquisition.

ERP studies with oddball paradigms

The above-described exogenous ERPs could be thought to reflect feature detection of the auditory stimuli. In contrast, the comparison processes, for example, between prior auditory input and a new deviating auditory event can be studied by using oddball paradigms.

In oddball paradigms, a frequently repeated tone forms a neuronal sensory-memory trace. Among these repetitive standard tones, a rarely occurring deviant stimulus, which does not fit with the existing memory trace, generates a mismatch process that is reflected in a negative deflection that reaches its maximum at ca. 200 ms over the frontal and central areas of the scalp in adults (mismatch negativity, MMN; Giard, Perrin, Pernier, & Bouchet, 1990; Näätänen, 1990, 1992; Näätänen & Alho, 1995, 1997; Näätänen, Gaillard, & Mäntysalo, 1978; Paavilainen, Alho, Reinikainen, Sams, & Näätänen, 1991). The MMN component is thought to reflect an auditory change detection process based on the functioning of sensory memory. The ERP results with oddball paradigms with young infants have been reviewed, for example, by Alho and Cheour (1997), Cheour, Leppänen, and Kraus (2000) and Cheour, Korpilahti, Martynova, and Lang (2001).

Our earlier published ERP studies in infants with and without familial risk for dyslexia were measured by using oddball paradigms. Leppänen et al. (1999) reported ERP data to a vowel duration change in consonant-vowel syllables in newborns who were in quiet sleep. A frequently occurring standard stimulus (/kaa/, duration 250 ms, probability 88%) was occasionally replaced with a deviant stimulus (/ka/, duration 110 ms, probability 12 %). The offset-to-onset interstimulus interval (ISI) was 425 ms in the fast rate condition blocks and 855 ms in the slow rate condition. In the slow rate condition, the ERPs of the at-risk infants (N = 12) to the deviant /ka/ were larger and more positive than those of the control infants (N = 11), predominantly at the right frontal and central areas. Also, the brain responses to the deviant and the standard stimuli differed more consistently in the right hemisphere in the at-risk group (at C4 and P4 electrode sites), whereas in the control group, this pattern occurred in the left hemisphere (at F3 and P3). Furthermore, in a study by Pihko et al. (1999) with 6-month-olds (at-risk group, N = 28, control group, N = 23), the hemispheric pattern of ERPs (the deviant /ka/ vs. the standard /kaa/, ISI 425 ms) in the at-risk group showed similar tendencies towards right-hemispheric predominance.

Leppänen et al. (2002) examined whether the 6-month-old at-risk and control infants would differ in their ERPs to a duration change in a stop consonant embedded in a pseudoword. In the first condition (data from 25 at-risk and 27 control infants), an /ata/ with a short /t/ (a voiceless stop with a silent period of 95 ms in the middle of the sound, the total pseudoword duration being 300 ms) was presented as a frequent standard stimulus with an

80 % probability of occurrence. On 10 % of the trials, /ata/s with an intermediate /t/- duration (silent period of 195 ms) and in the remaining 10 %, /atta/s with a long /t/ (silent period of 255 ms), were presented as rare deviant stimuli (with a fixed offset-to-onset ISI of 610 ms). The results indicated that the groups differed, both in their early obligatory responsiveness to stimulus onsets (larger positive responses in the at-risk group), and in their change-driven response. The response patterns to standard and deviant stimuli differed more clearly from each other around 600 ms in the left hemisphere (C3 electrode site) of the control group. In the second condition (data from 12 infants from each group), reversed probabilities for the short /ata/ (being the second deviant, 10%) and the long /atta/ (standard, 80 % with ISIs of 450 ms and 610 ms), were used to test whether the responses reflected the consonant duration change detection and not merely stimulus-specific effects. In the control infants, the short /ata/ elicited an additional bilateral change detection-related negative deflection which resembled the reported adult-like MMN. This peak was completely absent in the at-risk group (see also Richardson et al., 2003, for corresponding group differences in behavioral performance in a conditioned head-turn task using the same stimulus feature).

These earlier results demonstrated that brain electrical activation reflecting the processing of speech sounds and changes in sound duration embedded in syllables and pseudo-words, differed between the at-risk and the control groups. The responses to the deviant stimuli in the JLD studies with newborns (Leppänen et al., 1997, 1999; Pihko et al., 1999) were more positive than those to the standard stimuli. The standard responses that could be considered to reflect the similar responding of the auditory system to sound features per se, had a slow and widespread positivity around 300 ms. The deviant stimulus elicited prolonged positive responses. Such responses could reflect the processing of either a stimulus change, or new stimulus properties. Because the deviant stimuli were 140 ms shorter than the standard stimuli, the enhanced positivity to the shorter deviant was interpreted to reflect change detection (Leppänen et al., 1999; Pihko et al., 1999). Similarly, more positive responses to changes in pitch and speech sounds have been found in other studies of newborns or young infants (Alho, Sajaniemi, Niittyvuopio, Sainio, & Näätänen, 1990; Dehaene-Lamberz, 2000; Dehaene-Lamberz & Baillet, 1998; Dehaene-Lamberz & Dehaene, 1994; Friederici et al., 2002; Leppänen et al., 1997; Morr, Shafer, Kreuzer, & Kurtzberg, 2002), but reports of MMN-like negativity also exist (Alho et al., 1990; Čeponienė et al., 2002; Cheour et al., 1998, 2002, Cheour, Alho, et al., 1998; Cheour-Luhtanen et al., 1995, 1996; Kushnerenko, Čeponienė, Balan, Fellman, & Näätänen, 2002; Kushnerenko et al., 2001), including the reports of reduction of the positivity in the deviant responses (Kushnerenko et al., 2002; Leppänen et al., 1997).

Principal component analysis in the ERP data

ERPs elicited by equiprobably presented stimuli with slow rates do not reflect any well-known auditory discrimination processes such as pre-attentive change detection processing reflected in MMN. Thus, in contrast to the MMN studies, we have no comparable theoretical assumptions to make with regard to how stimulus-specific differences would manifest in the waveforms. Furthermore, in newborn ERPs, the mature multiple peak structure typical to older children and adults is still absent. Important information is "carried", not only in the peaks, but also in the whole waveform. This information can be missed in the traditional peak-to-peak analyses.

In the oddball paradigms with adults, the knowledge concerning where and when MMN is elicited is typically used as a guideline in the analyses of ERPs in which the examination of the latencies of interest is based on the visual identification of the largest deflections in the grand-average waves. This procedure, however, is problematic with very young infants whose brain responses are less well-known. Infant MMN studies have shown, for example, change detection responses in newborn ERPs, which, compared to those found in adult studies, occurred at the later latencies (around 270–300 ms in the study by Alho et al., 1990; 241 and 298 ms in the study by Kurtzberg, Vaughan, Kreuzer, & Flieger, 1995). There are also differences in the scalp distribution of MMN between adults and infants. In adults, MMN is usually largest fronto-centrally, but in infants, it has also been obtained in the parietal channels (Cheour et al., 1998: Leppänen et al., 1997). Furthermore, there are reports of change detection responses with opposite polarities in young infants (see earlier). Thus, one of the central problems concerning the analysis of infant ERPs is the identification of the waveform latencies that reflect common or overlapping processes and carry important experimental-related variation. For these reasons, an objective method such as principal component analysis (PCA) may provide a tool for locating the ERP responses of interest.

The application of PCA in the analyses of ERP data has been discussed, for example, by Donchin and Heffley (1978), Chapman and McCrary (1995), Möcks (1988), and van Boxtel (1998). PCA reduces the amount of data collected in the ERP-measurements by extracting a small number of components, each representing systematic influences on many dependent variables, or, in this case, ERP time points, from the total variance in the original data. PCA thus summarizes the complex relations between a large number of the original dependent variables (amplitude values with positive or negative polarity in successive time points in the application described here) in a more manageable manner. Extracted principal components are closely related to original variables (weighted linear combinations of the original dependent variables) so that PCA does not create effects which are not in the original data. The components or

factors are extracted from the data in a hierarchical manner: The first factor accounts for the largest proportion of the total variance in the data, and the following factors are orthogonal to the preceding, and account for the largest residual variance.

As described, for example, by van Boxtel (1998), the first step in PCA consists of computing the association (for example, covariance) between all individual time points or dependent variables, with the central tenet being that associated variables (time points) belong to the same underlying component. For the next step, the initial matrix can be rotated using, for example, the Varimax rotation in order to minimize the temporal overlap of the components. By Varimax rotation, one tries to find a solution that possesses the property of simple structure, according to which a single variable (amplitude of a data/time point) has a high loading on only one component, and a zero or negligible loading on all the other components (orthogonality). After rotation, the PCA assigns factor loadings and scores. Factor loadings represent the systematic contribution of each PCA component to the voltage at each time point. Factor scores, however, represent the contribution of each component to each individual ERP waveform (indicating the nature of the variability). These scores are used in further analyses of variance, which indicate whether the factor scores (the region of the variability in the ERPs identified by PCA) either systematically increase or decrease in size relative to some experimental conditions.

The use of PCA in ERP data have been criticized for misallocation of variance, i.e. attributing experimental effects to components that are not actually affected (Achim & Marcantoni, 1997). But as stated by Chapman and McCrary (1995) and van Boxtel (1998), this criticism of misallocation of variance has been overemphasized, as it is not peculiar to PCA alone, and this problem is even more serious in the peak and area measures of the ERPs. Furthermore, the simulation study by Chapman and McCrary (1995) did not show misallocation of variance or misinterpretations of experimental effects among overlapping components.

Developmental dyslexia

Familial risk for dyslexia

Developmental dyslexia has been defined, by the World Federation of Neurology, as a disorder manifested by difficulty in learning to read despite conventional instruction, adequate intelligence, and socio-cultural opportunity (Critchley, 1970). The etiology of dyslexia is thus 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 one of the major specific learning disabilities that causes severe limitations in many children, and affects not only their school achievement, but also their career choices. In Finland, about 6 % of school-aged children are estimated to suffer from these difficulties (Lyytinen et al., 1995).

Dyslexia is assumed to result from a combination of complicated interwoven genetic and environmental factors (Pennington, 1995). In studying the genetic effects of dyslexia, Pennington (1995) outlines four successive steps in transition from phenotype to genotype: familiality, heritability (twin and adoption studies), mode of transmission (segregation analysis), and gene locations (linkage analysis).

The familiality of dyslexia has been demonstrated, for example, by Vogler, DeFries, and Decker (1985) and Gilger, Pennington, and DeFries (1991). Pennington (1995) stated that these findings indicate strong evidence of familiality of dyslexia: the median relative increase in risk to a child having an affected parent was about eight times the population risk of 5 %. Evidence for the heritability of dyslexia comes from twin studies (DeFries, Fulker, & LaBuda, 1987; DeFries, Gillis, & Wadsworth, 1993; DeFries, Stevenson, Gillis, & Wadsworth, 1991; Olson, Gillis, & Rack, 1991; Olson, Wise, Conners, Rack, & Fulker, 1989).

With regard to the mode of transmission of dyslexia, there are studies of, for example, possible gender effects on transmission (strong male predominance in the rates of dyslexia, see e.g., Gilger et al., 1991). By using segregation analysis, Pennington (1995) provided evidence of sex-influenced major locus transmission (autosomal dominant transmission) in the large proportion of dyslexic families. This autosomal dominant mode was consistent with the results of Lubs et al. (1993). In the study by Pennington (1995), there was also evidence for significant familiarity and heritability for normal variation in reading skills of control subjects. These results may reflect the role of several, more frequent quantitative trait loci that are involved in the transmission of both dyslexia and normal variations in reading skills.

In the studies of gene locations in dyslexia, chromosome 15 (Fulker et al., 1991; Morris et al., 2000; Nopola-Hemmi et al., 2000; Smith, Kimperling, & Pennington, 1991) and chromosome 6 (e.g., Smith et al., 1991; 2001), for example, have been linked to dyslexia. There is also recent evidence from chromosome 3 (Nopola-Hemmi et al., 2001) and chromosome 2 in Finnish dyslexics (Kaminen et al., 2003). Furthermore, the study by Taipale et al. (in press) showed evidence of single gene (DYX1C1) in chromosome 15q21 as a candidate gene for developmental dyslexia. Among participants of the studies

by Kaminen et al. (2003) and Taipale et al. (in press), there were also families from the JLD project.

In the JLD project, the rationale that underlies the comparison of infants born to families with dyslexic parent or parents (and close relatives) with infants without familial indication of dyslexia, is based on the aforementioned assumption that dyslexia runs in families in higher proportions than would be expected to occur in the general population (Pennington, 1995). It is important to note that genetic factors affect cognitive abilities throughout the life-span and that the effect of genetics is modified by environmental factors (Plomin, Owen, & McGuffin, 1994). For these reasons, the effects of genetic factors are often impossible to differentiate from environmental influences (see e.g., Loehlin, 1989, Lykken, McGue, Tellegen, & Bouchard, 1992; Plomin, 1990; Plomin, Owen, McGuffin, 1994; Rose, 1995; and Segal, 1993). As stated earlier, the study of infants shortly after birth allows for the differentiation of those factors already present at birth (possibly genetic in nature), from those that result from complex environmental interactions later in development.

Speech processing in individuals with dyslexia: Behavioral studies

In dyslexia, one of the possible underlying causes is a deficit in phonological processing (Bradley, 1992; Bradley & Bryant, 1978, 1983; Lundberg et al., 1980; Wagner & Torgesen, 1987; Wagner et al., 1994). Problems in phonological processing are also very persistent, even in adulthood (Bruck, 1992; Leinonen et al., 2001) suggesting that these difficulties are not due to developmental lag but rather, are due to the more persisting processing deviation or deficit. Inadequate phonological processing can be characterized by problems, for example, in single word decoding (Lyon, 1995). Neurolinguistic studies assume that the main strategies for this single word decoding are phonological and orthographic strategies (Olson et al., 1989; Polich, McCarthy, Wang, & Donchin, 1983). The phonological strategy is characterized by the sub-word level decoding of letter strings to corresponding phonological identities, while the orthographic strategy utilizes orthographic pattern recognition in the word decoding process via direct access to the lexicon without prelexical phonological recoding. Problems in dyslexia may thus result from inadequate functioning of the phonological or/and orthographic routes (Høien & Lundberg, 1989).

Phonological processing deficits may, in turn, result from underlying auditory and/or speech processing deviations, such as altered perceptual or discrimination processes. Individuals with dyslexia have been reported to differ from controls in, for example, processing of brief auditory cues and rapidly changing sequential and amplitude information (Laasonen, Lahti-Nuuttila, &

Virsu, 2002; Laasonen, Service, & Virsu, 2001, 2002; Laasonen, Tomma-Halme, Lahti-Nuuttila, Service, & Virsu, 2000; McAnally & Stein, 1997; Reed, 1989; Richardson et al., 2003; Stark & Tallal, 1988; Tallal, 1980; Virsu, Lahti-Nuuttila, & Laasonen, 2003; in the visual modality, see e.g., Frith & Frith, 1996; Lovegrove, 1993; Stein & Walsh, 1997). In the perception of speech, the listener is required to make fine differentiations between complex and rapidly changing acoustic temporal and spectral characteristics within a brief time window (Fitch, Miller, & Tallal, 1997). According to Tallal (1980), the inaccuracies that poor readers demonstrate on tasks such as stop consonant identification, are thought to arise from nonlinguistic difficulty in processing the brief formant transitions in consonant stimuli (e.g., cues that differentiate /ba/ from /da/, and /da/ from /ga/).

Processing difficulties in adults with dyslexia related to the temporal or durational aspects of speech have been shown, for example, by Steffen, Eilers, Gross-Glenn, and Jallad (1992). In their experiment, 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 like /sa/, and with an increase in the duration of the silence, the syllable was perceived as /sta/. The dyslexics required a longer silence duration to identify the stimulus as /sta/.

The ability to discriminate between short and long consonants and vowels is essential, for example, in the Finnish language, as these duration variations are critical to the cueing of opposites and semantic differences. For example, perceived changes in durational patterns can contribute to the identification of a word. For example, the word /mato/ (worm), with short /t/-sound duration, has a different meaning than the word /matto/ (carpet), which has a long /t/-sound duration. Similarly, the word /tuli/ (fire), with short /u/-sound duration, has a different meaning than /tuuli/ (wind), with a long /u/-sound. Finnish dyslexics have been shown to have problems in the perception of these durational cues (Richardson et al., 2003). In comparison to normal readers, they also make disproportionately more errors when differentiating consonant and vowel durations while reading pseudowords (Lyytinen et al., 1995).

There is also some criticism with regards to the temporal processing deficit hypothesis (Brady, 1997; de Gelder & Vroomen, 1998; Mody, Studdert-Kennedy, & Brady, 1997; Rayner, Pollatsek, & Bilsky, 1995; Studdert-Kennedy & Mody, 1995). It should be noted that critical discussion surrounding the timing deficit issue relates to a debate about the speech vs. nonspeech nature of processing difficulties in dyslexia. This is beyond the focus of this work, as our data do not address this issue.

Speech processing in individuals with dyslexia: ERP studies

Several ERP studies have shown that brain electrical activation generated by speech sounds differs between individuals with dyslexia and controls. These results have shown that dyslexics have more general auditory-perception problems which may underlie their difficulties in phonological processing (Baldeweg, Richardson, Watkins, Foale, & Curzelier, 1999; Kujala et al., 2000; Kujala, Kallio, Tervaniemi, & Näätänen, 2001). ERPs have also been used to differentiate between various types of dyslexia subgroups (Aylward, 1984; Dool, Stelmack, & Rourke, 1993; Duffy, Denckla, McAnulty, & Holmes, 1988; Duffy & McAnulty, 1990; Fried, Tanguay, Boder, Doubleday, & Greensite, 1981). There is also evidence that ERPs can be used in the evaluation of the effects of intervention in dyslexics (Kujala et al., 2001). For reviews of ERPs and dyslexia, see Leppänen and Lyytinen (1997) and Lyytinen, Leppänen, Richardson, and Guttorm (2003). In the present summary, only the results relating to latency and laterality differences between dyslexics and controls are discussed.

The earlier described timing deficit could be reflected in the delayed N1[2] latencies in individuals with language deficits (for a review, see Leppänen & Lyytinen, 1997). It could be speculated that the delay in N1 latency results from the slower speed of sensory processing, which may then have an impact on higher level processing such as speech processing (Leppänen, Choudhury, Benasich, & Lyytinen, 2003). Delays in the exogenous component latencies of children with language disorders have been found, for example, in studies by Dawson, Finley, Phillips, and Lewy (1989), Jirsa and Clontz (1990), Lincoln, Courchesne, Harms, and Allen (1995), Neville, Coffey, Holcomb, and Tallal (1993), and Tonnquist-Uhlén, Borg, Persson, and Spens (1996).

There are also reports of laterality differences between individuals with and without reading problems. In control subjects, the ERPs to speech stimuli are generally greater in the left than in the right hemisphere, while those generated by pure tones, either lack this asymmetry, or are greater in the right hemisphere (Leppänen & Lyytinen, 1997). This pattern is consistent with a general observation that in most individuals, 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 the controls, or left asymmetry is lacking. This

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[2] N1 or N1-P2 complex is the first cortically generated auditory ERP that is thought to reflect sensory processing in the auditory cortex and informing of the arrival of the auditory information to the central auditory system (Näätänen, 1990, 1992).

implicates that there are differences in the hemispheric preponderance of processing involvement as reflected in the ERPs.

Fried et al. (1981) studied ERPs to words (/do/ and /go/) and musical chords (350 ms in duration and presented with an ISI of 2.8–3.8 s) in 8- to 12-year-old children whose reading difficulties were related to either auditory-verbal processing difficulties (dysphonetic group) or to visual-spatial processing difficulties (dyseidetic group). They found that the dysphonetic group did not exhibit the asymmetrical ERP pattern that was observed in the control group, or in the dyseidetic group (greater word versus musical chord ERP waveform differences over the left as compared to the right hemisphere). Differential asymmetric ERP patterns in children with dyslexia were also found in a study by Brunswick and Rippon (1994). They studied ERPs to consonant-vowel syllables (/ba/, /da/, /ga/, /pa/, /ta/, and /ka/, duration 320 ms, ISI 4 s) in a dichotic listening study (using free recall) in fifteen 7- to 11-year-old boys with dyslexia, and in fifteen 8- to 10-year-old control boys. The control children produced significantly greater N100 amplitudes over the left temporal region, whereas the children with dyslexia displayed approximately equivalent levels of amplitude bilaterally.

Differential asymmetry patterns have also been observed for pure tones. Pinkerton, Watson, and McClelland (1989) studied ERPs to tone bursts (2 kHz, duration 20 ms) and reported amplitude reduction of P1 (about 80 ms from the stimulus onset) at the left hemisphere in a group of fourteen 8- to 9-year-old poor readers as compared to a group of 18 control children with no reading problems. They suggested that this could reflect reduced or disturbed early auditory input to the left hemisphere in poor readers.

These studies, using different stimuli and a variety of techniques, revealed differences in hemispheric asymmetry, namely the reduced role of the left hemisphere in the processing of speech and auditory stimuli in children with dyslexia, as compared to those without dyslexia. Shucard, Cummins, and McGee (1984) reported lower amplitude of right hemispheric ERPs in disabled readers, as compared to controls, during tasks that involved visual-phonemic transfer of information and simple pattern recognition. They interpreted these results as reflecting a deficit in the right hemisphere functioning or deficit in the right-left hemisphere interaction, rather than impaired left hemisphere functioning. There is also evidence for more prominent activation of the right hemisphere in individuals with dyslexia. For example, Erez and Pratt (1992) reported differences in the ERPs to pure tones (1000 vs. 2000 Hz) and CV syllables (/da/ vs. /pa/) in the oddball target detection paradigm between children with dyslexia and controls. They suggested that these results reflected the language processing in the right hemisphere in these children. Enhanced right hemispheric processing was also found in event-related EEG responses to phonological processing and visual searching tasks by Rippon and Brunswick

(2000). The EEG responses from the dyslexic group were characterized by a lack of task-related reduction from resting levels in the amplitude of alpha frequency responses. There was also a marked parieto-occipital right > left hemisphere asymmetry in beta activity in the dyslexic group.

In our earlier ERP results from infants with and without familial dyslexia (for a more detailed description, see section ERP studies with oddball paradigms), it was found that the ERPs of the at-risk infants to the deviant /ka/ were larger and more positive in amplitude than those of the control infants, predominantly in the right hemisphere. The brain responses to the deviant and the standard stimuli also differed from each other more consistently in the right hemisphere of the at-risk group, whereas in the control group, this pattern occurred in the left hemisphere. There were similar group differences also in the 6-month-olds (Pihko et al., 1999). The hemispheric pattern of ERPs (deviant /ka/ vs. standard /kaa/) in the at-risk group showed similar tendencies towards right-hemispheric predominance.

Neurobiological alterations in individuals with dyslexia

The differential lateralization pattern of the ERPs in individuals with dyslexia and in infants at risk for familial dyslexia could reflect the same kinds of differences in the hemispheric lateralization that are also found in anatomical and functional studies of older individuals with dyslexia.

In anatomical studies of older individuals with dyslexia, observations have been made concerning larger temporal (Dalby, Elbro, & Stödkilde-Jörgensen, 1998) and posterior areas (angular gyrus and posterior pole: Duara et al. 1991) in the right hemisphere, larger neurons on the right than on the left side of the medial geniculate nuclei (MGN) of the thalamus (suggested to be a sub-system handling rapid temporal transitions according to Galaburda, Menard, & Rosen, 1994), and deviations from the usual pattern of left-greater-than-right planum temporale asymmetry (Galaburda, Sherman, Rosen, Aboitiz, & Geschwind, 1985; Humphreys, Kaufmann, & Galaburda, 1990; Hynd, Semrud-Clikeman, Lorys, Novey, & Eliopulos, 1990; Larsen, Høien, Lundberg, & Ødegaard, 1990). It has been speculated that the findings of altered planum temporale asymmetry may be related to qualitative alterations in the functional properties of the system, which in turn, may result, for example, in phonological coding deficits among individuals with dyslexia (Pennington, 1991b; van der Leij, Lyytinen, & Zwarts, 2001). It should be noted, however, that recent anatomical studies have questioned the earlier results that reduction or reversal of the normal leftward asymmetry of the planum temporale would be an indicator of a risk factor of developmental disorders of language and reading (Heiervang et al., 2000; Preis, Jäncke, Schittler, Huang, & Steinmetz, 1998).

Functional brain imaging studies in older individuals with dyslexia have also shown differences in the asymmetric nature of brain activation, and usually these differences are related to reduced left hemisphere activation, especially in the temporal lobes. However, there is also evidence of rightward asymmetry of brain activity. In PET studies by Rumsey et al. (1992) and Gross-Glenn et al. (1991), increased activation was found in the right temporal regions. In the latter study, this enhanced activation was localized in the posterior right hemisphere (lingual lobule). In an fMRI study of adults with dyslexia, Shaywitz et al. (1998) also found higher activation at the posterior aspect of the inferior and middle temporal gyri and the anterior aspect of the lateral occipital gyrus of the right hemisphere. Such over-activation in the right hemisphere could be due to compensatory processes in tasks that were difficult for individuals with dyslexia.

The variety of findings of differences in the brain functions and neurobiology between individuals with and without dyslexia suggests that developmental dyslexia is not explained by any single deficit or alterations in some sharply localized brain structure. However, it is still useful to pursue the identification of those specific features, for example, in speech processing that might be impaired in this disorder.

Early behavioral predictors of language development

Earlier newborn ERPs studies predicting later language development (Molfese; 2000; Molfese and Molfese, 1985, 1997; Molfese et al., 2001) showed that ERPs could be a useful tool in the attempt to isolate early precursors of language deficits and dyslexia. At the current stage of the JLD project, we do not yet know the final reading status or the possible diagnosis of dyslexia in all of our children (only the first cohort of about 50 children are in the 3rd grade when the diagnosis can be confirmed). We have, however, data from early language acquisition and pre-reading skills from all the children participating in the JLD project.

The results from the JLD study by Lyytinen, Poikkeus, Laakso, Eklund, & Lyytinen (2001) showed that children with and without familial risk for dyslexia differed in their expressive language skills. The maximum sentence length at 2 years and object naming and inflectional morphology skills at 3.5 years were higher in the control than in the at-risk group. The risk status did not contribute to receptive language, but provided a significant contribution to their expressive language at 3.5 years, even after the variance associated with parental education and children's previous language skills was controlled. The Reynell receptive score at 2.5 years, however, provided the greatest unique contribution to the prediction of receptive and expressive language skills.

Scarborough (1990) had earlier found that children with familial risk who later evidenced reading disabilities at school age (as opposed to at-risks who did not) were deficient in the sentence length, syntactic complexity, and accuracy of pronunciation of their spoken language at the age of 2.5 years (the first data collection). These children had also shown problems in their receptive vocabulary and object-naming skills at 3 years, and in object-naming, phonetic awareness, and letter-sound knowledge at 5 years. Corresponding findings were also found in a study by Gallagher, Frith, and Snowling (2000), where the largest differences between children at familial risk for dyslexia and controls emerged in vocabulary, naming, and digit span measures at 3 years 9 months.

These results show that early language skill differences between children with and without familial risk for dyslexia predict their later language acquisition and reading problems. As previously noted, evidence from behavioral studies and brain research suggests that these deficits may, in turn, result from underlying auditory and/or speech processing deviations, such as altered perceptual or discrimination processes. It is thus reasonable to assume that newborn ERPs measuring speech processing could also be associated with later language skills in children with and without familial risk for dyslexia.

AIMS OF THE EMPIRICAL STUDIES

In the present dissertation, the first aim was to investigate the possible group differences in the ERPs measuring both feature and change detection of speech stimuli between newborns with and without familial risk for dyslexia. Secondly, the results from the different analysis procedures of the ERP data were compared. The third major goal was to study whether these differences in the brain processing of speech stimuli at birth would be associated with later language and verbal memory skills in the at-risk and control children. More specific goals concerning Articles I–IV will be presented below together with the results of each study.

METHODS

Participants

Selection of participant families

Families expecting a baby between years 1993–1996 in the Province of Central Finland were contacted via the Mother Guidance Centers of Central Finland and requested to participate in the Jyväskylä Longitudinal study of Dyslexia (JLD; see Lyytinen, 1997; Lyytinen et al., 1995, 2001). They were screened and recruited according to the institutional informed-consent procedures. The criteria for allocation to the at-risk group were one or both parent's report of reading disorder, a comparable report concerning at least one close relative, and multiple diagnostic tests indicative of dyslexia. The literacy discrepancy criteria entailed the affected parent scoring at least 1 SD below the norm in accuracy or speed of oral text reading, or in accuracy of written spelling, plus at least two separate single-word reading measures (either accuracy or speed of word recognition, pseudoword decoding or lexical decision). The IQ of the diagnosed parents of the participating children was 85 or above (assessed with the Raven B, C, and D Matrices; Raven, Court, & Raven, 1992). Parents whose reading level did not satisfy the literacy discrepancy criteria but who had affected relatives and a very convincing self-reported history of school-age and present reading problems were included in the at-risk group as "compensated dyslexics". It should be noted that inclusion of the families with compensated dyslexics was 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. The parents of the control children gave no indication of reading problems and were matched at the group level with the dyslexic parents for

educational level and IQ. All the parents in both groups reported that they had normal hearing and that they had no speech deficits.

In the parents of the children participating in the present studies, there were no parental at-risk versus parental control group differences in educational status or IQ (see Table 1[3]). The educational and socio-economical status was determined on the basis of the length or level of education), when both basic (primary and high-school level education) and continued education (such as vocational or university education) were combined. This socio-economical status of the participating families was representative of its distribution in the Finnish population. For further details on the participant characteristics and selection criteria of the JLD families, see Leinonen et al. (2001) and Lyytinen et al. (1995).

TABLE 1 Analysis of variance for parental education (basic and continued education combined) and IQ differences between the at-risk and control parents.

Article	Parental education		Parental IQ	
	Mother	Father	Mother	Father
Articles I , II, & III	$F(1,39) = .00$, $p < 1.00$	$F(1,33) = 1.24$, $p < .73$	$F(1,30) = .25$, $p < .62$	$F(1,28) = 3.37$, $p < .08$
Article IV	$F(1,26) = 1.43$, $p < .25$	$F(1,23) = .00$, $p < 1.00$	$F(1,18) = .03$, $p < .87$	$F(1,20) = 1.82$, $p < .19$

Newborn participants

The data from newborn participants was obtained from 49 infants. Of these infants, 23 (10 girls, 13 boys) belonged to a control group and 26 (10 girls and 16 boys) belonged to the at-risk group. The infant's chronological age at the time of the ERP measurements was between a day and a week, and the gestational age (GA) was at least 38 weeks, except in the 4 at-risk infants whose GA was below this criterion and who were tested at about 40 weeks postconceptional age i.e. within 14–23 days from birth. All the babies had a birthweight of at least 3,000 g, except 1 infant from the at-risk group (2,970 g) and 3 from the control group (2,730–2.960 g). There were no statistically significant differences between the control and at-risk group in gestational age, birthweight, or in 1- and 5-minute Apgar scores (see Table 2). Medical birth records of the infants were collected by an authorized child physician. In addition to the routine medical

[3] All the information was not available for all families. From the at-risk families only the index parent with a diagnosis of dyslexia was initially tested for IQ. Every parents' IQ will be tested during the second phase of parent assessment.

examination, the infants were also tested by a neurologist. The infants had no central neurological or other major medical complications and were diagnosed as healthy at the time of testing. The infants did not have any reported hearing problems. They were screened at the hospital shortly after birth for possible hearing loss with a 100 dB SPL sound.

The distribution of the participants in the studies was:

Articles I & II:
49 newborns in the ERP measurements (26 control and 23 at-risk infants[4])
Article III:
49 newborns in the ERP measurements (26 control and 23 at-risk infants),
45 children in the later measurements (22 control and 23 at-risk children)
Article IV:
32 newborns in the ERP measurements (14 control and 18 at-risk infants),
31 children in the later measurements (14 control and 17 at-risk children)

TABLE 2 Summary of the participant's birth records.

	Control infants	At-risk infants	
	GA > 38 weeks	GA > 38 weeks	GA < 38 weeks
Articles I, II, & III[1]			
Age (days)	3.9 (1.7; 1.4–6.2) [a]	3.8 (1.6; 1.5–7.3)	19.1 (4.6; 14.7–23.6)
GA (weeks)	40.1 (1.0; 38.3–41.7)	40.0 (1.6; 36.9–43.0)	37.4 (.5; 36.9–37.9)
Birthweight (g)	3688 (535; 2730–4500)	3659 (508; 2970–4600)	3022 (67; 2970–3120)
1 min Apgar score	9.0 (.5; 8–10)	8.5 (1.2; 3–9)	8.8 (.5; 8–9)
5 min Apgar score	9.1 (.5; 8–10)	8.9 (0.9; 5–10)	9.0 (.0; 9–9)
Article IV[2]			
Age (days)	3.9 (1.8; 1.4–6.2)	3.7 (1.5; 1.5–5.9)	19.1 (4.6; 14.7–23.6)
GA (weeks)	39.7 (1.0; 38.3–40.7)	40.2 (1.2; 38.1– 40.7)	37.4 (.5; 36.9–37.9)
Birthweight (g)	3617 (426; 2960–4420)	3812 (467; 3080–4530)	3022 (67; 2970–3120)
1 min Apgar score	9.1 (.5; 8–10)	8.7 (.6; 7–9)	8.8 (.5; 8–9)
5 min Apgar score	9.2 (.6; 8–10)	9.1 (.5; 8–10)	9.0 (.0; 9–9)

[1] N = 49, control group N = 23 (10 girls, 13 boys), at-risk group N = 26 (10 girls, 16 boys).
[2] N = 32, control group N = 14 (8 girls, 6 boys), at-risk group N = 18 (10 girls, 8 boys).
[a] Mean (Standard deviation; Range).

[4] Six infants from the 29 at-risk newborns participating in Articles I, II, and III had a compensated dyslexic parent, and similarly four from 18 infants in Article IV (a sub-sample from studies of Articles I, II, and III).

Experimental settings

Stimuli and procedure

The stimuli and their parameters are presented in Table 3. In Articles I, II, and III, the stimulus set consisted of seven consonant-vowel (CV) syllables, three of which were synthetically (/ba/, /da/, and /ga/), and four naturally (/paa/, /taa/, /kaa/, and /ka/) produced. The synthetic stimuli were kindly provided by Professor Dennis Molfese (University of Louisville, USA) and the technical information of the stimuli can be found in the articles by Molfese and Molfese (1997) and Stevens and Blumstein (1978). In Article IV, the stimuli were naturally produced (digitized from natural speech) CV syllables varying in vowel duration (standard /kaa/ and deviant /ka/).

TABLE 3 Stimulus parameters.

Article	Stimulus	Probability %	Duration ms	dB	ISI ms
Articles I & III	/ba/	14.3	250	75	3,910–7,285
	/da/	14.3	250	75	3,910–7,285
	/ga/	14.3	250	75	3,910–7,285
Article II	/ba/	14.3	250	75	3,910–7,285
	/da/	14.3	250	75	3,910–7,285
	/ga/	14.3	250	75	3,910–7,285
	/paa/	14.3	250	75	3,910–7,285
	/taa/	14.3	250	75	3,910–7,285
	/kaa/	14.3	250	75	3,910–7,285
	(/ka/)[1]	14.3	110	75	3,910–7,285
Article IV	Standard /kaa/	88	250	75	425
	Deviant /ka/	12	110	75	425

[1] /ka/ was not included in the analyses of Article II.

In Articles I, II, and III, the interstimulus intervals (ISI, onset-to-onset) ranged at random from 3,910 to 7,285 ms in order to reduce the habituation effects. Furthermore, the stimuli were presented equiprobably and in a pseudo-random order, in which the same stimulus did not appear more than twice in a row. In Article IV, the stimuli were presented in an oddball paradigm, in which the deviant stimuli were occasionally and pseudo-randomly embedded among repeated frequent standard stimuli. The sequences were presented in short separate blocks of ca. 5 min. in all studies. The intensity of the stimuli was 75 dB

SPL (A-weighted), calibrated before the experiments from the estimated head position of the infant using the Brüel and Kjaer precision sound level-meter (Type 2235).

EEG and ERP recordings

The ERP-recordings were carried out in the EEG laboratory of the Central Hospital of Central Finland. The parents were invited to observe the experiments if they wished. The infants were lying in a slightly reclined position (5.3°) in a crib designed for the purpose, in which the mobility of the infant's head was minimized by a small pillow. 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 (the angle between the loudspeaker and the infants crib was 41°). The recordings were suspended when the infant was either crying or moving excessively.

The EEG/ERPs were recorded with disposable Ag/AgCl-electrodes (Blue sensor, Medicotest, Denmark) 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). The electro-oculogram (EOG) was recorded with two electrodes, one slightly above and lateral to the left eye and the other below the right eye. The EEG/ERP electrodes were referred to the ipsilateral mastoid and the EOG electrodes to the left mastoid. The electrical resistance or impedance of the electrodes before measurement was < 10 kilo-ohms (kΩ), except for five participants, where the impedance of a single channel exceeded 10 kΩ. EEG was recorded and signals were amplified by Nihon Kohden Neurofax EEG-5414K. The bandpass was 0.5–35 Hz, and the AC-filtering was on. EEG epochs of 950 ms pre-stimulus and 950 ms post-stimulus were stored at a sampling rate of 200 Hz during the measurement for later off-line analyses.

The reported data included only trials measured during quiet sleep. The EEG-epochs were initially classified into four categories according to the sleep / wakefulness state of the infant (wakefulness, active sleep, quiet sleep, or indeterminate state). The behavior of the infant during measurement (e.g., eyes open or closed, facial and bodily movements, and crying) was observed and coded on-line. Each one-minute period of the measurement was then classified as one of the states according to the behavioral criteria in the sleep state scoring manual by Anders, Emde, and Parmelee (1971). In addition, eye movements were monitored at the EOG-channels from the ongoing EEG. Also heart rate and respiration (measured with the Static Charge Sensitive Bed, SCSB, model BR8-P) of the infants were monitored (the polygraphic data obtained with SCSB was not used in the present studies). The procedure was the same as in the study by Leppänen et al. (1997), where the interrater agreement of the on-line-

coding of the infant's behavior between two independent observers was 95 %, and the comparable interrater agreement of the off-line classification of the EEG-epochs into the four sleep states was 92 %. This was calculated from the data of five randomly chosen participants and was defined as the percentage of the total number of EEG-epochs that the two observers agreed upon.

ERP averaging

Individual ERP averages were calculated separately for each stimulus type in each paradigm. The time window used for averaging was –50 to 950 ms (with the 50 ms pre-stimulus baseline) in Articles I, II, and III, and –50 to 535 ms in Article IV. Epochs contaminated by eye movements (EOG exceeding ± 150 microvolts, μV), and by muscle activity, or other extra cerebral artifacts (EEG exceeding ± 200 μV) during the analyzed time window, were excluded from the averaging.

Principal component analysis

In Article II, the averaged ERP responses were analyzed by using principal component analysis (PCA) in order to locate the experimental variation in the ERP data. The ERP data were standardized before entry to the PCA procedure in order to control for the amplitude differences between subjects. PCA consisted of computing the association (covariance) between all individual time points or dependent variables, with the central tenet being that associated variables belong to the same underlying component. For the next step, the initial matrix was rotated using the Varimax rotation in order to minimize the temporal overlap of the components (orthogonality). After rotation, the PCA assigned factor loadings and scores. Factor loadings represented the systematic contribution of each PCA component to the voltage at each time point. Factor scores represented the contribution of each component to each individual ERP waveform (indicating the nature of the variability). These scores were used in further analyses of variance, which indicated whether the factor scores (the region of the variability in the ERPs identified by PCA) either systematically increased or decreased in size relative to some experimental conditions. A similar procedure was also used in Article IV to identify the group-related variance in the ERP data. The more detailed comparison between the results obtained with the original averaged ERPs and PCA factor scores was carried out in Article II.

Later developmental language and verbal memory measures

In the studies of predicting later developmental skills with newborn ERPs (Articles III and IV), the later receptive and expressive language and verbal memory skills were assessed by using composite scores in order to obtain a more reliable measure of general language and verbal memory skills. The composite scores were calculated as means of the individual measures (see Table 4) that were first standardized with reference to the control group values of the whole JLD sample (for further details of assessment of early language development of the children participating on the JLD project, see Lyytinen, Poikkeus, et al., 2001). The composite scores were calculated for receptive and expressive language skills at 2.5, 3.5, and 5 years of age, and for verbal memory skills at 3.5 and 5 years of age.

TABLE 4 Composite scores for later language and verbal memory measures.

Receptive language 2.5 years (α = .68):
Reynell Developmental Language Scales (RDLS): Receptive score
Inflectional Morphology Test
Expressive language 2.5 years (α = .80):
Reynell Developmental Language Scales (RDLS): Expressive score
MacArthur Communicative Developmental Inventories (CDI):
Vocabulary production, Maximum sentence length
Receptive language 3.5 years (α = .56):
Developmental Neuropsychological Assessment (NEPSY):
Comprehension of instructions
Peabody Picture Vocabulary Test-Revised (PPVT-R)
Expressive language 3.5 years (α = .73):
Boston Naming Test (BNT)
Inflectional Morphology Test
Receptive language 5 years:
Peabody Picture Vocabulary Test-Revised (PPVT-R)
Expressive language 5 years (α = .66):
Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R): Vocabulary
Inflectional Morphology Test
Verbal memory 3.5 years (α = .66):
Developmental Neuropsychological Assessment (NEPSY): Sentence repetition
Digit Span
Verbal memory 5 years (α = .68):
Digit Span
Syllable Span

The measure of receptive language skills at the age of 2.5 years consisted of the receptive language score of the Reynell Developmental Language Scales (RDLS;

Reynell & Huntley, 1987), and the Inflectional Morphology Test (Lyytinen, 1982), which measured comprehension of the inflectional morphology of the highly inflected and agglutinative Finnish language. In this 12-item task, familiar words of two to four syllables were orally presented, each with three alternative pictures. The child was instructed to select the picture in which the target inflection occurred (e.g., This is a bird's nest. Give me the picture in which the bird is sitting-on-the-nest). The test covers inflections of the adjective (comparative), noun (inessive, in something), and verb (passive indicative perfect).

The measure of expressive language skills at the age of 2.5 years consisted of the expressive language score of the RDLS and two measures from the toddler version of the MacArthur Communicative Developmental Inventories (CDI; Dale, 1996; Fenson et al., 1994). The CDI provided a score for vocabulary production (computed from lists containing words from 20 semantic categories) and a score for maximum sentence length (based on the mean number of morphemes in the three longest utterances). The inventory was completed by the children's parents and reviewed together with the examiner to ensure accurate completion.

The composite score for receptive skills at the age of 3.5 years was based on the Comprehension of Instruction sub-test taken from the Developmental Neuropsychological Assessment (NEPSY; Korkman, 1998), which measured a child's ability to process and respond quickly to verbal instructions of increasing syntactic complexity (e.g., "Show me a bunny," "Show me a sad bunny," "show me a bunny that is little and blue" etc.) and a shortened version of the Peabody Picture Vocabulary Test-Revised (PPVT-R; Dunn & Dunn, 1981) which assessed children's comprehension of word meanings.

The measure of expressive skills at the age of 3.5 years included the Boston Naming Test (BNT; Kaplan, Goodglass, & Weintraub, 1983), which assessed naming vocabulary, and the Inflectional Morphology Test (Lyytinen, Poikkeus et al., 2001; Müller & Brady, 2001). In the Inflectional Morphology Test at this age, the child was required to express the inflection of the target word (archaic Finnish words that are no longer in use and thus not known by the child). The 20-item test covered inflections of adjectives (comparative, superlative), verbs (present), and nouns (elative, i.e. from something).

The measure of receptive language skills at the age of 5 years was based on the PPVT-R. The measure of expressive skills was based on the Vocabulary sub-test score of the Wechsler Preschool and Primary Scale of Intelligence-Revised (WPPSI-R; Wechsler, 1989), where the child had to give the correct name of pictured objects and explain the meaning of various words, and the Inflectional Morphology Test. The latter was expanded from the test administrated at 3.5 years to a 30-item version by adding two inflectional forms of adverbs and past tense.

As with the language measures, in the analyses of the verbal memory skills we used composite scores that were calculated as means of the individual measures (standardized z-scores). The reasoning for also studying the associations between ERPs and verbal memory skills was based on the results by Gathercole and Adams (1993, 1994) that showed that verbal working memory skills were closely linked to receptive vocabulary knowledge. Assessment of memory skills at the age of 3.5 years consisted of the Sentence Repetition subtest of the NEPSY and the Digit Span task modified according to Gathercole and Adams (1994). In the NEPSY Sentence Repetition task, which assessed verbal memory span and short-term memory, the child was required to recall sentences of increasing length and complexity. In the Digit Span test, the child repeated lists of two to six digits, and the score was the number of correctly repeated lists. The Digit Span test at the age of 5 years was similar to the previous, with the exception that the stimuli were presented by computer to ensure the same output for each child. In the Syllable Span test, the same procedure was used as for the Digit Span test, with the exception that the materials deployed meaningless syllables containing one to three phonemes.

SUMMARY OF THE STUDIES

Article I

Earlier results from the JLD project demonstrated group differences between at-risk and control newborns in the ERPs to vowel duration change in an oddball paradigm (Leppänen et al., 1999; Pihko et al., 1999). The results showed vowel duration change detection more consistently in the right hemisphere in the at-risk group, whereas in the control group, this pattern occurred in the left hemisphere. In Article I, we studied whether similar group differences could be also found in newborn ERPs to CV syllables (/ba/, /da/, and /ga/) presented equiprobably with long ISIs (3,910 to 7,285 ms). These kinds of responses can be thought to reflect basic afferent element-driven auditory responses to acoustic features of speech sounds (i.e., feature detection) instead of change detection responses related to oddball paradigms. The first research question was whether the at-risk and control infants would differ in their feature detection responses. Secondly, we were interested whether the role of the right hemisphere would be enhanced in the processing of speech sounds in the at-risk infants, as was the case in earlier vowel change detection studies (Leppänen et al., 1999; Pihko et al., 1999).

Results

Analyses of averaged ERPs at the latencies identified by PCA (Article II) revealed significant group differences in stop-consonant processing in several latency ranges. At the latency of 50–170 ms, there was a significant Consonant (/ba/ and /da/ versus /ga/) x Hemisphere x Group interaction. The within-group tests showed that the responses to consonants (/ba/ and /da/ versus /ga/) were

different between the left and the right hemisphere in the at-risk group. When the consonant contrasts were tested separately in the left and the right hemisphere, the only significant difference was found in the right hemisphere of the at-risk group.

A similar Consonant (/ba/ and /da/ versus /ga/) x Hemisphere x Group interaction was also found at the latency between 540 and 630 ms. This effect resulted from the groups responding differentially in the right hemisphere to various consonants, particularly to the /ga/ syllable. The responses to /ga/ were larger and more positive in the at-risk group. The within-group tests showed that the response patterns for /ba/ and /da/ versus /ga/ differed between the hemispheres both in the control and in the at-risk group. When the contrasts were tested separately in the left and the right hemisphere, the only significant difference between consonants was found, again, in the right hemisphere of the at-risk group. This response was an extension of the earlier major positive deflection around 300 ms. However, when the mean amplitude to /ga/ between 240–410 ms was used as a covariate, the at-risk and control newborns still differed from each other in their later responses to /ga/ between 540–630 ms at the right hemisphere, $F(1,46) = 9.94$, $p < .004$.

A significant Consonant (/ba/ versus /da/) x Anterior-posterior (frontal and central versus parietal electrode sites) x Group interaction was found at the latency of 740–940 ms. This effect was due to group differences in responding to consonants at the parietal electrode sites. The responses to /ba/ and /da/ syllables differed from each other between anterior and posterior electrode sites only in the control group.

Discussion

These results showed that ERPs reflecting feature detection of the speech stimuli differed between newborns with and without familial risk for dyslexia. The clearest hemispheric differences between groups were obtained at the latency of 540–630 ms, where the responses to /ga/ (with the longest CV transition) were more positive and longer lasting in the right hemisphere of the at-risk group. These results of enhanced right hemispheric processing of the speech sounds in the at-risk group were in line with our earlier studies using change detection paradigms (Leppänen et al., 1999, Pihko et al., 1999).

Article II

Our second study was a simultaneous publication with Article I. Article II had a methodological focus of using principal component analysis (PCA) in the infant ERP data. We wanted to investigate whether PCA could be used to successfully identify the ERP latencies which show differences between at-risk and control infants in the paradigm reflecting feature detection (equiprobably presented stimuli with long ISIs, see Article I). Our second goal was to compare these possible group-related differences revealed by the PCA based factor scores to the differences found by using traditional ERP averaging (mean amplitudes from the latency ranges suggested by the PCA factor loadings). In this article, we reported results from both synthetic (see Article I) and natural stimuli, and compared whether both of the stimulus sets revealed similar group and stimulus-related results.

Results

The results of the analyses using original averaged ERPs for the synthetic stimuli (/ba/, /da/, and /ga/) are presented in Article I.

In the analyses using PCA factor scores, the earliest latency where the group-related interactions could be found was between 50–170 ms (Factor 4 accounting for 16.3 % of the variance), where there was a significant Consonant x Hemisphere x Group interaction. The difference contrast revealed that the at-risk and control group showed a differential hemispheric response pattern when the scores for /ga/ were contrasted to the combined scores for /ba/ and /da/. When the consonant contrasts were tested separately at the left and right hemisphere, there was a marginally significant main effect of group, indicating that the groups showed a tendency towards differences in their consonant scores at the right hemisphere. The within-group tests showed that the only significant difference between consonant scores (/ga/ versus combined /ba/ and /da/) were found at the right hemisphere in the at-risk group.

Between 540 ms and 630 ms (Factor 3, accounting for 19.9 % of the variance), there was a similar Consonant x Hemisphere x Group interaction as was observed for Factor 4. Regarding Factor 3, the at-risk and control group showed a differential hemispheric response pattern when the scores for /ga/ were contrasted to the combined scores for /ba/ and /da/. When these consonant contrasts were tested separately at each hemisphere, the results indicated that the groups differed in their consonant scores, only at the right hemisphere, and that the scores were different in particular for /ga/. The within-group tests

further indicated that the consonant differentiation pattern occurred only at the right hemisphere of the at-risk group.

There was also a significant group-related effect in the later latency between 740 and 940 ms (Factor 2, accounting 24.7 % of the variance). However, contrary to the effects found for Factors 4 and 3, this Factor was characterized by within hemisphere differences between the groups in revealing a significant Anterior-posterior x Consonant x Group interaction. This effect was based on the group differences between the scores for /ba/ and /da/ at the parietal electrode sites. In the at-risk group, however, there were no such differences between the scores to the different stimuli. The within-group tests showed that the scores between /ba/ and /da/ at the parietal electrode channels differed only in the control group. There were no group-related interactions in the natural stimulus set.

Discriminant function analysis was used to assess how accurately group membership (at-risk vs. control) could be determined by the factor scores and original averaged ERPs. For this purpose, the following composite scores were used: For Factors 4 and 3, as well as for corresponding mean amplitudes of the original ERPs at the latencies of 50–170 ms and 540–630 ms, the scores for /ga/ at the right hemisphere (R-GA) were combined. For Factor 2, and for corresponding mean amplitudes of the original ERPs between 740 and 940 ms, the scores for /da/ were calculated from the parietal channels (P-DA).

In the factor scores, these three composite scores differentiated the groups with an accuracy of 73.5 %. Of the infants, 76.9 % were correctly classified as belonging to the at-risk group (20 from 26), and 69.6 % to the control group (16 from 23). In the original averaged ERPs, these three scores differentiated the groups with a slightly lower accuracy of 67.3 %. Of the infants, 65.4 % were correctly classified as belonging to the at-risk group (17 from 26), and 69.6 % to the control group (16 from 23).

Discussion

The PCA-ANOVA-procedure revealed significant stimulus- and group-related differences. Parallel between-group differences were also found by using original averaged ERPs. Both of these analyses confirm that cortical activation evoked by CV-syllables, varying in brief transitions of consonant sounds, was already at this very early age, different in at-risk infants. The clearest hemispheric differences between groups in both analyses were between 540–630 ms in the responses to /ga/, which clearly elicited more positive responses in the right hemisphere of the at-risk group. There were no group differences in the natural stimulus set.

The comparison between the results with the PCA factor scores and original averaged ERPs showed slightly more accurate classification in the discriminant function analyses for PCA factor scores. Furthermore, the statistical power and effect sizes were higher for Factor 2, which explained the largest portion of the variance in the factors with group differences, than in the corresponding amplitude measures of the original ERPs. For Factor 3 and corresponding ERP-averages (between 540–630 ms), the power and effect sizes were similar. These results demonstrated that the PCA-ANOVA-procedure is an effective way in which to identify the group-related variance, thus providing an objective analysis method for infant ERP data.

Article III

We were interested in whether the differences found in Articles I and II between at-risk and control infants, that could be obtained as early as in newborns, were related to the later skills at 2.5, 3.5, and 5 years of these same children. We chose the ERP index (the mean amplitude of the responses to /ga/ at 540–630 ms) of interest on the basis of the clearest hemispheric differences in CV-syllables between the at-risk and control group that were found in our earlier studies (Articles I and II). The rationale for using a composite score (frontal, central, and parietal channels combined) from left and right hemisphere was also based on the results of Articles I and II, where no significant anterior-posterior differences were found at the latency of 540–630 ms (Hemisphere x Consonant x Group). Secondly, this also reduced the number of tested associations with later skills, thus diminishing the possibility to obtain a spurious difference by chance. We were interested whether the at-risk group type of speech cue processing (longer lasting and more positive responses to /ga/) in the right hemisphere, which is not considered to be specialized for language processing, is related to poorer performance on tasks measuring language and verbal memory skills that are known to be affected in language disorders such as dyslexia.

Results

The correlation analyses showed that the mean ERP amplitudes to /ga/ between 540-630 ms were negatively correlated to a number of language and verbal memory measures at different ages. The results indicated that the more positive was their response at birth (the at-risk type of slower polarity shift from

positive to negative deflection), the lower were the scores of children in language and verbal memory tests.

Larger and more positive ERP responses in the right hemisphere had a statistically significant association with poorer receptive language skills at 2.5 years. The regression analyses further indicated that the receptive language skills at 2.5 years were predicted by ERPs recorded from the right hemisphere. ERPs from the right hemisphere, and also from left hemisphere, were nearly significantly associated also with receptive skills at 5 years. No statistically significant associations emerged between ERPs and later expressive language skills.

More positive ERP responses in the left hemisphere were associated with poorer verbal memory skills at the age of 5 years. The predictive value of the ERPs from the left hemisphere was further confirmed by regression analyses.

Discussion

The results showed that newborn ERPs reflecting feature detection predict later language development in children with and without familial risk for dyslexia. The at-risk type of response pattern in the right hemisphere at birth was related to poorer receptive language skills at the age of 2.5 years. There was also a trend for a similar association with receptive language skills at 5 years. The larger positive ERPs in the left hemisphere were associated with poorer verbal memory skills at the age of 5 years. The associations from newborn ERPs were more clearly linked to receptive than to expressive language skills. These results suggest that ERPs, which are thought to reflect fine auditory differentiations of speech cues, are related to those language skills that also rely on accurate discrimination of speech signals (receptive language skills).

Article IV

Based on the results from Article III which show that newborn ERPs measuring feature detection (equiprobably presented stimuli with long ISIs) can be used to predict later skills, we were interested in whether change detection responses of the vowel duration would similarly predict later language development. We used PCA, encouraged by the positive findings regarding the usefulness of the method (Article II), in locating the latencies with experimental variation in the ERP data. The participants for Article IV were a sub-sample of those from Articles I, II, and III (at-risk group, N = 18; control group, N = 14), which

allowed the comparison between feature and change detection processes within the similar subject population.

Results

A PCA-MANOVA-procedure revealed significant group differences at the latency of 290–320 ms where there was a Stimulus x Hemisphere x Group interaction. The most divergent response pattern was the clear positive responses to the deviant /ka/ at the right hemisphere of the at-risk group.

The mean amplitude values of the original averaged responses to the standard /kaa/ and deviant /ka/ from the left and right hemisphere at the latency of 290–320 ms were entered into the regression analyses separately for each group. This is because the correlation to later skills were of opposing directions between the groups. No significant associations were found between the ERPs of the control group and their later language or verbal memory measures. In the at-risk group, however, the ERPs to the standard /kaa/ in the left hemisphere significantly predicted receptive language skills at the age of 2.5 years. The association was negative, meaning that the more positive were the responses to the standard stimuli, the poorer was the at-risk children's performance on measures of receptive language skills at 2.5 years. The deviant responses produced a significant R^2 change in the model indicating its own contribution in explaining the variance in later language. Contrary to the responses to the standard stimuli, the larger positive responses to the deviant /ka/ in the left hemisphere predicted better receptive language skills. The standard responses also predicted receptive language skills at 3.5 years, and the more positive responses were related to poorer performance. There were no significant relationships between ERPs and expressive language skills.

The responses in the left hemisphere of the at-risk group also predicted later verbal memory skills in the regression analysis. For verbal memory at 3.5 years, the responses to the standard stimuli held no predictive value in the model, whereas the larger positive responses to the deviant /ka/ were associated with better performance in verbal memory skills at 3.5 years. Similarly to associations between ERPs and receptive skills, the responses to the standard stimuli from the left hemisphere were associated with poorer verbal memory skills at 5 years. Larger positive responses to the deviants in the right hemisphere also predicted poorer performance on this measure.

Discussion

The PCA–MANOVA-procedure detected group differences in the change detection of the vowel duration between at-risk and control infants. In line with the results from Article II, this study showed that PCA is an effective method with which to identify the group-related variance in the infant ERP data. Similarly to the results from Articles I and II with a feature detection paradigm, the role of the right hemisphere in stimulus differentiation was enhanced in the at-risk group (the participants of the present study were a sub-sample from the study using the feature detection paradigm).

In the study by Leppänen et al. (1999) using the same stimuli with another sub-sample of newborns participating in the JLD project, the group differences were more prominent in the slow rate condition (offset-to-onset interstimulus interval of 855 ms) than in the fast rate condition used in Article IV (offset-to-onset interstimulus interval of 425 ms). Group differences were, however, also found in the fast rate condition in Leppänen et al's study. These differences were related to the greater responsiveness in general in the at-risk group. A similar pattern of positive responding to both deviant and standard stimuli in the at-risk group was found in Article IV.

The results from Article IV further demonstrated that ERPs reflecting vowel duration change detection can be used to predict later skills. The associations between ERPs and later skills were observed to be in opposing directions between the at-risk and control group, and the significant associations were observed only in the at-risk group. Larger responses to the deviant stimuli (change detection) in the left hemisphere predicted better receptive language skills at 2.5 years and verbal memory skills at 3.5 years, whereas a similar pattern in the right hemisphere was associated with poorer verbal memory skills at 5 years. Larger positive responses to the standard stimuli (general responsiveness) in the left hemisphere were associated with poorer receptive language skills at 2.5 and 3.5 years, and verbal memory skills at 5 years. These results indicate that atypical change detection processes in the right hemisphere and enhanced general responsiveness to speech stimuli in the left hemisphere predict poorer language skills in children at-risk for familial dyslexia.

The above described results are also summarized in Figure 1.

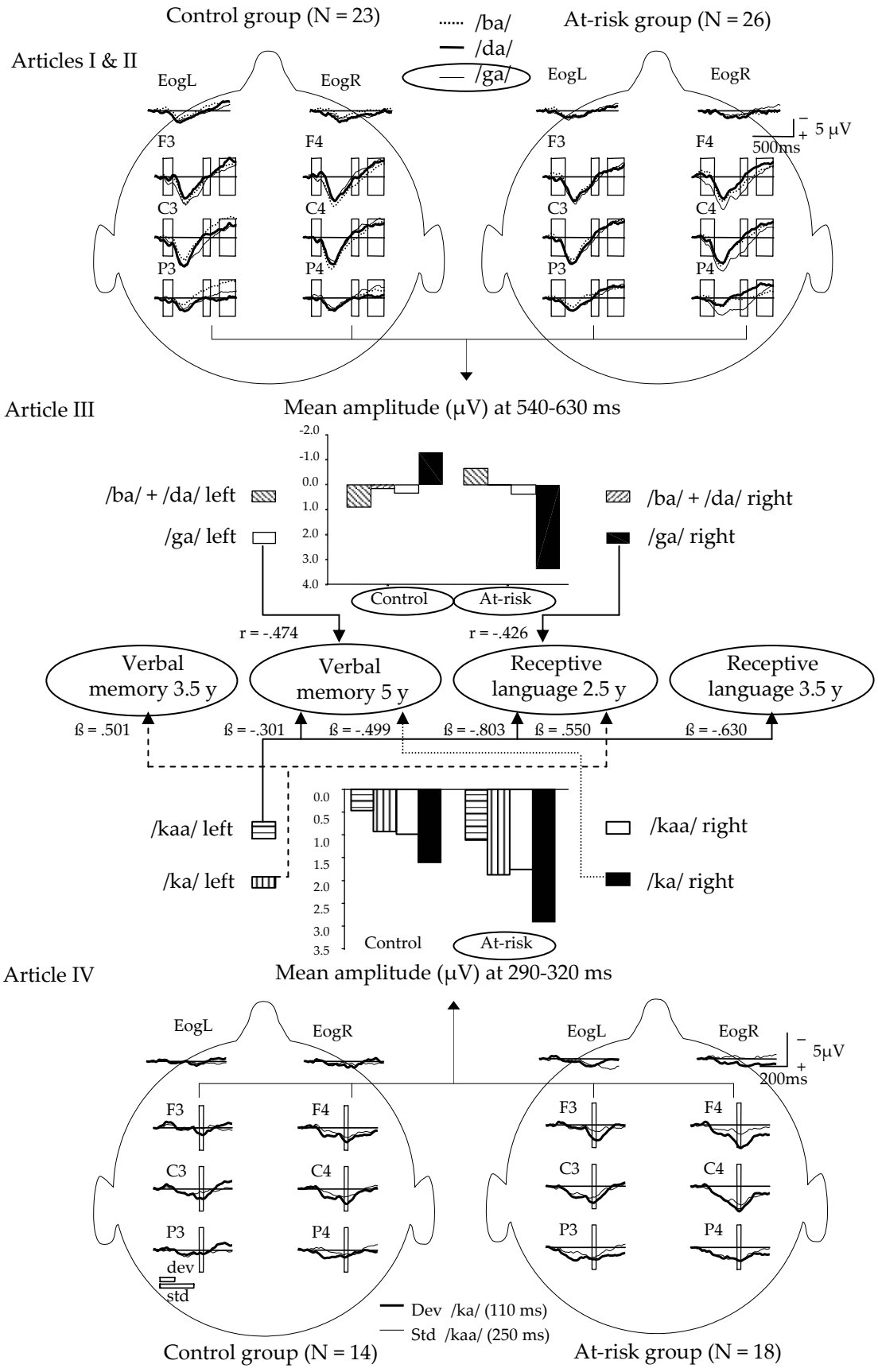

FIGURE 1 Summary of the studies.

GENERAL DISCUSSION

The present dissertation contributes new evidence indicating that the electrical brain activation evoked by speech stimuli (equiprobably presented stimuli with long ISIs) differs between newborns with and without familial risk for dyslexia. These responses that reflect feature detection or general responsiveness for speech stimuli per se, differed between at-risk and control newborns. The present dissertation also demonstrates, for the first time, that newborn ERPs measuring both feature and change detection processes can be used to predict later language development in children with and without familial risk for dyslexia.

Newborn ERPs measuring speech perception

Feature detection

Newborn ERPs to equiprobably presented consonant-vowel (CV) syllables (/ba/, /da/, and /ga/) with long interstimulus intervals (Articles I and II), were characterized by an initial small positive-negative deflection at 110 ms, a major positive deflection reaching its maximum around 300 ms, and a later occurring slow ongoing negative deflection that increased to the end of the recording window. The waveforms were similar to those observed in several other studies using similar types of CV-syllables in young infants (Barnet et al., 1975; Ellingson et al., 1974; Kurtzberg et al., 1984, 1986; Novak et al., 1989; Weitzman & Graziani, 1968).

The ERPs in Articles I and II reflect the brain's or auditory system's responses to speech sounds per se. It is plausible to interpret that these responses reflect processing of stimulus features (feature detection) and the

formation of the neural basis for differentiation between speech sounds. Thus, they do not reflect any well-known auditory discrimination processes such as the pre-attentive change detection process reflected in mismatch negativity (MMN). Contrary to the MMN studies, there were no comparable theoretical assumptions to make with regard to how stimulus-specific differences would manifest in these newborn ERPs. Furthermore, in newborn ERPs, the mature multiple peak structure typical to older infants and adults is still absent, and important stimulus-related information is carried in the whole waveform. The results from Article II demonstrate that principal component analysis (PCA) is an effective way to locate the experimental-related variance, thus providing an objective analysis method for infant ERP data.

Significant group differences were found in stop-consonant processing in several latency ranges. The clearest hemispheric differences were obtained at the latency of 540–630 ms, where the positive responses to /ga/ were clearly larger and more prolonged in the right hemisphere of the at-risk group. In this group, the right-hemispheric responses to /ga/ were also larger than those to /ba/ and /da/. The results concerning the enhanced responses to /ga/ could be explained by the differences in the shape of the stimulus spectrum during the transitions, as well as in the transition durations between the stimuli (Stevens & Blumstein, 1978). The F_2 frequency increased slightly during the transition in /ba/, but decreased for /da/ and /ga/ transitions. Although the shapes of the formant patterns are similar between the /da/ and /ga /stimuli, these two stimuli differ, particularly in the duration of the transitions. CV transition duration was longest for /ga/ (45 ms, whereas in the /ba/ and /da/, the durations were 20 ms and 35 ms, respectively). These durational differences, together with variations in the spectral shapes (direction of CV transition) between the stimuli, may well contribute to the larger responses for /ga/ in the at-risk group, and thus to the processing differences between the groups. The enhanced right-hemispheric responses to /ga/ in the at-risk group suggest that the neural network generating the measurable stimulus driven synchronized activation stays on longer in newborns with familial risk for dyslexia. This response pattern in newborns at risk for later language problems could be related to the findings of delayed N1 latencies found in children with language deficits (Dawson et al., 1989; Jirsa & Clontz, 1990, Lincoln et al., 1995, Neville et al., 1993; Tonnquist-Uhlén et al., 1996) that were speculated to result from a slower rate of sensory processing (Leppänen et al., 2003).

As reported in Article II, there were no significant group differences in the responses to the natural stimulus set (/paa/, /taa/, and /kaa/). The responses were of higher amplitude to natural than to synthetic speech stimuli. This trend could be explained by the fact that natural sounds have richer auditory features (Stevens & Blumstein, 1978). It could be inferred that natural sounds also activate broader neuronal networks, thus resulting in enhanced responses. The

enhanced amplitudes for more complex stimuli were also obtained in the earlier newborn studies from the JLD project, where speech stimuli (Leppänen et al., 1999) elicited higher amplitude responses than pure tones (Leppänen et al., 1997). The fact that the naturally-produced stimuli, with higher ecological validity (Article II) failed to elicit differential responses between the groups, could speculatively be interpreted as suggesting that a natural auditory environment may provide somewhat more redundant information that subsequently compensates for speech sound processing among children with innate vulnerability to language-related difficulties. Furthermore, it has been shown that when this kind of redundant information is reduced (e.g., noise among stimuli), the children with language deficits have problems in hearing the acoustic distinctions among successive brief sounds in speech (Wright et al., 1997). It should be noted, however, that even if there were no group differences in the responses to natural stimuli in this feature detection paradigm, we have also found group differences between at-risk and control infants in the oddball paradigms measuring change detection responses for speech sounds (Article IV, see also Leppänen et al., 1999; Pihko et al., 1999).

The differentiation of the consonant-vowel syllables appeared to be clearest in the parietal channels (Articles I and II). Involvement of the parietal channels in auditory and speech differentiation has also been found in the earlier auditory ERP studies with newborns. For example, in the pitch discrimination study (1300 Hz vs. 1000 Hz) with the JLD newborns, the MMN-like negative deflections occurred only at the parietal channels (Leppänen et al., 1997). Furthermore, in the vowel duration change detection (/kaa/ versus /ka/) study with another sample of newborns, the ERPs to the standard and deviant stimuli differed from each other in the control group more consistently at the left frontal and parietal channels. In contrast, in the at-risk group, this pattern occurred at the right central and parietal electrode locations (Leppänen et al., 1999). There is also evidence of vowel discrimination (Finnish vowels /i/ and /y/) in pre-term infants where the differentiation between the standard and deviant vowels occurred not only at the frontal electrodes of both hemispheres, but also at the right parietal channels (Cheour-Luhtanen et al., 1996). These findings that show auditory discriminative responses at the parietal sites, could be explained, for example, by differences between infant and adult brain structures. A study by Blume, Buza, and Okazaki (1974), for example, showed variability in the anatomical correlates of the ten-twenty electrode placement system in the infant brains, implying that the electrode locations in newborns may not correspond to those of adults. Furthermore, due to the developing state of the infant brain structures, the supratemporal dipole source of MMN found in adults (see e.g., Picton, Alain, Otten, Ritter, & Achim, 2000) could have a different orientation in infants, which could explain the activation also in the

parietal electrode channels (cf. Change detection section for discussion of polarity in infant ERPs).

In a comparison of the results of Articles I and II with those of Molfese and colleagues using similar paradigms, the following differences could be found. In the ERPs reported by Molfese and Molfese (1985, 1997), there was a clear negative deflection in the newborn ERPs around 200 ms that was not as marked in our study. There were also some differences in the later latencies of ERPs, even if the major positive deflection around 300 ms was found, both in the studies by Molfese and colleagues, and in our study. These differences could be explained, for example, by differences in the recording sites used (Molfese and Molfese, 1985: T3 and T4; 1997: frontal, parietal, and temporal; our study: F3, F4, C3, C4, P3, and P4), reference electrodes (Molfese and colleagues: linked ear electrodes; our study: ipsilateral mastoids), or stimuli (Molfese & Molfese, 1985: b/ and/g/ with vowels /a/, /i/, and /u/, and their non-speech counterparts; 1997: /b/, /d/, and /g/ with vowels /a/ and /i/; our study: /b/, /d/, /g/, /p/, /t/, and /k/ with vowel /a/). There were also differences in the number of trials of the averaged responses. In the studies by Molfese and colleagues, the number of presentations of stimuli was 16 (Molfese & Molfese, 1985), 20 (Molfese & Molfese, 1997), and 24 (Molfese, 2000; Molfese et al., 2001). In our study, the mean number of accepted trials for analysis after artifact rejection was at least 37 for each stimulus type. Furthermore, there were also differences in the arousal states of the participants. The newborns in the studies by Molfese and colleagues were in a quiet awake state, whereas in our study, the infants were in quiet sleep. It has been shown that that the ERPs of very young infants do differ between various stages of alertness (Duclaux et al., 1991; Ellingson et al., 1974; Friederici et al., 2002).

Regarding the group differences, Molfese and Molfese reported ERP differences between the consonants at the left hemisphere at 70–320 ms (Molfese & Molfese, 1985, 1997), and in both hemispheres at around 670 ms (Molfese & Molfese, 1985) in the group with better language skills by the ages of 3 and 5 years. In our study, the latency range at which only the control group showed differential responding to consonants was later (740–940 ms) and there were no hemispheric differences in this response pattern. In our study, the clearest hemispheric consonant differentiation (more positive and prolonged responses to /ga/) was obtained in the right hemisphere of the at-risk group at 540–630 ms. The differences in the group effects could be also due to the selection or grouping of the participants. In the studies by Molfese and colleagues, the children were grouped according to their performance in later language measures whereas in our study, the inclusion criterion for the at-risk group was a risk for a familial language deficit. Regarding the analysis procedures, Molfese and colleagues combined different latency ranges from both left and right hemispheres (Molfese, 2000; Molfese & Molfese, 1997) as well

as different ERP amplitude and latency measures (Molfese, 2000) in the same discriminant function analyses (the number of used ERP measures ranged between 3 and 7). In our studies, we tested the possible differences in each latency range separately.

The findings of the enhanced role of the right hemisphere in our studies were, however, in line with the results of Molfese (2000) and Molfese et al. (2001), whereby the ERPs in the right hemisphere played a significant role in discriminating between the diagnosed children with dyslexia, poor readers, and control children at the age of eight years. The ERP components with group differences at the right hemisphere were within similar latencies (Molfese: 0–174 ms, and around 460 ms; our study: 50–170 ms, and 540–630 ms) and to similar CV-syllables (Molfese: /gi/; our study: /ga/) between the studies. It should be noted, however, that any detailed comparisons between these studies cannot be made on the basis of the report by Molfese (2000), in which only summary data from a discriminant function analysis, based on a variable set including pooled peak latency and amplitude measures, are reported.

Change detection

We were interested in whether a similar enhanced right hemispheric speech processing pattern that was found in the feature detection paradigm (Articles I and II), could also be found in the ERPs reflecting change detection of the vowel duration in these same newborns. The participants of Article IV were a sub-sample of newborns from Articles I, II, and III, which allowed the comparison between feature and change detection processes within the similar subject population.

According to a theory proposed by Näätänen (1992), a frequently repeated stimulus forms a memory trace or neural model in the sensory memory. The sensory input generated by a deviating stimulus does not fit with the existing model, thereby resulting in a mismatch process reflected in the change detection responses of the ERPs. The PCA-MANOVA-procedure detected group differences in the change detection of the vowel duration between at-risk and control infants at the latency of 290–320 ms. In line with the results from Article II, this study showed that PCA is an effective method of identifying the group-related variance in the infant ERP data. Similar to the results in Articles I and II, the role of the right hemisphere in stimulus differentiation was enhanced in the at-risk group (the participants of the present study were a sub-sample from the study with the feature detection paradigm). Also the responses to standard stimuli were larger in the at-risk group.

The responses to the deviant stimuli in Article IV and in the study by Leppänen et al. (1997, 1999) and Pihko et al. (1999) with another sub-sample of

newborns participating in the JLD project, were more positive than those to the standard stimuli. In Article IV, the standard responses produced a slow and widespread positivity around 300 ms that reflected similar responses to auditory stimulation per se, as in our feature detection paradigm (Articles I and II). The deviant elicited a prolonged positive response that could reflect the processing of either a stimulus change, or the new stimulus properties. Because the deviant stimuli were 140 ms shorter than standard stimuli, the enhanced positivity to the shorter deviant could be interpreted as reflecting change detection processes, i.e., detection of the omission of the rest of the stimulus as compared to the representation of the previous longer stimulus (Leppänen et al., 1999). There are findings of similar larger positive responses to changes in pitch and speech sounds in studies with newborns or young infants (Alho, Sajaniemi, et al., 1990; Dehaene-Lamberz & Baillet, 1998; Dehaene-Lamberz, 2000; Dehaene-Lamberz & Dehaene, 1994; Friederici et al., 2002; Leppänen et al., 1997; Morr et al., 2002), but also reports of MMN-like negativity (Alho et al., 1990; Čeponienė et al., 2002; Cheour et al., 1998, 2002, Cheour, Alho, et al., 1998; Cheour-Luhtanen et al., 1995, 1996; Kushnerenko, Čeponienė, Balan, Fellman, & Näätänen, 2002; Kushnerenko et al., 2001) or reduction of the positivity in the deviant responses (Kushnerenko et al., 2002; Leppänen et al., 1997).

The positive change detection responses and the lack of clear adult-like negative responses in infants has been interpreted, for example by Alho, Sajaniemi, et al. (1990) and Kushnerenko, Čeponienė, Balan, Fellman, & Näätänen (2002) as resulting from the reduction of the mismatch negativity due to its latency overlap with the infant analogue of the adult P3a response that reflects involuntary orientation of attention. The P3a in adults is characterized by frontocentrally maximal positivity at 250-350 ms, and is elicited by a distracting or attention-catching stimuli such as a telephone ringing, electric drill, etc. (see e.g., Escera, Alho, Schröger, & Winkler, 2000). This explanation, however, may not be sufficient for the results of Article IV. The deviant stimuli that were shorter in their vowel duration could hardly be considered as distracting as those stimuli that are typically used in paradigms that elicit P3a components. There is also evidence that the P3a could be obtained for slightly deviant tones occurring among standard tones (600 Hz vs. 660 Hz) in adults (Alho et al., 1998). It should be noted, however, that in the study by Alho et al. (1998), there were also novel or distracting tones among the standard and deviant stimuli, which could enhance the involuntary attentional switching, not only to the novel tones, but also to the deviant stimuli.

It has also been proposed that positive amplitudes at the latency of MMN might reflect increased distractibility of the infants (Alho, Sajaniemi, et al., 1990). This increased distractibility could further be related to the attentional problems among older individuals with dyslexia (for a review, see Hari & Renvall, 2001). Our unpublished results, however, show that the ERPs to the

standard and deviant stimuli in the left and right hemisphere of the at-risk group at the latency of 290–320 ms, were not associated with the Attentional Focusing or Attentional Shifting scales of a behavioral questionnaire by Derryberry and Rothbart (1988) which were measured at 3 years of age, or with the Attentional problem or Hyperactivity scales of Behavioral Assessment System for Children (BASC, Reynolds & Kamphaus, 1992), measured at 4 and 5 years of age.

The positive polarity in the change detection responses of young infants, as compared to a more adult-like negative polarity, could be explained by maturational factors, such as functional immaturity of the neonatal auditory system. According to Moore (2002), the cortico-thalamical and cortical pathways appear to be immature at birth, thus suggesting that newborn ERPs would reflect activation of the subcortical structures. The polarity differences in infant studies could also reflect the variation in the maturational levels of infant ERPs described by Kurtzberg, Hilpert, Kreuzer, and Vaughan (1984). The least mature ERPs (pre-terms) show negative polarity at the midline and lateral sites, whereas the most mature responses (3 month-olds), show positive polarity at both of these sites. This notion of the relationship between ERP polarity and maturational factors receives support in the study from the JLD project using cardiac measures (Leppänen, 1999). These measures, Vagal tone (V) and Heart period (HP), are known to be associated with maturation during the first year of life (Fracasso, Porges, Lamb, & Rosenberg, 1994; Porges, 1988). When these measures with GA were entered into the regression model, the results showed that they significantly predicted ERPs at the F3, F4, and C3 channels (pitch discrimination paradigm). The more mature status, as indexed by cardiac measures, was related to the more positive ERP responses.

The inconsistencies between positive and negative change detection responses in infant studies could also be explained by the variation in the analysis procedures such as filtering (low frequency filter of 0.5 Hz in the present dissertation vs. ≥ 1 Hz used in some of the infant studies), and the sleep states of the infants. Regarding the effects of arousal states, newborn ERPs appear to be similar in both the active sleep and awake state (Kurtzberg et al., 1984; Novak et al., 1989). According to Martynova, Kirjavainen, Erkkola, and Cheour (2003), certain components such as MMN in newborns would not, unlike in adults, differ in amplitude or latency between quiet and active sleep stages, and it would thus be acceptable to average these ERP components across different sleep states in newborns. We should, however, exercise caution in adopting this kind of interpretation because there are also contradictory results which show differences in the ERPs of young infants between various sleep states (Duclaux et al., 1991; Ellingson et al., 1974).

Newborn ERPs predicting later skills

One of the major goals in the present dissertation was to study whether the differences in speech processing of newborns with and without familial risk for dyslexia would be associated with later language development in these same children. Regarding the feature detection paradigm (Article III), the mean amplitude of the responses to /ga/ at 540–630 ms (with the clearest hemispheric group differences in Articles I and II) was used as an ERP measure of interest. The results from Article III showed that the at-risk type of enhanced responding to speech stimuli (more positive and prolonged responses to /ga/ at 540–630 ms) in the right hemisphere, which is not considered to be specialized for language processing, was associated with poorer receptive language skills at 2.5 years, both in children with and without familial risk for dyslexia. There was also a tendency for a similar association with receptive language skills at 5 years after Bonferroni corrections. The Bonferroni correction was used to adjust the probability required for statistical significance in order to avoid a Type II error (obtaining a spurious difference by chance). This method, however, could also increase the likelihood of a Type I error (accepting the null hypothesis when a genuine difference exists). More positive ERP responses in the left hemisphere were associated with poorer verbal memory skills at the age of 5 years. The associations from newborn ERPs were clearer to the receptive than to expressive language skills. These results suggest that ERPs, which are thought to reflect fine auditory differentiation of speech cues, are more related to those language skills that also rely on accurate discrimination of speech signals (receptive language skills).

Regarding the change detection paradigm (Article IV), with a sub-sample from the feature detection paradigm (minimizing the population-related differences), the latency of interest (290–320 ms) was based on the results from the PCA-MANOVA-procedure. The results from Article IV further demonstrated that newborn ERPs can be used to predict later language and verbal memory skills. The associations between ERPs and later skills were significant only in the at-risk group. Larger positive responses to the standard /kaa/ in the left hemisphere were associated with poorer receptive language skills at 2.5 and 3.5 years and verbal memory skills at 5 years. Enhanced positive responses to the standard stimuli could thus reflect similar general responsiveness to stimulus features per se, as found in Articles I and II. There is also evidence from the magnetoencephalograpgy (MEG) study by Helenius, Salmelin, Richardson, Leinonen, and Lyytinen (2002) that adults with dyslexia (participants from the JLD project) process stimulus features differently than controls. Interestingly, the dyslexics had an abnormally strong response in the left supratemporal auditory cortex 100 ms (N100m) after the onset of the initial

vowel /a/ in the pseudowords (/ata/, /atta/, and /a a/). The results from Articles III and IV showed that general responsiveness to the stimulus features may not be adaptive in the aspects of language learning. For example, the non-selective and more enhanced responses, both to the standard and deviant stimuli in Article IV, could interfere with the accurate differentiation between the stimuli in the at-risk group, thus producing problems in later language development that requires fine discrimination of auditory information. The results from both Articles III and IV also showed that the ERPs were associated with receptive, but not with expressive language skills.

The responses to the deviant stimuli /ka/, reflecting auditory sensory memory functions and change detection processes had either positive or negative associations with later skills depending on the hemisphere in which they occurred. The vowel duration change detection in the left hemisphere, which is thought to be specialized in speech processing, predicted better performance on tasks reliant on short-term verbal memory demands (3.5 years). This response pattern was also significantly associated with better receptive language skills (2.5 years) that require fine discriminations of the speech input. The vowel change duration change detection in the right hemisphere, which is not specialized in processing language material, was associated with poorer verbal memory skills at the age of 5 years.

This kind of atypical change detection processing in the right hemisphere of the at-risk group could be related to problems in processing of the temporal or durational aspects of speech stimuli. The ability to discriminate between short and long consonants and vowels is essential, for example, in the Finnish language, as these duration variations are critical to the cueing of opposites and semantic differences. For example, perceived changes in durational patterns contribute to the identification of a word. For example, the word /tuli/ (fire), with short /u/-sound duration, has a different meaning than /tuuli/ (wind), with a long /u/-sound. Finnish dyslexics have been shown to have problems in the perception of these durational cues (Richardson et al., 2003). In comparison to normal readers, they also make disproportionately more errors when differentiating consonant and vowel durations while reading pseudowords (Lyytinen et al., 1995). The dyslexic children and adults have also been shown to have general temporal acuity impairment in visual, auditory, and tactile modalities (Laasonen et al., 2000, 2001, 2002; Laasonen, Service, et al., 2002; Virsu et al., 2003). As shown in Article IV, the atypical processing of the temporal elements of speech stimuli in the right hemisphere of the at-risk group was associated with poorer performance in verbal memory measures at 5 years of age. There is also evidence from the behavioral studies that the early temporal processing problems are associated with poorer language skills later on in the development of children with language deficits (Benasich, Thomas, Choudhury, & Leppänen, 2002).

In comparison of the results from Articles III and IV, there were some differences in the association between newborn ERPs and later skills, even though the participants in Article IV were a sub-sample (N = 32) of a larger population from Article III (N = 49). In Article III, the associations were similar, both in the at-risk and control group, whereas in Article IV, the correlations between newborn ERPs and later skills were of opposing directions between the groups. Similar results were also found in our study with ERPs to change detection in consonant duration at 6 month-olds (Leppänen, Guttorm, et al., 2003). Furthermore, in Article IV, the responses predicted later skills only in the at-risk group. This could be explained by the fact that the enhanced positive responses were more prominent in the at-risk group. The differences between results from Articles III and IV could also be due to the differences in paradigms (feature detection with long versus change detection with short interstimulus intervals) and stimuli (synthetic /ba/, /da/, and /ga/ versus natural /kaa/ and /ka/). Also the latencies of critical ERP measures varied between the studies (540–630 ms versus 290–320 ms).

The similarities in the results from Articles III and IV suggest that the overall general responsiveness to speech stimuli, both in the left and right hemisphere, is associated with poorer receptive language and verbal memory skills. Furthermore, speech processing (both feature and change detection) in the right hemisphere is related to poorer performance in these measures. The change detection in the left hemisphere, however, is associated with better receptive language and verbal memory skills. The significant associations in Article IV, not only to the deviant, but also to the standard stimuli, indicates that the traditional use of difference waves (responses to the standards subtracted from those to the deviants) might not be an ideal way of investigating change detection responses in newborns.

Results from Articles I, II, and IV, as well as from the studies by Leppänen et al. (1999) and Pihko et al. (1999), showed enhanced right hemispheric processing of speech stimuli in the at-risk group. This type of processing with atypical use of the right hemisphere could affect the formation of speech sound representations and thus have cascading effects on consequent language development. These findings are in line with the neurolinguistic development theory (Locke, 1994, 1997), which states the use of right hemisphere structures (non-specific for phonological operations) is minimally adequate, but not optimal, for the development of spoken language and may also disfavour phonological encoding and decoding operations. However, whereas the neurolinguistic development theory posits that the compensatory role of the right hemisphere (which would also lead to structural and functional changes in the right hemisphere, see below) becomes crucial after inactivation of the grammatical analytic mechanism at the age of 20 to 37 months, our study is based on observations of hemispheric differences in speech processing already

at birth. It should be noted, however, that the enhanced right hemisphere processing of the speech information does not necessarily mean poorer language skills, as shown, for example, by Knecht et al. (2001). Their results demonstrated that atypical language dominance in the right hemisphere was considerably more common in healthy right-handed subjects than previously suspected (Knecht et al., 2000).

Articles III and IV further demonstrated that enhanced right hemispheric responses to speech stimuli were associated with poorer performance in later receptive and verbal memory measures. Interestingly, earlier receptive language and verbal memory skills have been shown to predict later language development in behavioral studies with older children with familial risk for dyslexia (Gallegher et al., 2000; Lyytinen, Poikkeus, et al., 2001; Scarborough, 1990). The fact that brain activation differences in the present dissertation could be obtained already shortly after birth, suggests that there could be an early biological factor, perhaps genetic in nature, that contributes to the development of the later receptive language and verbal memory skills.

There is evidence of strong genetic control in the development of, for example, Wernicke's language areas (Thompson & Toga, 2002), which are involved in the comprehension of complex verbal information (see e.g., Lesser et al., 1986). As stated, for example, by Pennington (1991b), genetic factors can conceivably alter brain development through a large number of different pathways, and the parameters of brain structure affected would be, for example, neuronal number, neuronal migration, and axonal connectivity, all of which are determined with few exceptions before birth. It could thus be speculated that the genetic factors which could contribute to the enhanced right hemispheric processing of the speech stimuli in the at-risk infants in the present dissertation, could also have an effect on anatomical and functional differences related to the role of the right hemisphere in older dyslexics.

In anatomical studies of older individuals with dyslexia, observations have been made concerning larger temporal (Dalby et al., 1998) and posterior areas (angular gyrus and posterior pole: Duara et al. 1991) in the right hemisphere, larger neurons on the right than on the left side of the medial geniculate nuclei (MGN) of the thalamus (suggested to be a sub-system handling rapid temporal transitions according to Galaburda et al., 1994), and deviations from the usual pattern of left greater than right planum temporale asymmetry (Galaburda et al., 1985; Humphreys et al., 1990; Hynd et al., 1990; Larsen et al., 1990). It has been speculated that the findings of altered planum temporale asymmetry may be related to qualitative alterations in the functional properties of the system, which in turn, may result, for example, in phonological coding deficits among individuals with dyslexia (Pennington, 1991b; van der Leij et al., 2001). There are, however, also studies that have not replicated the results of reduction or reversal of the normal leftward asymmetry of the planum temporale that could

be an index of risk factor for developmental disorders of language and reading (Heiervang et al., 2000; Preis et al. 1998; Rumsey et al., 1997). Furthermore, as noted by Eckert and Leonard (2000), the results of imaging studies of the planum temporale have been inconsistent, perhaps due to diagnostic uncertainty, technical differences in measurement criteria, and inadequate control of handedness, gender, and cognitive abilities.

There is also evidence for more prominent activation of the right hemisphere in individuals with dyslexia as reported in the EEG study by Rippon and Brunswick (2000). Furthermore, Erez and Pratt (1992) reported differences in the ERPs of children with dyslexia and suggested that these reflect language processing in the right hemisphere in these children. Functional studies in older individuals with dyslexia have also shown differences in the asymmetric nature of brain activation, and usually these differences are related to reduced left hemisphere activation, especially in the temporal lobes. However, there is also evidence of rightward asymmetry of brain activity. In PET studies by Rumsey et al. (1992) and Gross-Glenn et al. (1991), increased activation was found in the right temporal regions. Such over-activation in the right hemisphere could be due to compensatory processes in tasks that are difficult for individuals with dyslexia. In the latter study, this enhanced activation was localized in the posterior right hemisphere (lingual lobule). Shaywitz et al. (1998) also found higher activation at the posterior aspect of the inferior and middle temporal gyri and the anterior aspect of the lateral occipital gyrus of the right hemisphere in an fMRI study of adults with dyslexia. The results of enhanced posterior activation in the right hemisphere of older individuals with language problems could reflect similar enhanced activation in the right parietal channels of the at-risk group that was found in the feature detection paradigm in the present dissertation.

The present dissertation showed that ERPs can be used to predict later language development in children with and without familial risk for dyslexia. However, as noted by Leppänen et al. (2003), a number of factors need to be considered before ERP techniques can be regarded as a clinical tool for diagnostic purposes. For example, there is a lack of normative developmental data with common recording and analysis criteria which would allow us to estimate deviations from the normal range. There is also individual variation in ERPs, and test-retest reliability needs to be improved. It is also important to clarify whether distinct features of different ERP components are specific to different disorders, and such profiles need to be linked with behavioral measures.

Concluding remarks

The present dissertation showed group differences in speech processing of newborns with and without familial risk for dyslexia. These differences were associated with later language development. These findings were strikingly clear in light of the fact that only approximately half of the at-risk infants are estimated to actually have a genetic predisposition for dyslexia (Pennington, 1995). These group differences cannot be explained by the perinatal factors because there were no group differences in the birth variables between at-risk and control infants. There were also no group differences in the parent-related factors such as educational status and IQ. The fact that these group differences could already be obtained so shortly after birth thus suggests that there could be an early biological factor, perhaps genetic in nature, that contributes to the development of later language and verbal memory skills.

In conclusion, the present dissertation demonstrated that newborn ERPs predict later language skills in children with and without familial risk for dyslexia. Overall, the more positive responses, both in the feature and change detection paradigms in the right hemisphere, which is not thought to be specialized in speech processing, were associated with poorer performance on later language and verbal memory skills. These results are in line with the assumption of lower processing level involvement in the language deficits, where the speech processing deviations, such as altered perceptual or discrimination processes, may underlie the difficulties in later language skills. These kinds of consistent differences in ERPs may have future applications for the early identification of children at risk for developmental language problems. This would further facilitate well-directed interventions even before language problems are typically diagnosed. In the forthcoming phases of our longitudinal project, we will further examine how these kinds of hemispheric differences in ERPs relate to reading skills and the possible diagnosis of dyslexia.

YHTEENVETO

Vastasyntyneiden aivovasteet puheäänteiden ja niiden muutosten havaitsemisessa sekä myöhemmän kielen kehityksen ennustamisessa dysleksiariskilapsilla

Kehityksellistä dysleksiaa eli lukemisen erityisvaikeutta pidetään periytyvänä ongelmana. Tässä väitöskirjassa tutkittiin kielellisen prosessoinnin eroja dysleksiariski- ja kontrollivauvojen välillä. Tutkimukset toteutettiin osana Jyväskylän yliopiston Lapsen kielen kehitys ja geneettinen dysleksiariski (LKK) – pitkittäistutkimushanketta. Riskiryhmään kuuluvat vauvat olivat perheistä, joissa toisella tai molemmilla vanhemmilla oli diagnosoitu dysleksia sekä vastaavanlaisia lukemisen ongelmia myös lähisuvussa. Kontrolliryhmän perheissä kyseisiä ongelmia ei esiintynyt. Vastasyntyneiden tutkimisen yhtenä motiivina oli selvittää perinnöllisten tekijöiden roolia mahdollisissa aivojen prosessointieroissa ennen kuin laajempi kielellinen ja sosiaalinen ympäristö vaikuttavat aivojen organisoitumiseen.

Vastasyntyneiden kielellisen prosessoinnin eroja ryhmien välillä tutkittiin aivojen herätevasteiden (event-related potentials, ERPs) avulla. Ärsykkeinä käytettiin konsonantti-vokaalitavuja (/ba/, /da/ ja /ga/), jotka esitettiin samalla todennäköisyydellä ja pitkillä aikaväleillä. Tämänkaltaisen koeasetelman ajatellaan heijastavan yleistä puheäänten piirteiden prosessointia. Tulokset osoittivat, että vastasyntyneiden puheäänten piirreprosessointi erosi riski- ja kontrollivauvojen välillä. Selkeimmät aivopuoliskoerot ryhmien vasteissa tapahtuivat n. 540–630 millisekuntia ärsykkeiden esittämisestä (aikaväli määritettiin pääkomponenttianalyysin avulla), jolloin riskiryhmän vasteet /ga/ -tavuun olivat selkeästi suurempia ja positiivisempia oikeassa aivopuoliskossa. Tässä ärsykkeessä konsonantti-vokaali –transitio (toisen formantin taajuus) oli suunnaltaan laskeva ja kestoltaan pisin verrattuna /ba/ ja /da/ ärsykkeisiin. On siis mahdollista, että nämä ärsykkeen ominaisuudet (etenkin transition pitempi kesto) aiheuttivat riskiryhmän aivojen reagoinnissa sen, että polariteetiltaan positiivinen herätevaste palautui negatiiviseksi myöhemmin kuin muiden ärsykkeiden vasteet. Yhtenä mahdollisena syynä tähän voidaan olettaa olevan riskiryhmän synkronisen aktivaation synnyttämän hermoverkkojen hitaampi palautuminen ei-aktiiviseksi. Samankaltaisia tuloksia riskiryhmän oikean aivopuoliskon korostuneesta osuudesta kielellisten ärsykkeiden prosessoinnissa on löydetty myös aikaisemmissa ERP tutkimuksissa LKK-projektissa (Leppänen ym., 1999; Pihko ym., 1999). Tuloksemme ovat mielenkiintoisia neuropsykologiseen teoriataustaan nähden, jonka mukaan normaali kielellisen prosessointi tapahtuu vasemmassa aivopuoliskossa.

Väitöskirjan toisena keskeisenä teemana oli tutkia mahdollisuutta käyttää herätevasteita myöhemmän kielellisen kehityksen ennustajina. Tulokset osoittivat, että riskiryhmälle tyypilliset positiivisemmat ja pitempikestoiset vasteet /ga/ ärsykkeeseen oikeassa aivopuoliskossa ennustivat heikompia vastaanottavan kielen taitoja 2.5 vuoden iässä. Samankaltainen prosessointitapa vasemmassa aivopuoliskossa oli yhteydessä heikompiin lyhytkestoisen muistin taitoihin 5 vuoden iässä.

Vastasyntyneiden herätevasteiden ennustearvo todennettiin myös toisessa koeasetelmassa, jossa lyhyin välein toistettu ns. standardi ärsyke (/kaa/) korvattiin satunnaisesti vokaalin keston suhteen poikkeavalla ärsykkeellä (/ka/). Tämänkaltaisella koeasetelmalla pyrittiin tutkimaan vastasyntyneiden reaktioita puheäänissä tapahtuviin muutoksiin, joka puolestaan heijastaisi sensorisen muistin toimintaan perustuvia erotteluprosesseja. Riski- ja kontrolliryhmän vasteet erosivat toisistaan 290–320 ms aikavälillä (määritetty pääkomponenttianalyysin avulla), jolloin riskiryhmän vasteet poikkeavaan /ka/ ärsykkeeseen oli selvästi positiivisempi oikeassa aivopuoliskossa. Tulokset korostuneesta ärsykkeiden erotteluprosessista riskiryhmän oikeassa aivopuoliskossa olivat yhteneviä piirreprosessoinnin löytöjen kanssa. Myös vasteet usein toistettuun /kaa/ ärsykkeeseen olivat positiivisemmat riskiryhmässä.

Vasteet ärsykkeisiin ennustivat myöhempiä taitoja vain riskiryhmässä. Positiivisemmat vasteet usein toistettuun /kaa/ -ärsykkeeseen vasemmassa aivopuoliskossa olivat yhteydessä heikompiin vastaanottavan kielen taitoihin 2.5 ja 3.5 vuoden iässä sekä heikompiin lyhytkestoisen muistin taitoihin 5 vuoden iässä. Tulosten tulkittiin liittyvän riskiryhmälle ominaiseen yleiseen reagoituvuuteen, joka olisi epäedullista myöhemmän kielellisen kehityksen kannalta. Suuremmat positiivisemmat vasteet poikkeavaan /ka/ ärsykkeeseen (muutoksen havaitseminen) vasemmalla aivopuoliskolla, jossa teorian mukaan kielellinen prosessointi pääasiassa tapahtuu, ennustivat parempaa suoriutumista vastaanottavan kielen tehtävissä 2.5 vuoden iässä sekä lyhytkestoisen kielellisen muistin tehtävissä 3.5 vuoden iässä. Vokaalin keston erottelu oikeassa aivopuoliskossa, jossa kielellistä informaatiota ei pääasiallisesti käsitellä, sen sijaan ennusti heikompia lyhytkestoisen muistin taitoja 5 vuoden iässä.

Väitöskirjan tulokset osoittavat, että vastasyntyneiden aivojen herätevasteet ennustavat myöhempää kielen kehitystä dysleksiariskilapsilla. Riskiryhmälle ominaiset korostuneet oikean aivopuoliskon vasteet kielellisten ärsykkeiden piirteiden ja erojen prosessoinnissa ennustivat heikompia myöhempiä vastaanottavan kielen ja lyhytkestoisen muistin taitoja. Tämänkaltaisia tuloksia voidaan tulevaisuudessa hyödyntää esimerkiksi varhaisina ennusmerkkeinä kielellisistä pulmista. Tämä puolestaan mahdollistaisi entistä varhaisemmat kuntoutus- ja tukitoimenpiteet, joilla voitaisiin ennaltaehkäistä tai lieventää kielen kehityksen vaikeuksia. Jatkotutkimuksillamme on tarkoitus selvittää miten

nämä varhaiset aivopuoliskoerot kielellisessä prosessoinnissa ovat yhteydessä mahdollisiin lukemisen vaikeuksiin.

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