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Kaisa Lohvansuu

Brain responses to speech sounds in infants and children with and without familial risk for dyslexia

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JYVÄSKYLÄ 2015

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ABSTRACT

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Dyslexia, a specific reading disability, runs in families. Therefore, the risk for a child to become dyslexic increases multifold if reading difficulties occur in the family. One risk factor for dyslexia is a deficit in speech perception. Using EEG, speech sound discrimination was found to be more demanding than non-speech discrimination in typical readers in Study I. In Study II, in children with dyslexia in 3rd grade, enhanced brain responses were observed and found to be associated with better performance in reading accuracy, spelling accuracy and phonemic length discrimination tasks. The brain responses of the most accurate readers in the dyslexia group originated from a more posterior site of the right auditory cortex, suggesting the employment of compensatory brain-processing for changes in phonemic length. In Study III, the brain responses of six-month-old infants at risk for dyslexia were found to predict their reading speed in adolescence at 14 years. The prediction was mediated via preschool-age rapid naming speed, which suggests that the same cognitive processes are needed in both fluent reading and naming. Possibly those common processes are related to automatization of the retrieval process from a mental lexicon via phonological representations. Atypical brain activation to speech in infancy seems to implicate a deficient development of phonological representations in at-risk infants that later hinders lexical access. These results indicate that even if a child is born with an increased risk for dyslexia, the risk is not insurmountable. Overall it seems that accurate speech perception, well-developed speech sound representations and automatized access to them are necessary for the development of fluent reading. This information is important in developing remediation for children at increased risk for dyslexia.

Keywords: dyslexia, familial risk, speech perception, electroencephalography (EEG), event-related potentials (ERP), infants, children

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TIIVISTELMÄ (FINNISH ABSTRACT)

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Aivojen herätevasteet puheääniin vauvoilla ja lapsilla, joilla on perinnöllinen lukivaikeusriski
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Dysleksia on perinnöllinen oppimisvaikeus. Siksi lapsella on monikertainen riski kohdata lukemisvaikeuksia kouluiässä, jos niitä on esiintynyt hänen vanhemmillaan tai muilla sukulaisillaan. Puheen kontrastien havaitseminen on dyslektikoille vaikeaa. Tässä tutkimuksessa tarkasteltiin lukiriskivauvojen ja kouluikäisten lukiriskilasten sekä tyypillisesti lukevien kontrollilasten aivojen tuottamia herätevasteita äänisarjoissa tapahtuviin puheen kontrasteihin. Lisäksi tutkittiin aivovasteiden yhteyttä lukemisen taustataitoihin esikouluiässä sekä lukemiseen ja kirjoittamiseen kouluiässä. Ensimmäisessä osatutkimuksessa tarkasteltiin tyypillisesti lukevien kouluikäisten lasten esitietoista kykyä havaita vokaalin muutoksia ja vokaaleja vastaavien monitaajuuksisien ei-puheäänten muutoksia. Havaittiin, että muutoksen havaitseminen puheäänisarjasta on viivästynyttä verrattuna havaitsemiseen monitaajuuksisien ei-puheäänten sarjasta. Toisessa osatutkimuksessa selvisi, että dyslektikoiden poikkeuksellisen suuret aivovasteet konsonantin lyhenemiseen olivat yhteydessä tarkempaan lukemiseen ja kirjoittamiseen. Tarkimmin lukevilla dyslektikoilla aivoaktivaatio puheeseen syntyi taaempana oikealla kuuloaivokuorella kuin muilla ryhmillä, mikä viittaisi korvaavien aivoprosessien käyttöönottoon eli kompensaatioon. Kolmannessa osatutkimuksessa havaittiin lukiriskivauvojen herätevasteiden epäsanoihin eroavan kontrollivauvojen aivovasteista ja ennustavan lukemisen nopeutta 8. luokalla. Ennustevaikutus välittyi esikouluiän nimeämisnopeuden kautta. Tästä pääteltiin, että samojen kognitiivisten prosessien, mahdollisesti fonologisten muistijälkien kautta tapahtuvan mielensisäisestä sanavarastosta haun, automatisoituminen sujuvoittaisi suoritusta sekä nimeämis- että lukemistehtävässä. Poikkeava aivoaktivaatio vauvana olisi siten varhainen merkki puutteellisesti kehittyvistä fonologisista muistijäljistä. Kokonaisuudessaan tulokset osoittavat, että tarkka puheen kontrastien havaitseminen, hyvin kehittyneet puheäänten pitkäkestoiset muistijäljet ja automatisoituneet yhteydet muistijälkiin ovat tarpeellisia tekijöitä siksi, että lapsesta voisi kehittyä sujuva lukija. Vaikka lukivaikeusriski on vaikea voittaa, se ei ole kuitenkaan mahdotonta. Se, miksi osa lapsista riskin voittaa, mutta kaikki eivät, kaipaa vielä jatkotutkimuksia.

Avainsanat: dysleksia, suvullinen riski, puheen havaitseminen, herätevasteet, vauvat, lapset

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LIST OF ORIGINAL PUBLICATIONS

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III Lohvansuu, K., Hämäläinen, J. A., Ervast, L., Lyytinen, H., & Leppänen, P. H. T. Infant brain responses at 6 month predict reading at 14 years. *Submitted manuscript.*

Taking into account the instructions given and comments made by the co-authors, the author of the thesis conducted the data analyses and wrote the reports of the three publications. In Study I she participated in the study designing and had a significant role in the stimulus preparation, data collection and coordination. In Studies II and III she used the previously collected data.

FIGURES

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CONTENTS

1 INTRODUCTION

Dyslexia is a common learning disability affecting approximately 10% of school-aged children (Lyon, Shaywitz, & Shaywitz, 2003; Vellutino, Fletcher, Snowling, & Scanlon, 2004). Although the relationship between auditory and speech processing problems and reading problems has been found decades ago and has been well explored, there is still a theoretical gap in understanding the causality of speech processing problems leading to manifestations of dyslexia. The neural basis of dyslexia is also partly unknown. The objective of the current research was to investigate speech processing in infants and children with and without a familial risk for dyslexia, and therefore, event-related potentials (ERPs) were measured. Another aim was to study how brain activation to speech in infancy and childhood is associated with reading-related cognitive skills of preschool age and with reading of school age. The third aim was methodological: to define the latency of change detection processing of speech and corresponding non-speech stimuli in children.

1.1 Background and causal factors of dyslexia

Dyslexia is a neurological disorder that impairs learning to read and write in normally developing children, independent from cognitive level, training, and other extraneous factors (Lyon et al., 2003; Norton, Beach, & Gabrieli, 2015; Vellutino et al., 2004). Genetic factors behind dyslexia have been demonstrated: in studies inspired by the early observation of dyslexia running in families, a number of susceptibility genes for dyslexia have been found operating via neuronal migration and axonal guidance during the prenatal period (Galaburda, 2005; Lyon et al., 2003; Lyytinen et al., 2004; Pennington, Gilger, Pauls, Smith, Smith, & DeFries 1991; Scerri & Schulte-Körne, 2010; Vellutino et al., 2004). However the phenotypic appearance of dyslexia results from a very complicated combination of genes and environmental factors. It seems that, similar with other complex disorders, there is no single necessary, sufficient,

and specific cause of dyslexia (Pennington, 2006). Instead, dyslexia can be seen as a condition that is caused by cumulative genetic and environmental risk factors which interact and induce several cognitive dysfunctions (Pennala et al., 2013; Pennington, 2006; Willcutt et al., 2010). Molecular genetic studies give support for a multiple risk factor explanation because of the lack of replicability, conflicting findings of risk factors, and small effect sizes (Cardon, Smith, Fulker, Kimberling, Pennington, & DeFries, 1994; Cardon, Smith, Fulker, Kimberling, Pennington, & DeFries, 1995; Fisher & DeFries, 2002; McGrath, Smith, & Pennington, 2006; Willcutt et al., 2010). Furthermore, it has been shown, for example, that the effect of dyslexia susceptibility genes on reading level is mediated by white matter volume (Darki, Peyrard-Janvid, Matsson, Kere, & Klingberg, 2012).

1.1.1 Language-related structural and functional abnormalities in dyslexic brain

The brain basis of dyslexia is still partly unsolved. There is, however, strong evidence for neurobiological risk factors for dyslexia (for reviews, see Démonet, Taylor, & Chaix, 2004; Habib, 2000; Richlan, Kronbichler, & Wimmer, 2011, 2013). In areas relevant to auditory and speech processing, both functional and structural abnormalities have been reported in dyslexic brains (Galaburda, Sherman, Rosen, Aboitiz, & Geschwind, 1985; Richlan et al., 2011, 2013). The risk factors related to speech include abnormalities at perisylvian regions. For example, these include reduced gray matter volume at posterior Sylvian areas (Richlan et al., 2013), neuronal ectopias and microgyria around the Sylvian fissure (Galaburda et al., 1985), and abnormal activation and connectivity in posterior and perisylvian systems (Démonet et al., 2004).

Functional neuroimaging studies have revealed a predominantly left-hemispheric cortical reading network, including frontal, temporo-parietal and occipito-temporal cortical regions, that is deficient in children and adults with dyslexia. Both hypoactivation and hyperactivation at reading-related brain areas have been described in reviews and meta-analyses (Brunswick, McCrory, Price, Frith, & Frith, 1999; Démonet et al., 2004; Eden & Zeffiro, 1998; Richlan et al., 2011). Structural connectivity and volume of the white matter tracks, left superior corona radiata and left arcuate fasciculus connecting anterior and posterior language regions of the human brain are deficient in adult dyslexics between regions of the reading network and related to poor reading skills (Vandermosten, Boets, Poelmans, Sunaert, Wouters, & Ghesquière, 2012; Vandermosten, Boets, Wouters, & Ghesquière, 2012). In kindergartners at risk for dyslexia, better phonological awareness, but not rapid naming or letter naming, was positively correlated with the volume of the left arcuate fasciculus being smaller and having less integrity (Saygin et al., 2013). A consistent finding across neurofunctional studies is left ventral occipito-temporal dysfunction, which has been reported in both children and adults with dyslexia; hypoactiva-

tion in superior temporal regions was found for adults only (Richlan et al., 2011).

Autopsies and brain-imaging studies have reported anatomical differences between dyslexics and controls (Eckert, 2004; Galaburda et al., 1985; Habib, 2000; Richlan et al., 2013). In post-mortem studies, the most consistent physiological abnormalities seen are ectopias and microgyria. Ectopias are dislocated nests of neurons from the ventricles to the first cortical layer (Galaburda et al., 1985). Microgyria are minor gyri in the cortex affecting language areas (Galaburda, 1999). In dyslexic brains, ectopias and migrogyria are seen mostly in the left perisylvian regions (Galaburda, 1999; Galaburda, 2005; Galaburda et al., 1985; Ramus, 2004). Both ectopias and microgyria most probably develop due to disrupted neuronal migration during the fetal period. Reduced gray matter volume has been detected at posterior Sylvian areas, which are relevant for speech and reading processing (Frye, Liederman, Malmberg, McLean, Strickland, & Beauchamp, 2010; Richlan et al., 2013; Steinbrink et al., 2008). These changes in gray matter suggest differences in dyslexic's brains to originate from early cortical development because gray matter volume is determined during prenatal brain development (Frye et al., 2010).

Dyslexic brains have been reported to have more symmetrical hemispheres in general, as well as being more symmetrical in specific brain structures (Galaburda, LeMay, Kemper, & Geschwind, 1978; Galaburda et al., 1985; Illingworth & Bishop, 2009; Leonard & Eckert, 2008; Sun, Lee, & Kirby, 2010). In dyslexics the gray matter volume in the right superior temporal gyrus and left superior temporal sulcus has been found to be consistently reduced across studies, and the reduction was found to be associated with reading-related underactivation in the left superior temporal sulcus (Richlan et al., 2013). Reduced leftward asymmetry of the planum temporale in the posterior Sylvian fissure has been observed, compared to controls (Galaburda et al., 1978; Galaburda et al., 1985; Illingworth & Bishop, 2009; Leonard & Eckert, 2008; Sun et al., 2010). However, an extreme leftward asymmetry of the planum temporale has also been reported in compensated dyslexic adults with familial risk, which has been suggested to be a consequence of enhanced top-down processing (Chiarello et al., 2006; Leonard et al., 1993). It has been stated that probably deviation in both directions from average on a symmetry-asymmetry scale can lead to deficient reading skills: small symmetrical brain structures would be associated with deficits in multiple domains of language and larger asymmetrical structures with more isolated phonological deficits that are compensated for until adulthood (Leonard & Eckert, 2008). Across studies, reduced or reversed asymmetry has been seen systematically in dyslexics and thought to be related to deviations in normal patterns of corticogenesis (Hynd, Semrud-Clikeman, Lorys, Novey, & Eliopulos, 1990; Shapleske, Rossell, Woodruff, & David, 1999). The brain symmetry in dyslexics suggests anatomical differences in areas relevant for speech and language (Galaburda et al., 1985; Petersen, Fox, Posner, Mintun, & Raichle, 1988). Deficits linked to the anatomical differences in dyslex-

ics include speech processing problems, which probably is causal to phonological deficits (e.g., Blomert, 2011; Price, 2012).

1.1.2 Cognitive profile and characteristics of dyslexia

Typical cognitive deficits underlying dyslexia can be broken into three types: visual deficits, language and language-based deficits, and low-level auditory deficits (Hämäläinen, Salminen, & Leppänen, 2013; Vellutino et al., 2004). Of these, the current research concentrates on deficits in language but especially on speech perception-related deficits. Furthermore, language and language-based deficits can be divided into semantic and syntactic deficits (like vocabulary deficits) and phonological deficits, but a double-deficit hypothesis has also been introduced. The double-deficit hypothesis suggests the existence of three subtypes of reading disability: phonological deficits (like phonological awareness and letter-sound decoding), a rapid naming deficit that disrupts orthographic processing and reading speed, or both of the aforementioned types of deficits (Bowers & Wolf, 1993; Wolf & Bowers, 1999; Wolf et al., 2000). Rapid automatized naming (RAN) is a task of naming a series of familiar items as quickly as possible (Denckla & Rudel, 1976). RAN has been found to be linked to reading via lower-level cognitive processes, like automatization of (lexical) retrieval processes (Denckla & Rudel, 1976; see Georgiou & Parrila, 2013, and Norton & Wolf, 2012, for recent reviews). Through the years, however, many – even contradictory – definitions have been suggested, including efficiency, automatization and quality of visual-verbal access, but also speed of lexical access, speed or automaticity of phonological access or lexical retrieval, and even general processing speed (for reviews, see Norton & Wolf, 2012; Vukovic & Siegel, 2006). In dyslexics, early failure to develop automaticity in the lower-level retrieval processes impacts the reading process (Denckla & Rudel, 1976). In adult average readers, functional magnetic resonance imaging (fMRI) during RAN revealed neural activation in the areas related to eye movement control, attention, and reading including the inferior frontal cortex, temporo-parietal areas, and the ventral visual stream (Misra, Katzir, Wolf, & Poldrack, 2004). The inferior frontal areas of the reading network activated similarly, regardless of the task of naming objects or letters, but posterior areas activated more during letter naming task. In dyslexic readers, reduced activation in the posterior lobe during alphanumeric rapid naming tasks has been reported (Lymberis, Christodoulou, O'Loughlin, Del Tufo, & Gabrieli, 2009).

It is worth noting that dyslexia is not determined by cognitive profiles: individuals with similar profiles may or may not be diagnosed as a dyslexic (Vellutino et al., 2004). In addition, familial risk negatively influences reading acquisition in spite of adequate performance in rapid naming and phonological awareness (Torppa et al., 2012; Puolakanaho et al., 2008). The transparency of orthography also has an effect on dyslexia: with its opaque orthography, English is much more challenging to learn to read compared to very transparent languages like Finnish, with almost one-to-one consistent mapping between letters and phonemes. Therefore, the rate of learning to read in transparent or-

thographies is faster than that of children learning to read less transparent languages (Harris & Hatano, 1999; Seymour, Aro, & Erskine, 2003). In fact, children learning to read the more transparent languages read rather accurately and fluently at a basic level after the first school year (Seymour et al., 2003), and their phoneme awareness also develops faster (Cossu, 1999). Consequently it has been argued that the predictive ability of rapid naming and phonology on subsequent reading achievement varies in relation to the transparencies of the languages: phonological skills play a more significant role in opaque orthographies, compared to rapid naming in transparent languages (Bradley & Bryant, 1983; de Jong & van der Leij, 1999; Kirby, Georgiou, Martinussen, & Parrila, 2010; Wimmer, Landerl, & Schneider, 1994). However, not all studies support this claim (Landerl et al., 2012).

1.1.3 Speech perception deficits in dyslexia

Dyslexia, as well as a familial risk for dyslexia, has been shown to be strongly connected to deficits in speech perception (Hämäläinen et al., 2013; Leppänen et al., 2012; Lyytinen et al., 2008; Pennala et al., 2010; van der Leij, Bergen, van Zuijen, Jong, Maurits, & Maassen, 2013; van Zuijen, Plakas, Maassen, Maurits, & van der Leij, 2013). At birth, infants have the possibility to learn the phonemic contrasts needed to learn all the languages. Until six months of age, however, the speech perception system specializes itself in contrasts essential for the language/languages frequently heard by the infant. In quantity languages, like Finnish and Japanese, phonemic length is a semantically distinguishing feature and therefore essential to be differentiated (Lidestam, 2009; Richardson, 1998; Tervaniemi et al., 2006). Phonemic length must be categorized as long or short in relation to other phonemes within a word (Suomi, Toivanen, & Ylitalo, 2008; Vainio, 2001). The failure to perceive the quantity differences is one of the characterizing deficits in Finnish dyslexics: quantity errors are the most common errors in reading and spelling in Finnish adult dyslexics (Lyytinen, Leinonen, Nikula, Aro, & Leiwo, 1995). The ERP responses to syllables with changes in vowel or consonant duration reveal differences between children at risk for dyslexia and control children already at birth and early childhood (Guttorm, Leppänen, Richardson, & Lyytinen, 2001; Guttorm, Leppänen, Tolvanen, & Lyytinen, 2003; Leppänen, Pihko, Eklund, & Lyytinen, 1999; Leppänen et al., 2002; Pihko, Leppänen, Eklund, Cheour, Guttorm, & Lyytinen, 1999), and differences continue in childhood and adulthood (e.g., Hämäläinen et al., 2013; Kujala et al., 2006; Lovio, Näätänen, & Kujala, 2010; Sharma et al., 2006).

However, gateway which connect problems in speech perception with the manifestation of dyslexia are still partly unknown (for a review, see Protopapas, 2014). Theories have been proposed to explain the route from auditory and speech processing deficits to reading problems (bottom-up route, see Figure 1). One of the theories, the rapid auditory temporal processing (RATP) theory, suggests that language-impaired persons and dyslexics are unable to perceive rapid (< 75 ms) auditory stimuli if presented in sequences with short (< 200 ms) interstimulus intervals (Tallal, 1980; Tallal & Piercy, 1973). This line of studies is

well established, but not commonly agreed on (for a review, see Farmer & Klein, 1995; Tallal, 2004). A more recent theory proposes that perception of sharpness of the amplitude increase in speech (i.e., rise time discrimination) would be impaired in dyslexics (Goswami, 2011; Goswami et al., 2002). Rise time discrimination has been suggested to cause problems in phonological processing, the ability to manipulate speech sound components, and reading skills.

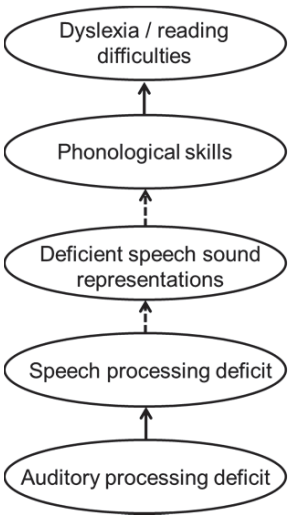

FIGURE 1 Simplified illustration of potential impact of auditory processing on dyslexia.

What is known is that phonological skills are deficient in, and most probably causal to, dyslexia (Goswami, 2002; Ramus, 2003; Snowling, 2000; Stanovich, 1988; Torgesen, Wagner, Rashotte, Burgess, & Hecht, 1997; Vellutino et al., 2004; Wagner & Torgesen, 1987). Auditory or speech processing deficits have been suggested to lead to phonological deficits via inaccurate or inadequate phonological representations (Elbro, Borstrøm, & Petersen, 1998; Griffiths, & Snowling, 2002; McBride-Chang, 1995; Mody, Studdert-Kennedy, & Brady, 1997; Snowling, 2000). Poor speech perception abilities in dyslexics are seen as difficulties to discriminate and categorize speech sound contrasts like syllables, consonants and vowels (e.g., Bradley & Bryant, 1978; Godfrey, Syrdal-Lasky, Millay, & Knox, 1981; Manis et al., 1997; Mody et al., 1997; Pennala et al., 2010; Reed, 1989).

Phonetic discrimination and speech perception are crucial for language development and reading acquisition (i.e., at neural level for formation of distinct phonological representations). Defective representations probably impede the learning of fluent and automatic decoding of phoneme-grapheme correspondences, leading to reading and spelling difficulties (Elbro et al., 1998; Pasquini, Corriveau, & Goswami, 2007; Share, 1995; Snowling, 2000; Talcott & Witton, 2002). Nevertheless, the route of the phonological deficit leading to dyslexia is not yet fully established and indeed top-down effects also have been suggested. The deficits in higher linguistic processes at sub-lexical and lexical levels have been argued to be a cause for phonological problems and lower-level

problems would just co-occur, but not as causal for dyslexia (Ramus et al., 2003; White et al., 2006). Brain research has also shown top-down effects for reading and dyslexia: learning to read has been reported to enhance phonological activation to speech in the planum temporale (Dehaene et al., 2010), with brain-level abnormalities in the reading network in dyslexics being the consequence of different reading experiences (Clark et al., 2014). However, it is also possible that bottom-up versus top-down effects vary across languages because of the differences in their orthographic transparency.

1.2 Brain event-related potentials in studying speech perception

Speech perception is often studied using event-related potentials (ERPs). In particular, speech sound discrimination has been frequently studied using discriminative ERP components; mainly mismatch negativity (MMN) but also late discriminative negativity (LDN) are thought to be pre-attentive indices of cortical accuracy of sound processing. Both discriminative and obligatory ERPs capture low-level processing, and since they are not influenced by level of motivation, attention or arousal, or behavioral and performance-related demands to the same degree as in behavioral measurements, they provide a reliable and objective measure of speech perception in children (for reviews, see Bishop, 2007; Näätänen, Jacobsen, & Winkler, 2005; Schulte-Körne & Bruder, 2010). Brain research methodologies like ERPs also provide an opportunity to study speech, language and reading-related processes at a very early age, far before children begin to speak or read.

1.2.1 Event-related potentials as signatures of atypical speech perception in dyslexia

In studies investigating speech sound discrimination, usually abnormally small change detection responses have been reported in dyslexics (e.g., Bishop, 2007; Kujala et al., 2006; Maurer, Bucher, Brem, & Brandeis, 2003; Schulte-Körne, Deimel, Bartling, & Remschmidt, 1998), but abnormally large obligatory responses have been found (e.g., Hämäläinen et al., 2013; Helenius, Salmelin, Richardson, Leinonen, & Lyytinen, 2002).

Using event-related potentials (ERPs), the brain activity associated with auditory as well as speech processing has been studied in children at different ages with and without familial risk for dyslexia (for reviews see Leppänen et al., 2012; Lyytinen et al., 2008) in the Jyväskylä Longitudinal Study of Dyslexia (JLD, see Lyytinen, 1997; Lyytinen et al., 2001). The stimuli have been chosen to represent the features of language which are important to differentiate, but are seen to be difficult for dyslexic readers. In the quantity languages, including Finnish, phonemic length is a semantically distinguishing feature, and the quantity errors are the most common reading and spelling errors (Lyytinen, Leinonen, Nikula, Aro, & Leiwo, 1995). Furthermore, problems in phonemic

length discrimination have been shown to be associated with reading accuracy (Pennala et al., 2010). Therefore, pseudo-words varying either in consonant or vowel duration have been used for Finnish speakers. In studies investigating vowel duration, atypically large (more positive or more negative, depending on the time window) responses in at-risk infants were observed, compared to controls at birth and at the age of 6 months (Leppänen, Pihko, Eklund, & Lyytinen, 1999; Pihko et al., 1999). Also in regard to consonant duration, atypically large responses were found in 6-month-olds as well as in 6.5-year-olds (Hämäläinen et al., 2013; Leppänen et al., 2002). Atypical brain processing suggests that speech is processed differently in the brains of at-risk children.

1.2.2 The development of auditory ERP components

While the obligatory auditory ERPs have been exclusively studied in adults, much less is known about their emergence and functions in children. In the developmental studies, the naming of the components is varied: sometimes according to the adult components if they seem to correspond with the adult equivalents with small differences in latency and/or amplitude, but other naming conventions also exist. Moreover, it is not clear if these components at different ages are equivalent to each other in their functions (Čeponienė, Cheour, & Näätänen, 1998; Kushnerenko, Čeponienė, Balan, Fellman, & Näätänen, 2002). In adults, however, the functions of the components are known to a certain extent. The obligatory P1 and N1 responses have been suggested to reflect sensory encoding of auditory stimulus attributes (Näätänen & Picton, 1987), which are followed by a pronounced component N2 that is affected by attention and cognition, as well as by the probability, modality and intensity of the stimulus (Ponton, Eggermont, Kwong, & Don, 2000). The function of the P2 response is not clear, but similarly as P1 and N1, P2 indexes detection of the onset and offset of auditory stimuli and is modulated by attention (Crowley & Colrain, 2004; Näätänen, Gaillard, & Mäntysalo, 1978; Näätänen & Picton, 1987; Picton & Hillyard, 1974). In dyslexic children, the development of ERP components has been found to be delayed (Blomert, 2011; McArthur & Bishop, 2004), but the brain responses of compensated readers, who have a history of reading difficulty but are currently at an appropriate reading level, have been reported to be similar to controls of the same age (Sharma et al., 2006).

During development, brain physiology slowly changes, causing enormous changes in the morphology, latency, and amplitude of ERP responses (Bishop, Hardiman, Uwer, & Von Suchodoletz, 2007; Johnstone, Barry, Anderson, & Coyle, 1996; Moore & Guan, 2001; Ponton, Eggermont, Khosla, Kwong, & Don, 2002; Ponton et al., 2000). In early infancy, ERP waveforms are typically broad and they sharpen during maturation. Amplitudes in general decrease and latencies shorten with maturation (Leppänen, Eklund, & Lyytinen, 1997; Leppänen, Guttorm, Pihko, Takkinen, Eklund, & Lyytinen, 2004; Leppänen, Pihko, Eklund, & Lyytinen, 1999; Pihko, Leppänen, Eklund, Cheour, Guttorm, & Lyytinen, 1999; Ponton et al., 2000; Thomas & Crow, 1994). The shortening of the latencies is thought to result from myelination, synaptic density and neural

synchrony increase with age (Eggermont, 1988; Moore & Guan, 2001; Ponton et al., 2000; Thomas et al., 1997). It has also been stated that maturational changes are related to development of the thalamic-cortical portions of the central auditory system (Ponton et al., 2000). Until preschool the predominant morphology is P1-N2 complex, which begins to diminish in early school age at 7–8 years when the adult-like N1-P2 complex arises to take dominance by adulthood (Kushnerenko et al., 2002; Ponton et al., 2000).

P1 has a fronto-central distribution (Bruneau & Gomot, 1998; Čeponienė, Rinne, & Näätänen, 2002; Kurtzberg, Hitpert, Kreuzer, & Vaughan, 1984; Kurtzberg, Vaughan, Kreuzer, & Fliegler, 1995). In preschool children, P1 has been recorded at the latency of 80 ms (Ponton et al., 2002), with latency and amplitude declining with age, such that typical adult latency is observed to be 40–60 ms (Čeponienė et al., 2005; Cunningham, Nicol, Zecker, & Kraus, 2000; Ponton et al., 2000). The P1 response originates from the secondary auditory cortex, more specifically from the lateral part of the Heschl's gyrus (Liegeois-Chauvel, Musolino, Badier, Marquis, & Chauvel, 1994).

N1 peaks in children at 100–150 ms with fronto-central distribution, with the latency decreasing with age (Bruneau & Gomot, 1998; Čeponienė et al., 2002; Cunningham et al., 2000; Johnstone et al., 1996; Ponton et al., 2000; Sharma, Kraus, McGee, & Nicol, 1997; Tonnquist-Uhlén, Borg, & Spens, 1995; Wunderlich & Cone-Wesson, 2006). N1 has been reliably detected in childhood with long ISIs (> 1 s) only, showing increase with age (e.g., Čeponienė et al., 2002; Gilley, Sharma, Dorman, & Martin, 2005). In adults, N1 is elicited at 90–110 ms after the stimulus onset (Ponton et al., 2000). N1 has several sub-components, like frontal and supratemporal sub-components (Bruneau & Gomot, 1998; Näätänen & Picton, 1987).

P2 has more posterior topography than the other ERPs, especially in childhood (Oades, Dittmann-Balcar, & Zerbin, 1997; Ponton et al., 2002). It peaks at around 200–250 ms in young infants (Wunderlich & Cone-Wesson, 2006). Infants reach the adult latency range of 140–170 ms by the age of 15 months (Barnet, Ohlrich, Weiss, & Shanks, 1975; Johnstone et al., 1996; Ponton et al., 2000). Both amplitude increases and decreases with age have been reported (Wunderlich & Cone-Wesson, 2006). Altogether, the reported developmental changes concerning the P2 response are relatively small. The P2 response is thought to be generated by widespread sources in the planum temporale and the auditory association cortex (Crowley & Colrain, 2004; Godey, Schwartz, de Graaf, Chauvel, & Liégeois-Chauvel, 2001).

N2 (also often referred to as N250) is the most remarkable peak in childhood. N2 peaks at latency around 300–550 ms in early infancy, and it declines to around 220–245 ms until preschool age (Wunderlich & Cone-Wesson, 2006). Amplitude also gradually decreases in school age, stabilizing by early adulthood (Cunningham et al., 2000; Tonnquist-Uhlén, 1996; Wunderlich & Cone-Wesson, 2006). Curiously, it has been demonstrated that the N2 of 9-year-old children increases in size as a function of stimulus repetition (Karhu et al., 1997). N2 has fronto-central distribution (Čeponienė, Alku, Westerfield, Torki, &

Townsend, 2005) and bilateral sources in the supratemporal auditory cortex (Bruneau & Gomot, 1998).

The auditory change detection component mismatch negativity (MMN) peaks in adults around 100–200 ms after stimulus deviancy onset (Näätänen, 1992; Näätänen, Jacobsen, & Winkler, 2005; Näätänen et al., 2007). MMN is detectable from a very early age (Cheour, Leppänen, & Kraus, 2000; Kujala et al., 2004; Kushnerenko et al., 2002; Martynova, Kirjavainen, & Cheour, 2003). MMN reflects the change detection process for a deviating sound. It has been shown to be relatively stable over the course of lifetime, being highly comparable with the adult response by early school-age (Čeponienė et al., 1998; Cheour et al., 2000; Cheour, Korpilahti, Martynova, & Lang, 2001; Hämäläinen et al., 2008; Hämäläinen et al., 2011). However, in infancy its correspondence is sometimes called a mismatch response (MMR), because the polarity of the response can also be positive (Cheour et al., 2000; Dehaene-Lambertz, 2000; Leppänen et al., 2004; Maurer et al., 2003; Morr, Shafer, Kreuzer, & Kurtzberg, 2002).

The scalp distribution shows fronto-central negativity and polarity reversal below the Sylvian fissure, and the activity originates from at least two sources. The temporal source associated with sensory memory processing of the auditory features is generated bilaterally in the auditory cortex (Giard, Perrin, Pernier, & Bouchet, 1990; Näätänen, 1992; Näätänen et al., 1978). The frontal source with a right hemispheric predominance is generated from the frontal cortex and is related to the involuntary switching of attention to deviant stimuli (Giard et al., 1990; Gomot et al., 2000; Opitz, Rinne, Mecklinger, von Cramon, & Schröger, 2002; for a review, see Deouell, 2007).

Mismatch negativity is typically generated automatically and pre-attentively to deviations (e.g. frequency, duration and intensity changes) embedded among a repeated stimulus train in an oddball condition (Näätänen, 1992; Näätänen & Alho, 1997; Näätänen et al., 1978; Näätänen et al., 2005; Näätänen et al., 2007). Although the current view of the mechanism-generating MMN is that the divergence of sensory input (deviant stimuli) with the memory trace created by the repetition (standard stimuli) elicits MMN. An alternative explanation claims that the deviant stimulus merely activates new afferent neuronal populations causing the diverging response, and thus the detection of change (Jääskeläinen et al., 2004; May & Tiitinen, 2010; Näätänen, 1992; Näätänen et al., 2005; Paavilainen, Alho, Reinikainen, Sams, & Näätänen, 1991).

The MMN response can be difficult to separate from the obligatory ERP components N1 and N2 because they all overlap in time and space, producing a mixture of responses. Several studies controlling for the MMN-N1 overlap in adults exists (e.g., Campbell, Winkler, & Kujala, 2007; Horváth, Czigler, Jacobsen, Maess, Schröger, & Winkler, 2008; Jacobsen, Horenkamp, & Schröger, 2003; Jacobsen & Schröger, 2001; Jacobsen & Schröger, 2003; Schröger, 2007; Schröger & Wolff, 1996). In children, however, there is only one study using a control condition and it concerns maturation of N1 rather than separation of MMN from N1 (Ruhnau, Herrmann, Maess, & Schröger, 2011).

Another discriminative component, late discriminative negativity (LDN), is elicited around 400–600 ms (Čeponienė et al., 2004). It has been suggested to reflect further processing of the deviating sound (Čeponienė et al., 2004; Cheour et al., 2001; Kraus, McGee, Carrell, Sharma, Micco, & Nicol, 1993). LDN resembles MMN in being detectible from birth, being elicited by unattentive deviancy detection, and having fronto-central scalp distribution (Čeponienė et al., 2004). However, unlike MMN its amplitude diminishes with age and LDN is therefore more easily detected in infants and children than in adults (Cheour et al., 2001).

1.3 Aims of the research

The aim of Study I was to separate the mismatch negativity (MMN) component temporally and spatially from the mixture of the obligatory ERP components peaking at the same latency in children, and especially to define the latency of change detection processing of speech and non-speech stimuli. The earlier, corresponding studies using an equal probability control paradigm were conducted only for adults (e.g., Schröger & Wolff, 1996). However, developmental studies controlling MMN are important due to the differences between adults and children in ERP morphology and timing. Based on corresponding adult studies and latencies found in MMN studies in school-aged children it was hypothesized, that context-based change detection processing would be found within rather similar latencies as in adults.

The aim of Study II was to examine speech perception ability in children with and without familial risk for dyslexia. Of those, a subgroup of children were diagnosed as dyslexics and analyzed as a separate group. Earlier it has been shown that individuals with dyslexia, as well as infants at risk for dyslexia, show atypical ERPs to speech and tones, compared to controls, and therefore group differences were expected between the RDFR group and typically reading groups. In the RDFR group smaller amplitudes for the change detection responses whereas larger responses for the obligatory responses were expected. Much less effort has been put into understanding what those differentiating brain responses imply, and how they are associated with reading and related skills. Therefore, the associations between ERPs and outcomes in phonemic length discrimination, reading accuracy, reading speed, and writing accuracy tasks were also investigated for a deeper understanding of brain activation differences between groups. Based on the previous studies associations between auditory ERP amplitudes and reading, spelling, and phonological skills were hypothesized. The associations were, however, expected to be different within the groups.

The aim of Study III was to investigate the brain responses of infants with and without risk for dyslexia: to explore how the risk for dyslexia affects infant brain responses and predicts reading achievement much later at the age of 14 years. Another point of interest was the role of pre-reading skills, including phonology, rapid naming, verbal short-term memory, and letter knowledge as

possible mediators between early ERPs and later reading. Previous studies would suggest phonological skills to be associated more with reading accuracy, whereas rapid naming ability more with reading speed. Speech perception indices were hypothesized to be associated with phonological skills and reading accuracy.

The overall objective of the research was to investigate speech processing in infants and children with and without a familial risk for dyslexia, and to clarify the meaning of the atypical speech processing manifested by auditory ERPs in infants and children at risk for dyslexia. Therefore, the associations of the ERP responses and behavioral measures – phonemic length discrimination, reading and spelling in school-aged children, and rapid naming, letter knowledge, phonological skills and verbal short-term memory in preschool-aged children – were investigated. There was also a methodological aim: to define, by controlling the presentation probabilities of the stimuli, the latency of change detection processing of speech and non-speech stimuli in school-aged children.

2 METHOD

2.1 Samples and participants

The participants included in Studies I-III were Finnish-speaking children with normal cognitive and hearing levels. Children with any neurological disorder or condition (including ADHD and Asperger's syndrome) were excluded. Informed consents were obtained from all parents according to the Declaration of Helsinki.

The sample of Study I was recruited for a collaborative cross-linguistic study of WP7 of the NeuroDys Consortium (the European Union Sixth Framework Programme #018696 "NeuroDys Dyslexia Genes and Neurobiological Pathways") according to institutional informed consent procedures approved by the Ethical Committee of the Central Hospital of Central Finland. In Study I, the participants included 50 (25 boys, 25 girls) normally developing children with a mean age of 10.27 years (SD = .43, range = 9.55–11.05).

The samples of Studies II and III consisted of children in the Jyväskylä Longitudinal Study of Dyslexia (JLD; for reviews, see Lyytinen et al., 2001, 2004, 2008), in which around 100 children at risk for dyslexia and around 100 controls were followed since birth until adolescence. Infants were selected into the at-risk group if at least one first-degree relative had a confirmed diagnosis of dyslexia and, in addition to that, at least one second-degree relative was self-reported to have reading disability (for details for inclusion criteria, see Leinonen et al., 2001). The studies were approved by the ethics committee of the University of Jyväskylä.

In Study II, a total of 139 children (66 boys, 73 girls) fulfilled the criteria to be included in the analysis. Data were collected when the JLD children were at a mean age of 9.41 years (SD = .34; range = 8.18–10.23). The children were grouped into three groups according to their reading performance at the end of 2nd grade at the age of 9 years and their family risk status (for dyslexia criteria, see below). The groups were as follows: typically reading control children with no familial risk for dyslexia (TRC, N = 58), typically reading children with a

familial risk for dyslexia (TRFR, N = 51), and children with a familial risk for dyslexia and reading disability (RDFR, N = 30).

In Study III, the data of 48 healthy infants (24 boys, 24 girls) was included in the analysis; of these, 26 (13 boys, 13 girls) belonged to the at-risk group with a family background of dyslexia. Twenty-two of the infants (11 boys, 11 girls) were control infants with no dyslexia in their families, and they were assessed to be typical readers in 2nd grade (see below; for details, see Puolakanaho et al., 2007; Eklund et al., 2015). The ERP data were obtained when children were at a mean age of 0.52 years (SD = .03; range = 0.49–0.64). Preschool-age cognitive measures were assessed at 5.0 and 5.5 years, performance IQ at 8 years, and reading at 14 years.

2.2 Criteria for classification of dyslexia group

The criterion for dyslexia was determined at the end of 2nd grade at the age of 9 years. The criterion was based on performance in five reading and spelling tasks: (1) oral word and non-word reading; (2) word and non-word spelling; (3) oral text reading; (4) oral pseudo-word text reading; and (5) Standardized word list reading test (see below). Based on those, four measures of reading speed and four measures of reading/spelling accuracy were calculated. The children were defined as belonging to the reading disability group if their reading performance outcome at the end of 2nd grade fell below the 10th percentile of the performance of the control children in at least three out of four measures of reading/writing accuracy or reading speed, or in two out of four in reading accuracy and two out of four in reading speed measures (for details of the procedure, see Puolakanaho et al., 2007). Otherwise, a child's reading skills were considered to be typical. The accuracy and speed measures for the criteria were derived from the following tasks.

Oral word and non-word reading. 40 three-syllable and four-syllable words and non-words were presented separately via computer. The children were asked to read items aloud as quickly and accurately as possible. The number of correctly read items was used as an accuracy measure and the mean of the response times (reaction time + response duration) to the correctly read items as a speed measure.

Word and non-word spelling. 18 four-syllable words and non-words were presented separately via headphones. The children were asked to write items with a pencil. The number of correctly spelled items was used as an accuracy measure.

Oral text reading. The participants were asked to read aloud a typical Finnish text as accurately and quickly as possible. The percentage of correctly read words was used as an accuracy measure, and the number of words read per minute as a speed measure.

Oral pseudo-word text reading. The children read a text composed of 19 pseudo-words structured like a typical normal Finnish text. The pseudo-words

were modified from actual words by switching consonants or vowels (e.g., from 'matkoja' (adventures) to 'tenkoja'). The percentage of correctly read pseudo-words was used as an accuracy measure, and the number of pseudo-words read per minute as a speed measure.

Standardized word list reading test "Lukilasse". The participants were asked to read aloud as many of the 90-item word list as possible in two minutes (Häyrinen, Serenius-Sirve, & Korkman, 1999). The number of correctly read words within the time limit was transformed into a standard score reflecting accuracy and speed. This measure represented the reading speed measure for criterion purposes.

2.3 Behavioral measures

In Study II, correlations of behavioral assessments at the end of 2nd grade in phonemic length discrimination, word reading accuracy, word reading speed, and pseudo-word writing accuracy were calculated with electrophysiological measures.

In the *phonemic length discrimination task*, children were asked to determine whether 22 two-, three- and four-syllable pseudo- and non-word pairs varying in phonemic length were identical or not. To eliminate the occurrence of possible response biases, d' values were calculated by subtracting the z-score of the percentage of hits from the z-score of the percentage of false alarms.

Word reading accuracy and speed were assessed using three- and four-syllable word (20 items) and non-word list reading tasks (20 items): accuracy was measured as an average of the number of correctly read items of the abovementioned tasks, and speed as an average of reading times in the same tasks.

Spelling accuracy was measured by the number of correctly spelled four-syllable non-words in dictation tests (12 items). For details regarding the measures, see Pennala et al. (2010) and Puolakanaho et al. (2007).

In Study III, reading performance in 8th grade was predicted by infant ERP to speech, and the mediating role of preschool cognitive skills between infant ERP and reading skills in 8th grade was studied.

Preschool cognitive skills were measured at the age of 5–5.5 years. As a measure for *phonological skills*, a mean score of five tests in identification, production, and segmentation at the levels of phonemes, syllables, and words was used. For *RAN objects* (Denckla & Rudel, 1976), a reduced 30-item matrix was applied, and total time in seconds was used as a measure. The composite score for *verbal short-term memory (STM)* was comprised of the average of correct answers in the digit span (Wechsler, 1991) and the memory for names - tests (NEPSY; Korkman, Kirk, & Kemp, 1998). In the *letter knowledge* task, 23 capital letters were presented one by one, and the sum of correct answers (phoneme or letter name) was used in the analysis.

Performance intelligence quotient (PIQ) was assessed at 8 years with four subtests of the Wechsler Intelligence Scale for Children-III: block design, picture completion, object assembly, and coding (Wechsler, 1991).

The performance in three reading tasks – oral text, oral pseudo-word text, and oral word list reading – was used to calculate the average scores for *reading accuracy* (the percentage of correctly read words) *and reading speed* (letters read/second) in 8th grade at the age of 14 years (for details, see Puolakanaho et al., 2008; Eklund, Torppa, Aro, Leppänen, & Lyytinen, 2015).

2.4 Stimuli and procedure

For Studies I–III, stimuli were presented in an unattended oddball paradigm and, in addition for Study I, in an equal probability (EQ) paradigm. For details of the measurement and analysis settings in Studies I-III, see Table 1.

The stimulus set of Study I consisted of two synthetically produced vowels, /y/ and /i/, and two corresponding complex non-speech stimuli. Stimuli were presented in pseudo-randomized stimulus sequences in passive oddball and EQ conditions. In the speech oddball condition, /y/ was presented as a rarely presented deviant (18%, 129 times) among repeated standard stimuli /i/ (82%, 588 times), and respectively in a non-speech oddball condition for their non-speech counterparts. After the oddball conditions, a control condition was conducted. In the control EQ condition, all four stimuli were presented in the same sequence with an equal probability of 25%, with each stimulus occurring 129 times. For the details of creating and selecting the stimuli, see Bruder et al. (2011a, b). The duration of all stimuli was 150 ms.

In Studies II and III, naturally produced pseudo-words differing only in the length of the silent gap between the initial vowel and the following stop consonant were used. Study II used two variations, the short /ata/ (total duration 300 ms) and the long /at:a/ (460 ms), and Study III additionally used the intermediate /at:a/ (400 ms). For all stimuli, the duration of the first part of the stimulus, including the initial glottal stop and the vowel /a/, was 72 ms, and the duration of the second part, containing the explosion of the /t/ and the vowel /a/, was 133 ms. For the short, intermediate and long stimuli the voiceless stop between syllables measured 95 ms, 195 ms and 255 ms, respectively.

In Study II, two oddball paradigms were conducted: first the short /ata/ was presented as a standard (80%, 1010 trials) and the long /at:a/ as a deviant (10%, 125 trials) and then other way around: the long /at:a/ as a standard (80%, 1010 trials) and the short /ata/ as a deviant (10%, 125 trials). In both paradigms, there was another deviant as well: the deviant stimuli differing from the standard in consonant quality (either short /apa/ or long /ap:a/ (10%, 125 trials each). However, the results of the consonant quality deviant stimuli are reported elsewhere.

In Study III, the short /ata/was presented as a repeated standard stimulus (300 ms, 80%), and the intermediate (400 ms, 10%) and long (460 ms, 10%) variations of /at:a/ as rarely presented deviant stimuli.

TABLE 1 Summary of the EEG recording and pre-processing settings in Studies I-III.

	Study I	Study II	Study III
No. of electrodes	128 Ag/AgCl	128 Ag/AgCl	10 Ag/AgCl
Reference	Cz	Cz	Ipsilateral mastoids
Sampling rate	500 Hz	500 Hz	200 Hz
Online filtering	0.1–200 Hz	0.1–100 Hz	0.5–35 Hz
Offline filtering	0.3–30 Hz, 50 Hz	0.53–35 Hz, 50 Hz	-
Baseline	-50–0 ms	-50–0 ms	-50–0 ms
Averaged epoch	-50–600 ms	-300–1060	-50–840 ms
Artefact criteria	> ±200 μV	> ±200 μV	> ±200 μV
ISI	450–550 ms	610 ms	610 ms
Impedances	< 50 kΩ	< 50 kΩ	< 5 kΩ
Stimulus intensity	70 dB(A) SPL	75 dB(A) SPL	75 dB (C) SPL

Note. Ag/AgCl, silver/silver chloride electrode; ISI, Inter-stimulus interval; SPL, sound pressure level.

2.5 Recording and preprocessing of the EEG data

The EEG data of the Studies I and II were recorded with a high-density net including 128 Ag/AgCl electrodes (Electric Geodesics Inc.). Electro-oculogram (EOG) was recorded with electrodes located above, below, and lateral to both eyes. During the experiment, impedances for the majority of the electrodes were kept below 50 kΩ. EEG data were preprocessed using BESA software. Blink correction was implemented before averaging by using PCA algorithm in Besa (Ille, Berg, & Scherg, 2002). Channels with bad data were omitted from the averaging and interpolated using a spherical spline interpolation method after the averaging (Perrin, Pernier, Bertrand, & Echallier, 1989).

In Study I, as a pre-processing step for temporal principal component analysis (tPCA), ERPs were transformed into reference free current source density (CSD) waveforms to improve both spatial and temporal resolution, resulting in the interpolation to the standard 81 channels of the 10-10 system (Kayser & Tenke, 2006; Law, Rohrbaugh, Adams, & Eckardt, 1993; Nunez, 1981; Nunez & Srinivasan, 2006; Perrin et al., 1989). During the EEG measurements, participants watched a self-selected silent video and were instructed not to pay attention to the sounds.

In Study II, EEG data were re-referred to an average reference. The participants watched a silenced video or played a computer game during the recordings.

For Study III, EEG data were recorded using DSAMP Software from ten scalp sites according to the 10-20 electrode system with Ag/AgCl electrodes attached to the electrode cap. EOG were recorded with one electrode lateral to

and above both eyes, and referenced to the left mastoid. During the measurement infants were sitting on a parent's lap.

2.6 Statistical analyses

2.6.1 Group and stimulus comparisons

In Study I, differences in amplitudes between stimuli and conditions were tested using multivariate analyses of variance (MANOVAs). Before that, for the CSD transformed ERP data, temporal PCA using a covariance matrix and Promax rotation was performed for time points ranging from -50–550 ms and across all participants, stimuli, conditions, and channels (Kayser & Tenke, 2006; Spencer, Dien, & Donchin, 1999). Temporal principal components (PCs) accounting for a cumulative variance of 99% were included in the rotation (Kayser & Tenke, 2003). The PCs occurring at the latencies (approximately 100–200 ms) typically reported in the literature for MMN in school-aged children (e.g., Kraus, McGee, Carrell, Sharma, Micco, & Nicol, 1993; Shafer, Morr, Kreuzer, & Kurtzberg, 2000) and showing comparable topographic distribution between the grand averaged CSD maps and PCA factor score maps were selected for further statistical analysis.

The electrodes with the largest responses were chosen for analysis and tested against zero to confirm showing a systematic activation. Four average electrode clusters were computed: the left (F5, FC5, C5) and right (F6, FC6, C6) at fronto-central, and left (P7, TP9) and right (P8, TP10) at inferior and posterior temporal electrodes. MANOVA were implemented separately for fronto-central and temporal electrodes and for non-speech and speech stimuli. Repeated measures of the MANOVA models Stimulus (standard, deviant) × Hemisphere (left, right) were used to test the deviant-standard contrasts and the corresponding MANOVA models, including Stimulus (deviant, control) × Hemisphere (left, right) to test the deviant-control contrasts. For the post hoc analyses, paired *t*-tests with Bonferroni corrected *p*-values were used.

In Studies II & III, permutation tests were used to test group and stimulus differences (BESA Statistics 1.0). Paired comparisons for the responses with channel and time-point clustering were conducted (Maris & Oostenveld, 2007). The cluster-based permutation test adapted for multi-sensor analyses clusters the selected sensor-time pairs on the basis of spatial and temporal adjacency. The permutation *p*-value was driven from the permutation distribution as a proportion of random samples that resulted in a larger test statistic than the observed *p*-value. Therefore, permutation test handles for multiple comparison problems followed from a multi-sensor and multi-time point approach. The number of permutations was set to 1000 and the cluster alpha level to .05 in both studies. The channel cluster distance was set to 3 cm in Study II and 9 cm in Study III. In Study II, an analysis time window of 50–900 ms was used, and in Study III time windows of analysis were defined on the basis of preliminary *t*-tests showing significant temporally adjacent time points (for the standard 40–

230 ms, for the intermediate deviant 630–835 ms, and for the long deviant stimulus 40–190 ms and 380–820 ms). For further information on the permutation testing, see Bullmore, Suckling, Overmeyer, Rabe-Hesketh, Taylor, & Brammer, 1999; Ernst, 2004; Maris & Oostenveld, 2007).

2.6.2 Correlation, phase-locking and source analysis

In Studies II and III, correlations between brain responses and behavioral measures were calculated. In Study II, in addition, phase-locking and source analysis was conducted, while Study III included regression analyses.

In Study II, amplitude values around 294 ms ± 30 ms and 600 ms ± 50 ms showing significant group differences were averaged across time and correlated within the groups in each measured channel with phonemic length discrimination, reading and writing accuracy, and reading speed in Matlab. Significant correlations (ps < .05) were plotted as topographic maps separately for each of the three groups using an EEGLAB toolbox, and statistical significances of the correlations between groups were tested using Matlab (for further information on correlation testing, see McNemar, 1969).

For the phase-locking analysis, no offline filters were applied to the raw EEG data. Data were transformed to 26 channels corresponding to the 10-10 system. The 2–46 Hz frequencies were examined using 1 Hz frequency resolution and 50 ms time resolution). The inter-trial phase-locking values were calculated across the trials for each child by using a complex demodulation method of the coherence module in BESA Research 6.0. Differences between groups in the inter-trial phase-locking values were examined using permutation tests in BESA Statistics 1.0.

The source localization was performed for the grand average ERP waveforms of the groups (RDFR, N = 30; TRFR, N = 51; and TRC, N = 58) for the short /ata/ deviant stimulus at a time window of 264–324 ms, showing the most significant group differences in permutation tests, and a stable topography. The RDFR group was divided into three groups (N = 10 for each) based on their reading accuracy performance. A realistic approximation head model for 8- to 10-year-old children was used (brain-to-skull conductivity ratio = 30) (Hoechstetter, Berg, & Scherg, 2010).

In Study III, the averages of the amplitudes around the main deflections in the grand average waveforms were computed: for the standard response in four time windows of 40–80 ms, 135–215 ms, 260–340 ms, and 370–470 ms, for the shorter deviant response in one time window of 470–550 ms, and for the longer deviant response in two time windows of 420–500 ms and 540–620 ms. Pearson's correlation coefficients were calculated between the averages, and the neurocognitive measures and reading within the at-risk and control groups for left and right hemisphere electrode sets (the means of frontal, central, and temporal electrode of hemisphere). A false discovery rate correction of q = .05 was applied (Benjamini & Hochberg, 1995). Based on the correlations, linear regression analyses were performed with reading speed as the dependent variable and infant ERPs and neurocognitive measures at preschool age as the independent variables.

3 OVERVIEW OF THE ORIGINAL STUDIES

3.1 Study I: Controlling MMN in school-aged children

Study I aimed to separate auditory change detection brain response (MMN) from the obligatory ERP components reflecting basic auditory processing occurring at the same latency. ERPs to vowel change and corresponding non-speech stimuli in school-aged children were measured. A temporal PCA was used, and five principal components (PCs) peaking at 112 ms, 136 ms, 160 ms, 184 ms, and 204 ms were selected for the MANOVA analysis. An equal probability (EQ) control condition, in which all stimuli are presented with same probability, was used to study the role of the stimulus context effect. The CSD-transformed brain responses to deviant stimuli measured in the oddball condition were compared to the responses to the same stimuli recorded in an EQ condition, in addition to the deviant minus standard response comparison usually used to determine the existence of the MMN. The deviant response was supposed to be larger than the responses to the standard and control stimuli at both the fronto-central and at the temporal areas below the Sylvian fissure.

It was found that for non-speech stimuli, MMN was observed at the fronto-central and temporal sites for the three earliest PCs peaking at 112 ms, 136 ms, and 160 ms no matter if the EQ control criteria were taken into account or not (see Figure 2). For the speech stimuli, both the deviant-standard and the deviant-control contrasts were significant only for the PC peaking at 160 ms at the temporal site, while at the fronto-central channels contrast were significant for the four last PCs peaking at 136 ms, 160 ms, 184 ms, and 204 ms (see Figure 3).

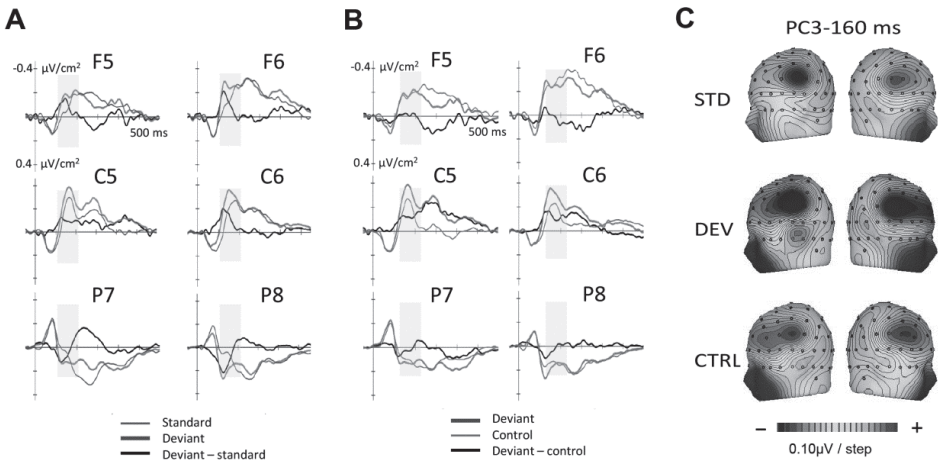

FIGURE 2 Non-speech condition. Current source density (CSD) transformed brain responses A) to the standard (blue line) and deviant stimuli (red line) presented in oddball non-speech condition, and their subtraction curve (black line), B) to the deviant stimuli (red line) and to the control (green line) (i.e., the same stimuli presented in equal probability (EQ) condition), and their subtraction curve (black line). The grey area represents the time window of 112–204 ms. C) Brain topographies of the factor scores to the standard, deviant and control stimulus for temporal PC 3 peaking at 160 ms.

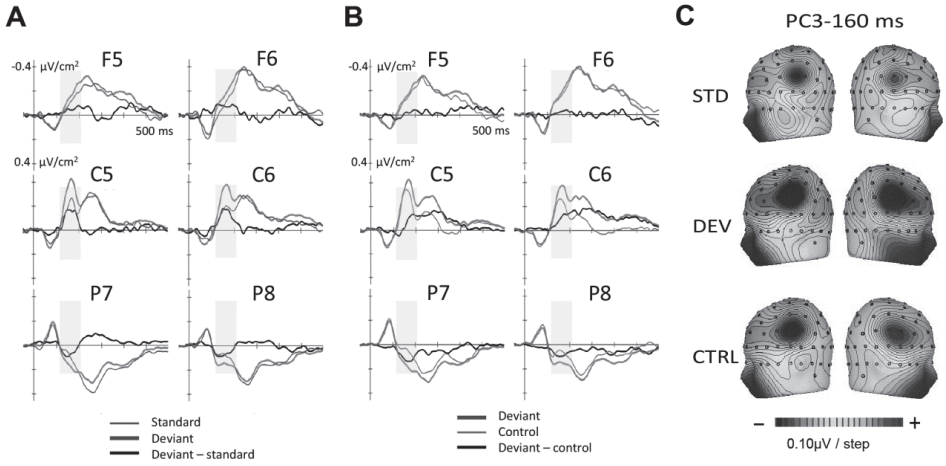

FIGURE 3 Speech condition. Current source density (CSD) transformed brain responses A) to the standard (blue line) and deviant stimuli (red line) presented in oddball speech condition, and their subtraction curve (black line), B) to the deviant stimuli (red line) and to the control (green line) (i.e., the same stimuli presented in equal probability (EQ) condition), and their subtraction curve (black line). The grey area represents the time window of 112–204 ms. C) Brain topographies of the factor scores to the standard, deviant and control stimulus for temporal PC 3 peaking at 160 ms.

Employment of the additional deviant-control contrasts had no effect on significance of MMN at fronto-central scalp sites. However, controlling influenced the MMN latencies below the Sylvian fissure. If the additional contrast was ignored, the difference in the responses to speech stimuli was observed to arise at the temporal site already at PC 112 ms (i.e., around 50 ms earlier than if the deviant-control contrast was taken into consideration). Therefore, it was concluded that the early temporal activation at 112 ms is composed of obligatory processing, not representing a context-based change detection process. However, on grounds of Study I it seems that obligatory responses do not fully explain the elicitation of the negativity at the MMN time window in children.

3.2 Study II: Enhanced responses for shortening of the phonemic length in school-aged dyslexic children

In Study II, group differences of auditory event-related potentials (ERPs) of school-aged children were examined. The pseudo-words /at:a/vs. /ata/, differing in phonemic length, which is a semantically distinctive feature in the Finnish language, were used as stimuli. Two oddball paradigms were conducted: first /ata/ presented as repeated standard stimuli and /at:a/ as rarely presented deviant stimuli, and secondly vice versa. Also, associations of ERP amplitudes with phonological skills, reading and spelling were investigated. Three groups of nine-year-old children were included in the study: reading-disabled children with a familial risk for dyslexia (RDFR, N = 30), typically reading children with a familial risk for dyslexia (TRFR, N = 51), and typically reading control children with no familial risk for dyslexia (TRC, N = 58). Group differences were expected between RDFR and typically reading groups. The RDFR group showed larger amplitudes for the obligatory responses, but smaller amplitudes for the change detection responses, compared to other two groups (Hämäläinen et al., 2013).

Group differences between the RDFR group and both typically reading groups were found, but only for a shortening of consonant duration (i.e. to the pseudo-word /ata/presented as rarely presented deviant stimuli among repeated standard stimuli /a:ta/(see Figure 4)). Furthermore, dyslexics showed enhanced responses instead of more typically reported smaller responses. Group differences were located at frontal (more negative for RDFR group) and occipital (more positive for RDFR group) areas, and the groups differed at several time windows. The most significant differences between the RDFR group and both typically reading groups were shown around 300 ms after stimulus onset (130–230 ms after the deviancy of the standard and the deviant stimuli) and around 600 ms after stimulus onset (380–480 ms after the deviancy of the standard and the deviant stimuli). The earlier time window covers the typical time window for both the obligatory N250 response and processing of the change detection of deviancy, and the latter the typical time window for late discriminative processing.

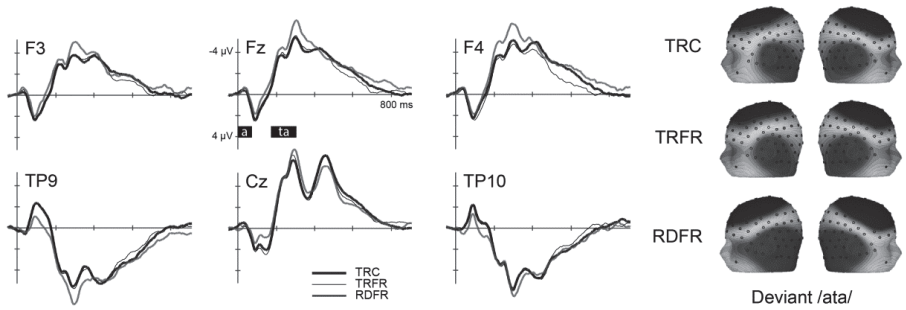

FIGURE 4 ERP responses and brain topographies to the rarely presented deviant stimuli pseudo-word /ata/in three groups: children with a familial risk for dyslexia and reading disability (RDFR, N = 30), typically reading children with a familial risk for dyslexia (TRFR, N = 51), and typically reading controls (TRC, N = 58).

For further understanding of the meaning of the group differences, associations of ERP amplitudes for the short deviant /ata/ between a time window of 264–324 ms and 550–650 ms with behavioral measures were examined. Enhanced brain responses within the RDFR group were found; those were associated with better performance in behavioral phoneme length discrimination tasks, as well as better reading and writing accuracy. In the TRC and TRFR groups, associations were less systematic. For phonological skills, reading accuracy and speed and writing accuracy associations were significantly different between the RDFR group and the typically reading control (TRC) group at the right frontal area between 264–324 ms. In addition, the RDFR group differed from the typically reading familial risk (TRFR) group in all but reading speed. At the later time window between 550-650 ms at the right frontal area, correlations with reading accuracy in the RDFR group were significantly different from those of the other groups, and correlations with writing accuracy in the TRC group differed from both familial risk groups. Based on the associations and the differences in topographies of the RDFR group, compared to other groups, the RDFR group was divided into three groups according to their reading accuracy level, and source localization analyses were conducted for the deviant /ata/ between 264–324 ms for three groups of dyslexics as well as for two typically reading groups. Source analyses revealed that the brain responses of the subgroup of dyslexic children with the largest responses originated from a more posterior area of the right temporal cortex, compared to the responses of the other groups.

The enhancement of the responses in dyslexic group could refer to a larger cortical area activated by stimulation in dyslexic children at the right hemisphere, compared to typically reading groups, which was reflected also in the more posterior source location for the subgroup of children with the largest responses within the dyslexic group. Another possible explanation for the enhancement and different source location could be a dissimilar center of gravity

of the active cortical area, referring to a larger or different cortical area activating. The findings from correlation and source analyses suggest that different brain areas are involved in processing of the tasks in the different groups. This could possibly show evidence for a compensatory speech perception mechanism in dyslexia. It is possible that the most accurate readers within the dyslexic group had developed alternative strategies which employ compensatory mechanisms to substitute for their earlier deficit in phonological processing. These new strategies and mechanisms could have helped them to outperform in phoneme length discrimination and reading and writing accuracy tasks. The compensatory mechanism is further supported by the earlier finding in a partly overlapping population: in dyslexics tested three years before at the age of 6.5 years, the larger brain responses were related to poorer reading performance in 2nd grade (Hämäläinen et al., 2013). It is also rational that for reading speed, compensatory mechanisms are more difficult to build and some of the dyslexic children remain slow readers during their whole life.

3.3 Study III: Processing of the phonemic length in infants at familial risk for dyslexia predicts reading performance in adolescence

In Study III, ERPs to the pseudo-words /ata/and /at:a/ were measured at the age of 6 months to study the speech processing of infants with and without familial risk for dyslexia. The aim was to examine whether infant brain responses would be related to later reading at 14 years, and therefore their reading skills were also evaluated in 8th grade. In addition, to see the possible mediator roles between the infant ERPs and adolescent reading, the associations with preschool cognitive measures assessed at the age of 5.5 years – phonology, letter naming, RAN, and verbal STM – were studied. As previously seen, phonological skills are associated with reading accuracy, and rapid automatized naming (RAN) with reading speed (Georgiou, Parrila, & Papadopoulos, 2008; Norton, & Wolf, 2012; Puolakanaho et al., 2008). Studies have suggested a link between early speech processing and later reading by finding differences between the ERPs in infants with and without family risk for dyslexia (Guttorm et al., 2001; Guttorm et al., 2003; Leppänen et al., 1999; Leppänen et al., 2002). Also, electrophysiological speech perception indexes have been shown to be related to phonological skills and reading accuracy (Hämäläinen et al., 2009).

Group differences in ERP responses found earlier in study of Leppänen et al., 2002 were confirmed using permutation tests. The brain responses of the infants at risk for dyslexia differed statistically significantly from the responses of the control group for several electrode clusters and time windows. Larger negativity in the at-risk group denoted better performance in reading and cognitive tests (see Figure 5). Within the at-risk group, a strong association between infant ERPs for short /ata/ at the left fronto-central electrodes and reading

speed at 14 years was found (see Figure 5c). Within the at-risk group, infant brain activation was also correlated with rapid naming (see Figure 5b) and phonology at preschool age, as well as with performance IQ at 9 years with larger negative amplitudes denoting better performance. Correlations between rapid naming and reading speed at 14 years, PIQ and phonology, and letter naming and phonology were also significant. Within the control group, rapid naming was correlated with reading accuracy. In the control group, no correlations with brain measures survived the FDR correction, but significant correlations between letter naming and non-verbal IQ, and between rapid naming and reading accuracy in 8th grade, were found. In addition, several significant correlations between reading speed and accuracy measures in 1st, 3rd, and 8th grades were observed in both groups.

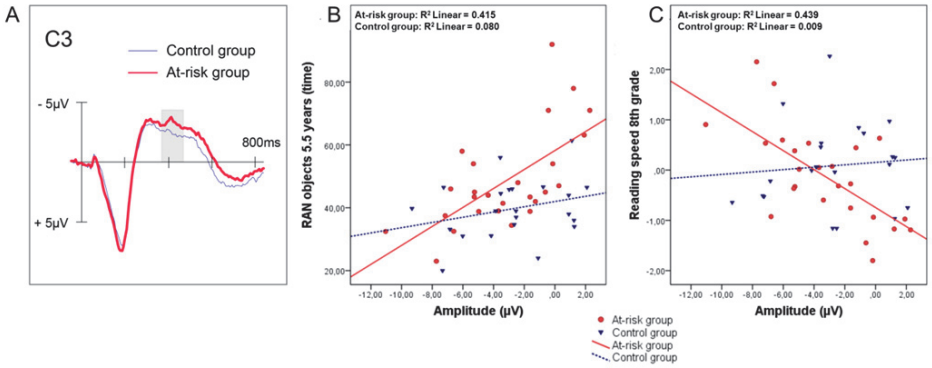

FIGURE 5 Associations of infant ERPs to phonology, RAN and reading speed. (A) Grand average ERP waveform of 6-month-old infants with (red line) and without (blue line) familial risk for dyslexia for a standard stimulus at C3 channel. The gray box indicates the time scale of 370–470 ms used for correlations. Linear scatter plots of the infant ERP amplitude to the standard /ata/ stimuli at the left hemisphere (mean across electrodes F3 and C3, at time points between 370–470 ms) with (B) RAN at 5.5 years (time in seconds), and (C) the reading speed in 8th grade.

On the basis of the correlation analysis, regression analyses were carried out. Regression analyses showed that the infant brain responses to the repeated pseudo-word /ata/ at left fronto-central electrodes (at the time window of 370–470 ms) explained 42% of reading speed scores in 8th grade. Importantly, the brain index significantly improved the prediction if inserted into the model after preschool neurocognitive measures of phonology, letter naming, and verbal STM. Rapid naming itself explained 51% of reading speed in the at-risk group, and if the ERP amplitude was forced (entered) into the model after rapid naming the improvement to the prediction of reading speed at adolescence was not significant. None of the measures predicted reading speed in the control group.

The infant brain responses to the standard stimuli shared common variance with RAN, phonology, letter naming, and verbal STM before formal read-

ing instruction. This refers to the early brain responses reflecting cognitive processing that partly underlie preschool age cognitions, which are important for good reading performance. However, the association between infant ERPs and reading speed was mostly mediated by preschool-age rapid naming ability. Because good performance in RAN demonstrates that lexical access to visual stimuli has been automatized, it was assumed that similar cognitive processes are needed both in RAN and fluent reading in automatized access to representations of the phonological lexicon storing the auditory sound form of words (Norton & Wolf, 2012).

4 DISCUSSION

The current research investigated event-related potentials (ERPs) to speech in six-month-old infants and in school-aged children with and without familial risk for dyslexia. In Study I, the change detection processing of speech was studied by contrasting responses to speech and non-speech stimuli in normally developing school-aged children. The MMN response to speech stimuli was found to emerge later than to the corresponding complex non-speech sounds. In this research, though, the main interest was to study which processes at the behavioral level are linked to altered brain responses to speech in dyslexic readers and at-risk children. Therefore, in Studies II and III, the associations of brain responses and cognitive abilities were examined. In Study II, better behavioral speech sound discrimination and more accurate reading and spelling were found in dyslexics in 3rd grade to be related to larger brain responses to a shortening of phonemic length. Source localization analysis revealed that for the subgroup of the best reading dyslexics who had the largest EEG responses, the source of brain activation is more posterior at right auditory areas, compared to the other participants. These findings suggest that the best readers within the dyslexic group might have developed alternative strategies which employ compensatory mechanisms to substitute for their deficit in phonological processing. This seems to provide the first electrophysiological evidence for a compensatory speech perception mechanism in dyslexia. In Study III, infant brain responses measured at six months of age were studied in relation to preschool skills – rapid naming speed, phonological awareness, letter naming, and verbal short-term memory – and reading. In the at-risk group, infant brain activity predicted reading speed in 8th grade at the age of 14 years. Infant ERPs have earlier been found to predict reading in the initial years of school, but this is the first time to show the prediction up to adolescence.

4.1 Change detection in children

In Study I, the latency for the mismatch negativity (MMN) was pursued to be isolated from other simultaneously occurring brain activity in school-aged children. The responses elicited in an oddball paradigm to the deviant stimuli were contrasted with responses produced by exactly the same stimuli in EQ paradigm where all stimuli were presented with equal probability. The MMN response emerged earlier for non-speech stimuli, compared to speech stimuli, even if the two stimulus types were equal in stimulus complexity. This possibly indicates that in school-aged children processing of deviancy in speech is more demanding and long-lasting than change detection processing for corresponding complex non-speech sounds.

Study I is the first study of children aimed at separating the MMN response by using an equal probability paradigm for controlling the effect of an inter-deviant interval and dissimilar probabilities of stimuli in sound streams. This is important, because the differences in stimulus repetitions and the acoustic differences between stimuli alone could cause differences between responses, regardless of whether there actual sensory memory-based change detection processing is involved or not (May & Tiitinen, 2010, Näätänen et al., 2005). Beyond that, Study I is important for the research field in that it contrasts the responses to speech with responses to equally complex non-speech stimuli. This was done in order to be able to determine which of the results could be unique to speech features itself. The results suggest that change detection in speech sounds is a more demanding task than change detection in non-speech.

Although in the literature there are no other MMN studies of children using a EQ paradigm control, efforts have been made to reduce the effect of acoustic differences between stimuli and unequal probability (Bonte, Mitterer, Zellagui, Poelmans, & Blomert, 2005; Bonte, Poelmans, & Blomert, 2007). For example, in Study II, a reversed oddball design was used. In a reversed oddball design, standard and deviant stimuli are reversed between two oddball paradigms so that one of the stimuli is first presented as standard and the other as deviant stimuli, and then the previous deviant is presented as a standard and the previous standard as a deviant. This approach allows for a comparison of the responses elicited by physically identical stimuli presented in a different role (i.e., with different probability, in the oddball paradigm). The reversed oddball design works well for controlling for the probability effect. Here it was also helpful for controlling the differing durations of the stimuli (/ata/ vs. /at:a/). However, the stimulus onset asynchrony (SOA) also differed (because of the stimulus duration changes and fixed inter-stimulus interval), which complicated interpretation of the ERPs and determining of the latency of the change detection processing. Therefore, the large negativity peaking at 300ms (130 ms after deviancy) was named N250/MMN.

4.2 Interaction of internal resources and external factors in school-aged dyslexics

In Study II, larger responses to shortening of the phonemic length were found in dyslexic readers in 3rd grade as compared to typically reading children. The enhancement was largest at around 300 ms after the stimulus onset (133 ms after the stimulus deviancy). This ERP deflection was named N250/MMN response for three reasons. The responses to the deviant stimulus were used in the analyses instead of the difference waveforms (deviant response minus standard response), because the short deviant /ata/ and the short standard /ata/ were presented in different conditions among the long deviants or standards, which most probably would have caused some context effects in the analyses. However, because of the stimuli were presented in traditional oddball paradigm which usually elicits MMN in response to deviancy, it is likely that the change detection processes contribute to the response around 150 ms after the stimulus deviancy (the response to the deviant /ata/was clearly larger in all groups when compared to the response to the standard /ata/).

The larger responses in the RDFR group were related to more accurate reading and spelling, and better phonemic length discrimination skills at right frontal areas. Furthermore, for the most accurate readers of the dyslexics who had the largest brain responses, the source of the brain activity originated from a more posterior site in the right auditory cortex, compared to other groups, including less accurately reading dyslexics. Different source location and more widespread activation in the voltage map referred to the employment of wider or different brain areas in speech processing. Correlation and source analyses suggest also that different brain areas are involved in the processing of the reading, spelling, and phoneme length discrimination tasks in the different groups.

That dyslexic readers had an enhanced N250/MMN response can be due to the activation of more synchronized neuronal population, or the sensitization of the neuronal population involved in the stimulus processing (Karhu et al., 1997). The same kind of hyperactivation was found in a partially overlapping sample at 6.5 years, just before formal reading instruction (Hämäläinen et al., 2013). The hyperactivation was then related to poorer performance in reading in 2nd grade, although in that study the association was found across control children typically reading at-risk children, and dyslexics. Altogether these findings could for the first time show evidence for a compensatory speech perception mechanism in dyslexia, revealed by ERPs. It is possible that the most accurate readers within the dyslexic group have developed alternative strategies which employ compensatory mechanisms to substitute for their earlier deficit in phonological processing. These new strategies and mechanisms could have helped them to outperform in phoneme length discrimination and reading and writing accuracy tasks.

In Study II, the enhanced responses to speech deviant stimuli correlated with reading accuracy, spelling accuracy, and phoneme length discrimination at

the right frontal electrodes. The right hemisphere has previously been found to be involved in reading in dyslexics, and it has been thought to compensate for the underachievement of corresponding left temporal and parietal areas (Pugh et al., 2000; Shaywitz & Shaywitz, 2005). In functional magnetic resonance imaging (fMRI) studies, hyperactivation in several functional brain studies have been reported and found to be linked to compensatory processes of reading and reading related skills. Hyperactivation of the right temporo-parietal neocortex was observed in dyslexic children during an auditory same-different word identification test, suggesting atypical reliance on the right posterior cortex in phonological processing due to a compensatory mechanism in dyslexics (Kovelman et al., 2012). Similarly, employment of the right superior temporal gyrus instead of the corresponding left brain area was found in dyslexics during a pseudo-word reading task (Simos et al., 2002). However, activation at the left posterior area was found to increase after remediation. It has been proposed that hyperactivation of the right temporal and parietal regions represents an enhanced compensatory neural mechanism caused by the more demanding reading process in dyslexic children (Shaywitz & Shaywitz, 2005; Simos et al., 2002). This is in line with the findings of Study II where the most accurate readers of the dyslexic group were shown to compensate for their speech processing at a more posterior site in the right hemisphere, compared to others.

Brain hypoactivation has also been found in dyslexics in many fMRI studies (for meta-analysis, see Maisog, Einbinder, Flowers, Turkeltaub, & Eden, 2008; Richlan, 2012; Richlan, Kronbichler, & Wimmer, 2009; Richlan et al., 2011). An fMRI study in at-risk kindergartners reported hypoactivations at left posterior regions before formal reading instruction at brain areas corresponding to previously identified areas in adult and school-aged dyslexics (Raschle, Zuk & Gaab, 2012). Brain activity at left occipito-temporal and temporo-parietal areas was positively correlated with pre-reading skills in both groups. These findings were thought to show evidence for some of the differences not being caused by reading failure, but also for compensatory mechanisms for reading failure not yet being present.

4.3 Predicting reading until adolescence

In Study III, infant brain responses were found to predict reading speed until adolescence in the at-risk group. Previously, in the Jyväskylä Longitudinal Study of Dyslexia (JLD) as well as in other longitudinal studies, infant brain measures have been shown to predict preschool language and elementary school reading problems (Guttorm, Leppänen, Poikkeus, Eklund, Lyytinen, & Lyytinen, 2005; Guttorm, Leppänen, Hämäläinen, Eklund, & Lyytinen, 2010; Leppänen et al., 2010; Molfese, 2000; van der Leij et al., 2013). In the current study, within the at-risk group, brain responses at the age of six months were strongly related to reading speed at 14 years in 8th grade, and also to preschool cognitive skills phonology, letter knowledge, rapid automatized naming (RAN),

and verbal short-term memory (verbal STM). The left fronto-central brain response around 400 ms predicted over 40% of the variation of eighth-grade reading speed, and it improved on the prediction of the preschool measures of phonology, letter knowledge, and verbal STM, suggesting that these skills are at least partly independent from infant speech perception abilities. However, the rapid naming (RAN) task of familiar objects alone predicted approximately 50% of reading speed in 8th grade in the at-risk group. This is in line with earlier findings that RAN, at least the alphanumeric versions, is the best single predictor of word reading in transparent orthographies, as possessed by Finnish (Wolf, Pfeil, Lotz, & Biddle, 1994). Furthermore, in the current study, RAN was found to act as a mediator between infant brain responses and reading speed, explaining the relationship between infant brain activation and adolescent reading speed. Because the association is mediated via RAN, the result suggests that infant brain activation to speech, RAN and reading speed at adolescence share a similar cognitive processing. However, on the basis of the results in this research it is not clear what the common process or processes linking infant brain responses, rapid naming, and reading speed would be. One potential explanation is that in infants at risk for dyslexia, the poor formation of speech sound representations for the repeated stimuli or a defective access to those representations reflects the deficit that later hinders rapid naming speed and reading speed. Most likely, automatization of the access to a lexicon via phonological representations is deficient in at-risk children.

RAN has been suggested to reflect processes like general processing speed, automatization, and retrieval from a mental lexicon (for reviews, see Norton & Wolf, 2012; Vukovic & Siegel, 2006). It has been shown to be a good predictor of reading speed in several languages, regardless of orthographical transparency (e.g., Georgiou, Parrila, & Papadopoulos, 2008; Tan et al., 2005). Previously, there have been no studies exploring the relationship of infant brain responses and RAN. Furthermore, only a few studies have investigated neural systems for RAN (Lymberis et al., 2009; Misra et al., 2004). Therefore, mere speculations can be made about the underlying neural processes behind the results of this research. Most probably, infant brain activation to speech is a part of the processing that is critical for the development of automatization of lexical access.

In the at-risk group, the connection between infant brain responses (evoked by speech) and adolescent reading speed was mediated via rapid naming speed. Rapid naming has several underlying cognitive processes such as motor processes for articulators, access to lexicon and phonological representations as well as visual identification. Because visual processing is not included in infant auditory ERPs and pseudo-words without lexical representations were used as stimuli, it could be concluded that the most likely processes behind the mediating nature of rapid naming speed could involve phonological processing. Indeed, the phonology is correlated with both reading speed and infant ERPs in the at-risk group. Because no significant correlations between non-verbal IQ and ERPs, rapid naming and reading were found, general non-verbal ability does not play a significant role in the relationship between ERPs, RAN, and reading speed.

In Study III, both phonology and rapid naming correlated with infant ERPs to the pseudo-words and with reading speed, but only in the at-risk group. There was also a strong association between rapid naming and infant brain responses, as well as between phonology and brain responses. The association of phonology and rapid naming is equally strong with early reading speed in 1st grade, but the association with rapid naming increases after the initial school years, while the associations with phonology stay at the same level until 8th grade. This is in line with previous research reporting that rapid naming ability is relatively persistent until adulthood (Norton & Wolf, 2012; van den Bos, Zijlstra, & lutje Spelberg, 2002; Vukovic, Wilson, & Nash, 2004). It has also been shown that rapid naming plays a more significant role in more regular languages, like the highly transparent Finnish language, than in opaque languages like English (Bradley & Bryant, 1983; de Jong & van der Leij, 1999; Kirby, Georgiou, Martinussen, & Parrila, 2010; Wimmer, Landerl, & Schneider, 1994). However, the aforementioned associations were seen only in the at-risk group, although the majority of the at-risk children had caught up with the controls in reading speed by adolescence. These findings suggest that the role of cognitive measures depends, at least partly, on familial risk. This is consistent with earlier findings that although many dyslexics compensate for their reading deficit and become relatively fluent readers in adulthood, their deficits in phonology, RAN, and verbal STM tasks usually persist (Snowling, 1998).

4.4 The effect of familial risk on dyslexia

All in all, the results suggest that speech processing is a demanding task for humans and, in particular, for dyslexics. Indeed, speech perception mechanisms are deficient in infants at risk for dyslexia (Guttorm et al., 2001; Guttorm et al., 2003; Leppänen et al., 2002; van Zuijen et al., 2012). However, not all at-risk infants develop into dyslexics. Different levels of the severity of the risk and/or dissimilar genetic profiles may explain why this is the case. It could also be that environmental factors or an interaction between environmental and the genetic factors of an individual make the difference. It has been also seen that several dissimilar genetic profiles can lead to similarly manifesting phenotypes of dyslexia (Pennington, 2006; Willcutt et al., 2010).

Many brain studies show anatomic and functional abnormalities in the brains of at-risk children before formal reading instruction, even at birth (e.g., Clark et al., 2014; Guttorm et al., 2001; Guttorm et al., 2003; Leppänen et al., 2002; Raschle, Zuk & Gaab, 2012; van Zuijen et al., 2012). It has been claimed, however, that the dissimilarities seen between the brain responses of dyslexics and controls at school age and as adults could in fact be caused by differences in reading experiences instead of being inherited. Indeed, there is evidence showing that learning to read alters brain activity (Dehaene et al., 2010). On the basis of Studies II and III, and taking into account the earlier findings of the Jyväskylä Longitudinal Study of Dyslexia, an interaction of environmental fac-

tors and inherited factors can be seen. In infancy, the brain responses of at-risk infants and controls differed, although only a few of the at-risk children developed into dyslexics later on. However, at the age of 6.5 years (Hämäläinen et al., 2013), as well as in 3rd grade, measured brain responses of the typically reading at-risk children and typically reading controls were similar, while the brain responses of dyslexics of the at-risk group differed clearly from other groups. Therefore, it can be stated that between 6 months and 6.5 years of age, it is most probably environmental factors that alter the brain responses of at-risk children. Possibly some of the differences in brain level are inherited, while others develop due to experiences. Thus, the phrasing of the question should perhaps be about which one is more predominant: can innate processing problems be overcome with preventative factors, and can low genetic risk be overruled by environmental risk factors? In fact, genetic background should be considered as an individual's set of resources that limits how the outcome varies due to external factors.

4.5 Role of speech perception deficit in dyslexia

As introduced earlier in this report, speech perception is deficient in dyslexia but also in infants and children with familial risk, regardless of dyslexia status at school age (Hämäläinen et al., 2013; Leppänen et al., 2012; Lyytinen et al., 2008; Pennala et al., 2010; van der Leij et al., 2013; van Zuijen et al., 2013). However, there is still a gap in the chain of reasoning between auditory and speech processing deficits and manifestation of dyslexia or reading difficulties (Figure 1, page 17; for a review, see Protopapas, 2014). The evidence gained from the current research supports a bottom-up route from auditory and speech processing deficits via deficient speech sound (phonological) representations, that leads to phonological problems, and further to dyslexia or reading difficulties. In this research, deficient speech perception of at-risk infants, at-risk children and dyslexics manifested itself by abnormal ERPs to pseudo-words varying in phonemic length. While the discriminative ERPs represent a pre-attentive index of cortical accuracy of sound processing, they afford an opportunity for objective measurement of speech perception. The enhancement of the ERPs in the dyslexic group was associated with performance in behavioral phonemic length discrimination, but also with better reading and spelling accuracy. It seems that speech perception is compensated for and, as a result, reading and spelling improve. It is thought that defective phonological representations impede the automatization of phoneme-grapheme correspondences and therefore fluent reading (Elbro et al., 1998; Pasquini, Corriveau, & Goswami, 2007; Share, 1995; Snowling, 2000; Talcott & Witton, 2002). Although the exact nature of the compensatory processes is not revealed by the results of this research, together with earlier findings they give a reason to speculate that compensation could be related to more accurate or better phonological representations. Furthermore, infant ERPs predict reading speed in adolescence and the association is mostly

mediated via rapid naming. Because infant brain activation to speech sounds has been thought to act as an index of deficient development of phonological representations, which in turn affects lexical access, the results suggest that rapid naming and reading speed share a similar cognitive process of automatized access to a lexicon via phonological representations. This interpretation proposes the bottom-up route from speech perception to reading failure through phonological representations and phonological deficit.

4.6 Methodological comparison of Studies I–III

Studies I-III used ERPs to study auditory speech perception in children. Differences existed in methodologies between sub-studies. The data of the Studies I and II were collected using a common vertex reference (Cz). During preprocessing, the data applied in Study I was transformed into reference-free current source density (CSD) waveforms. CSD transformation was employed to sharpen the broad ERP voltage topographies caused by volume conduction throughout physiological tissues (Law et al., 1993; Nunez, 1981; Nunez & Srinivasan, 2006). It acts as a valuable, although not necessary, preprocessing step for temporal principal component analysis by giving a rough estimate of inner surface (dura) potential by filtering off the volume conduction (tPCA; Kayser & Tenke, 2006; Kayser & Tenke, 2015a; Tenke & Kayser, 2012). However, the use of the CSD in Studies II and III was not possible, because while applying longitudinal data, it was reasonable to use similar methods as in the previous publications of the same data.

The EEG data applied in Study II was online referred to the Cz electrode and re-referenced to average reference. In theory, the sum of all recorded EEG activity approximates zero, and because no neutral reference location exists on the human body because of volume conduction, the average reference has been preferred to all other known reference schemes when using high dense-electrode arrays (e.g., Dien, 1998; Kayser & Tenke, 2015b; Nunez & Srinivasan, 2006). The data analyzed in Study III was collected with DSAMP data acquisition software in 1990's with a limited number of channels available in the system, which made the average-referencing infeasible solution.

There is a possibility that the use of the different reference schemes could have affected the results of Studies I–III. However, a recent study comparing the reference schemes show that the reference used has not remarkable impact on results if brain area used in analyses corresponds the areas were the actual sources are (Kayser & Tenke, 2015b). In the case of the current research, it is assumed that primary sources of the activation to the auditory stimuli are bilaterally at the auditory cortices. It was confirmed in Study I using CSD transformation as an estimate of dura potential and in Study II by source analysis. When original average referenced ERP waveforms, i.e., not CSD transformed, are analyzed the predominant field topography summates at the midline and laterally to it. This is due to the volume conduction of the activations originat-

ing from both hemispheres summate at midline. This causes the frontal distribution (with reversal of the polarity at occipital areas) to be dominant. This applies to Study II, where group differences were found at frontal and occipital sites. However, the main conclusions of Study II would remain the same regardless of the reference because they were done on correlation analysis and source localization analysis within groups.

The infant data was measured in 1990's. After that, measuring and analyzing practices of EEG/ERP data have changed in many ways. Unfortunately, applying the recent practices is not possible for that dataset due to the limited number of recording electrodes. However, the value of the data is remarkable, and because the main conclusions of the data are related to correlations between ERPs and behavioral measures, the referencing has no crucial effect on interpretations made.

4.7 Conclusion

To conclude, the results show that obligatory responses do not fully explain the elicitation of the negativity within MMN time window in children, but there is a context-based change detection processing besides that. The change detection processing seems to emerge in children earlier for non-speech stimuli, compared to equally complex speech stimuli. This could indicate that in school-aged children processing of deviancy in speech is more demanding and long-lasting than change detection processing for corresponding complex non-speech sounds.

Also, together with earlier studies, the results suggest that even if a child is born with increased risk for dyslexia, the risk is not totally insurmountable. Some of the dyslexic children with familial risk have been able to develop alternative strategies for substitute their deficit in speech processing which helps their performance in reading and writing However, the question why some of the at-risk children, even those who had reading difficulties in past, develop into relatively good readers while others do not, requires further studies. In this research, only speech processing was studied while also visual and audio-visual processing might play a role in the overall picture. Nevertheless, children at familial risk for dyslexia require significantly more effort and support to achieve an adequate reading level, compared to children without familial risk. The results indicate that accurate speech perception, well-developed speech sound representations, and automatized access to those representations are necessary for fluent reading development. The retrieval process from a mental lexicon, in turn, works well and would be automatized if no impediments exist for the lower processes. This information helps in developing remediation for children in need of special support for their reading development. However, to further advance knowledge about the processes related to compensatory mechanisms at the neural level, more research is needed.

YHTEENVETO (FINNISH SUMMARY)

Aivojen herätevasteet puheääniin vauvoilla ja lapsilla, joilla on perinnöllinen lukivaikeusriski

Suvuittain esiintyvä lukemisvaikeus eli dysleksia on oppimisvaikeus, jota esiintyy noin joka kymmenennellä koululaisella. Todennäköisyys, että lapsi tulee kohtaamaan koulussa lukemisvaikeuksia, on moninkertainen, jos hänen äidillään tai isällään on havaittu dysleksia tai lukemisvaikeutta. Tässä tutkimuksessa tarkasteltiin lukiriskivauvojen ja kouluikäisten lukiriskilasten sekä tyypillisesti lukevien kontrollilasten aivojen herätevasteita puheääniin. Ärsykkeinä käytetyt puheäänet olivat joko epäsanoja, eli sanoja jotka eivät tarkoita mitään (*ata* ja *atta*), tai vokaaleja (*i* ja *y*). Ärsykkeet esitettiin äänisarjoissa, joissa usein toistuvan standardiäänen seassa esiintyi silloin tällöin poikkeava devianttiääni. Aivojen reaktioita tutkittiin sekä usein toistuviin, että poikkeaviin ääniin. Vertailun vuoksi ärsykkeinä käytettiin myös vokaaleja vastaavia monitaajuuksisia ei-puheääniä. Aivojen esitietoista muutoksenhavaitsemista puheääni- ja ei-puheäänisarjoissa tutkittiin poikkeavuusnegatiivisuusvasteen avulla.

Aiemmissa tutkimuksissa on löydetty useita tekijöitä, joiden on havaittu olevan yhteydessä dysleksiaan ja dysleksiariskiin. Syy-seuraussuhteet noiden tekijöiden ja dysleksian ilmenemisen välillä ovat vielä kuitenkin osin epäselviä. Merkittävä dysleksian riskitekijä on puheen havaitsemisen ongelmat. Dysektikkojen on vaikea havaita puheessa esiintyviä kontrasteja. Suomenkielessä tyypillinen kontrasti on vokaalien ja konsonanttien kestoero. Äänteen kesto merkitään kirjoitetussa tekstissä joko yhtä (lyhyt) tai kahta (pitkä) kirjainmerkkiä käyttäen, kuten sanoissa *tuli - tuuli* ja *aita - aitta*. Koska kestoerovaihtelu muuttaa sanan merkityksen, eli on suomenkielessä semanttisesti erotteleva piirre, on sen havaitseminen olennaista lukemisen ja kirjoittamisen kannalta. Suomalaisille dyslektikoille kestoerojen havaitseminen puheesta on kuitenkin hankalaa, ja he tekevätkin eniten virheitä vokaalien ja konsonanttien kestoihin liittyen lukiessaan ja kirjoittaessaan.

Ensimmäisessä osatutkimuksessa tarkasteltiin tyypillisesti lukevien kouluikäisten lasten esitietoista kykyä havaita muutoksia puhe- ja ei-puheäänisarjoista. Tutkimuksessa kontrolloitiin usein ja harvoin toistuvien ääniärsykkeiden esiintymistodennäköisyyttä vertaamalla koesarjassa syntyneitä aivovasteita samojen ärsykkeiden synnyttämiin vasteisiin tilanteessa, jossa ne esiintyivät keskenään samalla todennäköisyydellä. Kun esiintymistodennäköisyyden vaikutus aivovasteisiin oli näin minimoitu, havaittiin aivojen poikkeavuusnegatiivisuusvasteen syntyvän puheäänisarjassa tapahtuviin vokaalimuutoksiin myöhemmin kuin vastaaviin muutoksiin monitaajuuksisien ei-puheäänten sarjassa. Tästä pääteltiin, että muutosten havaitseminen puheäänisarjasta on todennäköisesti vaativampaa verrattuna muutoksen havaitsemiseen ei-puheäänten sarjasta.

Toisessa osatutkimuksessa tutkittiin kolmasluokkalaisten lasten aivovasteita epäsanasarjassa tapahtuviin konsonantin keston muutoksiin. Lasten luku-

taito oli määritelty toisella luokalla eli vuotta ennen herätevastemittauksia. Tutkittavista muodostettiin kolme ryhmää dysleksiariskin ja lukutaidon perusteella. Ensimmäisen ryhmän muodostivat lukiriskilapset, joilla oli havaittu dysleksia 2. luokalla. Koska osalla lukiriskilapsista ei ollut lukemispulmia 2. luokalla, heistä muodostettiin oma ryhmänsä. Kolmantena ryhmänä tutkimuksessa oli kontrolliryhmä, johon kuuluvien suvussa ei esiintynyt dysleksiaa eikä myöskään lapsilla itsellään ollut lukemispulmia 2. luokalla. Tutkimuksessa havaittiin, että dyslektikkolasten aivovasteet konsonantin lyhenemiseen olivat suuremmat verrattuna molempiin tyypillisten lukijoiden ryhmiin. Tyypillisesti lukevien dysleksiariskilasten aivovasteet olivat hyvin kontrollilasten kaltaisia. Huomionarvoista oli, että dyslektikkojen suuremmat aivovasteet olivat yhteydessä virheettömämpään lukemiseen ja kirjoittamiseen, sekä parempaan suoriutumiseen äänteiden pituuden erottelutehtävässä: mitä suurempi vaste, sitä parempi suoritus. Lisäksi huomattiin, että dysleksiaryhmän kaikkein virheettömimmin lukevilla lapsilla aivoaktivaatio konsonantin lyhenemiseen syntyi taaempana oikealla kuuloaivokuorella kuin muilla ryhmillä, mukaan lukien enemmän lukemisvirheitä tekevät dyslektikkolapset. Nämä tulokset antavat viitteitä siitä, että osa dyslektikoista on onnistunut ottamaan käyttöön korvaavia aivoprosesseja selviytyäkseen paremmin vaikeassa äänteiden pituuden erottelussa.

Kolmannessa osatutkimuksessa tarkasteltiin kuuden kuukauden ikäisten lukiriskivauvojen aivojen tuottamia herätevasteita epäsanoihin, sekä aivovasteiden yhteyttä esikouluiän kognitiivisiin taitoihin ja yläkouluiän lukutaitoon. Tutkimuksessa havaittiin, että lukiriskivauvojen aivovasteet erosivat kontrollivauvojen aivovasteista, ja lisäksi ennustivat lukemisen nopeutta 8. luokalla. Suurempi negatiivinen aivovaste vauvana oli yhteydessä nopeampaan nimeämiseen ja parempiin fonologisiin taitoihin esikouluiässä. Ennustevaikutus vauvana mitatuista aivovasteista välittyi esikouluiässä tehdyn nopean sarjallisen nimeämisen kautta. Nimeämisen nopeus puolestaan oli yhteydessä nopeampaan lukutaitoon 8. luokalla. Tämä viittaa siihen, että samojen kognitiivisten prosessien automatisoituminen sujuvoittaa suoritusta sekä nimeämis- että lukemistehtävässä. Tämän tutkimuksen perusteella voidaan päätellä, että automatisoituminen liittyisi mielensisäisestä sanavarastosta hakuun, ja että reitti kulkisi fonologisten, pitkäkestoisten muistijälkien kautta. Puolivuotiaan lukivaikeusriskivauvan aivoaktivaatio puheeseen jo ennen puhumaan ja lukemaan opettelua näyttäisi olevan varhainen merkki puutteellisesti kehittyvistä fonologisista muistijäljistä, jotka myöhemmällä iällä hidastavat yhteyksiä mielensisäiseen sanavarastoon ja hankaloittaa niin nimeämis- kuin lukemissuoritusta.

Kokonaisuudessaan tutkimuksen tulokset osoittavat, että tarkka puheen kontrastien havaitseminen, hyvin kehittyneet puheäänten pitkäkestoiset muistijäljet ja automatisoituneet yhteydet muistijälkiin ovat tärkeitä tekijöitä, että lapsesta voisi kehittyä sujuva lukija. Vaikka lukivaikeusriski on vaikea voittaa, sen voittaminen ei ole kuitenkaan täysin mahdotonta: näyttäisi siltä, että osa lukivaikeusriskilapsista onnistuu kehittämään vaihtoehtoisia tapoja hyödyntää aivojensa kapasiteettia kielen prosessoinnissa, jolloin lukeminen helpottuu. Sen selvittämiseksi, miksi toisista riskilapsista tulee ajan myötä suhteellisen hyviä

lukijoita, mutta toisista ei, tarvitaan kuitenkin vielä jatkotutkimuksia. Selvää on ainakin se, että lapset jotka lukivaikeusriskin syntymässään saavat, tarvitsevat paljon tukea ja harjoitusta. Tässä tutkimuksessa saadut tulokset antavat uutta tietoa aivovasteiden, lukemisen ja lukemiseen liittyvien taitojen välisistä yhteyksistä. Tällainen tieto on tärkeää, että voitaisiin kehittää menetelmiä lukivaikeusriskilasten lukivaikeuden ennaltaehkäisyyn tai jo kehittyneen lukivaikeuden kuntouttamiseen.

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ORIGINAL PAPERS

I

SEPARATING MISMATCH NEGATIVITY (MMN) RESPONSE FROM AUDITORY OBLIGATORY BRAIN RESPONSES IN SCHOOL-AGED CHILDREN

by

Kaisa Lohvansuu, Jarmo A. Hämäläinen, Annika Tanskanen, Jürgen Bartling, Jennifer Bruder, Ferenc Honbolygó, Gerd Schulte-Körne, Jean-François Démonet, Valeria Csépe, & Paavo H. T. Leppänen, 2013

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II

ENHANCEMENT OF BRAIN EVENT-RELATED POTENTIALS TO SPEECH SOUNDS IS ASSOCIATED WITH COMPENSATED READING SKILLS IN DYSLEXIC CHILDREN WITH FAMILIAL RISK FOR DYSLEXIA

by

Kaisa Lohvansuu, Jarmo A. Hämäläinen, Annika Tanskanen, Leena Ervast, Elisa Heikkinen, Heikki Lyytinen, & Paavo H. T. Leppänen, 2014

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Enhancement of brain event-related potentials to speech sounds is associated with compensated reading skills in dyslexic children with familial risk for dyslexia

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ABSTRACT

Specific reading disability, dyslexia, is a prevalent and heritable disorder impairing reading acquisition characterized by a phonological deficit. However, the underlying mechanism of how the impaired phonological processing mediates resulting dyslexia or reading disabilities remains still unclear. Using ERPs we studied speech sound processing of 30 dyslexic children with familial risk for dyslexia, 51 typically reading children with familial risk for dyslexia, and 58 typically reading control children. We found enhanced brain responses to shortening of a phonemic length in pseudo-words (/at:a/ vs. /ata/) in dyslexic children with familial risk as compared to other groups. The enhanced brain responses were associated with better performance in behavioral phonemic length discrimination task, as well as with better reading and writing accuracy. Source analyses revealed that the brain responses of sub-group of dyslexic children with largest responses originated from a more posterior area of the right temporal cortex as compared to the responses of the other participants. This is the first electrophysiological evidence for a possible compensatory speech perception mechanism in dyslexia. The best readers within the dyslexic group have probably developed alternative strategies which employ compensatory mechanisms substituting their possible earlier deficit in phonological processing and might therefore be able to perform better in phonemic length discrimination and reading and writing accuracy tasks. However, we speculate that for reading fluency compensatory mechanisms are not that easily built and dyslexic children remain slow readers during their adult life.

1. Introduction

1.1. Background

Specific reading disability, dyslexia, is a problem in learning to read and write despite adequate cognitive level, training, motivation, and other extraneous factors (Lyon et al., 2003; Vellutino et al., 2004). Heritability and familial clustering of dyslexia has been well established pointing to genetic factors behind dyslexia (Galaburda, 2005; Lyon et al., 2003; Lyytinen et al., 2004; Vellutino et al., 2004). Phonological skills, i.e., ability to recognize and manipulate speech sound elements, is one of the key components for acquiring the ability to read, and deficit in phonological processing is one of the most relevant factors linked to dyslexia (Goswami, 2002; Ramus, 2003; Snowling, 2000; Stanovich, 1988; Torgesen et al., 1997; Vellutino et al., 2004; Wagner and Torgesen, 1987). However, the underlying mechanism of how the impaired phonological processing mediates resulting dyslexia or reading disabilities remains still unclear. Here, we studied the brain event-related potential (ERPs) responses in dyslexic and typically reading children with and without familial risk for dyslexia to pseudo-words. Pseudo-words varied in consonant duration, i.e., phonemic length, which is a semantically distinguishing feature in the Finnish language. Also association of brain responses with outcomes in phonemic length discrimination, reading, and writing tasks were investigated.

1.1.1. Phonological processing deficit

Deficit in phonological processing is often suggested to derive from auditory or speech processing problems via inaccurate or otherwise inadequate phonological representations (Elbro et al., 1998; Griffiths and Snowling, 2002; McBride-Chang, 1995; Mody et al., 1997; Snowling, 2000). The brain's ability to discriminate between acoustic features in speech, crucial for formation of speech sound representations, may be insufficient in dyslexic readers. Defective representations in turn may lead to disability in reading and spelling by hindering the learning of fluent and automatic decoding of phoneme-grapheme correspondences

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(Elbro et al., 1998; Share, 1995; Snowling, 2000). Several theories have been formulated for the association between auditory and speech processing deficits and reading problems. The rapid auditory temporal processing (RATP) theory suggests that dyslexics have difficulties in perceiving brief auditory stimuli when they are presented in rapid succession (Tallal and Piercy, 1973; Tallal, 1980, 2004). It has been proposed that perception of slow modulations in speech, reflected in rise time discrimination, would be impaired in dyslexics (Goswami et al., 2002; Goswami, 2011). Furthermore, studies using functional magnetic resonance imaging (fMRI) to investigate speech processing have found deficits in access to phonetic representations without deficits at the cortical processing of speech sounds (Boets et al., 2013). However, there is no consensus yet on the mechanism how the deficit in phonological awareness is associated with the reading deficit or dyslexia. Nevertheless, there is strong evidence for neurobiological risk factors for dyslexia (for reviews see Habib, 2000; Démonet et al., 2004; Richlan et al., 2011, 2013). These neurobiological risk factors specifically related to speech include, for example, reduced gray matter volume at posterior Sylvian areas (Richlan et al., 2013), structural brain anomalies, such as neuronal ectopias around the Sylvian fissure (Galaburda et al., 1985), and abnormal activation and connectivity in posterior and perisylvian systems (Démonet et al., 2004).

1.1.2. Structural brain differences

Anomalies in dyslexic brain have been seen in autopsy and brain imaging studies (for reviews see Eckert, 2004; Habib, 2000). Reduction in gray matter volume has been found in areas relevant in speech and language processing, such as the superior temporal gyrus and the inferior frontal gyrus (Frye et al., 2010; Steinbrink et al., 2008). Gray matter volume in the left anterior fusiform gyrus/hippocampus, left precuneus, right hippocampus, and right anterior cerebellum have been found to increase during reading intervention in dyslexic children (Krafnick et al., 2011). Furthermore, in typical readers, gray matter thickening in the left inferior frontal cortex has been found to be associated with improving phonological skills (Lu et al., 2007). Compared to typical readers, many areas in dyslexics have been found to contain more ectopias, displacements of neurons developed during neuronal migration, near and around Sylvian fissure, particularly in the left hemisphere (Galaburda et al., 1985; Galaburda, 2005; Ramus, 2004). Also, dyslexic brains are often characterized by reduced asymmetry particularly at the posterior superior temporal gyrus, i.e., symmetrical plana temporale in the posterior Sylvian fissure (Galaburda et al., 1978, 1985; Illingworth and Bishop, 2009; Leonard and Eckert, 2008; Sun et al., 2010). The brain symmetry in dyslexics suggest anatomical differences in areas activated heavily by speech and language and possibly differences in the distribution of activity in the left and right perisylvian cortex (Binder et al., 1996; Galaburda et al., 1985). However, also different hemispheric symmetry patterns of posterior perisylvian areas, including planum temporale, have been observed in dyslexic individuals (Chiarello et al., 2006; Leonard et al., 1993).

1.1.3. Speech perception related brain responses

Deficits linked to the abovementioned anatomical differences include speech processing problems, which could be a cause for phonological deficits (e.g., Blomert, 2011; Price, 2012). In dyslexics, poor speech perception manifests itself as difficulties to discriminate and categorize speech sound contrasts like syllables, consonants and vowels (e.g., Bradley and Bryant, 1978; Godfrey, Syrdal-Lasky, Millay, and Knox, 1981; Manis et al., 1997; Mody et al., 1997; Pennala et al., 2010; Reed, 1989). Nevertheless, there are studies that fail to find differences between dyslexics and controls for some speech contrasts (Blomert et al., 2004; Groth et al., 2011). For example, Groth et al. (2011) found that dyslexics were poorer in discriminating longer vowels from shorter ones if they were made shorter by manipulation (only durational cues available), but they found no group effect for naturally shorter versus longer vowels (both spectral and durational cues available). Further, using functional magnetic resonance imaging (fMRI), Steinbrink et al. (2012) observed decreased activation of left inferior frontal gyrus and insular cortices in dyslexics during processing of the same temporal stimuli, but only in the subgroup of low performing dyslexics (Steinbrink et al., 2012). Also, it should be kept in mind that in certain conditions dyslexics can be even more sensitive to speech sound contrasts, i.e., dyslexics have been reported to be poorer in discriminating between phoneme categories, but more sensitive in discriminating within category contrasts (Serniclaes et al., 2001, 2004).

Speech sound discrimination is often studied using event-related potentials (ERPs), especially the discriminative components, which are thought to be a pre-attentive index of cortical accuracy of sound processing. They capture low level processing, and therefore work as an objective measure that is not determined by level of motivation, attention or arousal (for reviews, see Bishop, 2007; Näätänen et al., 2005; Schulte-Körne and Bruder, 2010). Using ERPs to study speech sound discrimination, abnormal responses have been found in dyslexics. In most studies responses have been smaller (e.g., Bishop, 2007; Kujala et al., 2006; Maurer et al., 2003; Schulte-Körne et al., 1998), although in some studies larger responses have been reported (e.g., Helenius et al., 2002; Hämäläinen et al., 2013). In dyslexic children, the development of ERP components has been reported to be delayed, being similar to younger typically developing children (Blomert, 2011; McArthur and Bishop, 2004), but the brain responses of children who have a history of reading difficulty but are currently reading age appropriately, i.e., compensated readers, have been found to follow those of same aged controls (Sharma et al., 2006). Sharma et al. (2006) studied three groups of school-aged children: children with current reading difficulty, compensated readers, and age appropriately reading controls. They found that compensated readers were similar in their brain responses and in behavioral auditory tasks as was the control group, whereas children with reading difficulty differed from other groups in their performance in both brain and behavioral measures.

1.1.4. Atypical quantity perception

In the 'Quantity languages' like Finnish, Japanese, and Swedish, phonemic length is a semantically distinguishing feature (Lidestam, 2009; Tervaniemi et al., 2006). Two qualities exist: a phoneme can be perceived either as short or long in relation to other phonemes in the word, although physically both phoneme durations vary and may even overlap in duration (Suomi et al., 2008; Vainio, 2001). Differences between children at risk for dyslexia and non-risk control children have been seen in ERP responses to syllables with vowel or consonant duration changes already at birth and early childhood (Leppänen et al., 1999; Leppänen et al., 2002; Pihko et al., 1999). More recently, corresponding results have been found in children and adults with dyslexia (e.g., Hämäläinen et al., 2013; Kujala et al., 2006; Lovio et al., 2010; Sharma et al., 2006). Impaired perception of phonemic length has also been found using behavioral tasks (e.g., Hämäläinen et al., 2009; Pennala et al., 2010; 2013; Richardson et al., 2003, 2004).

Although corresponding group differences between dyslexic and control children have been found, speech perception abilities change during development. In early childhood, native language environment starts to shape the perception of speech sounds (Kuhl et al., 1992; Kuhl et al., 2006; Ortiz-Mantilla et al., 2013), and improvements in speech perception accuracy are still seen during the first three grades (Pennala et al., 2010; 2013). Further, longitudinal studies have found that the differences in speech perception ability between children with and without dyslexia vary depending on age (Pennala et al., 2010), and suggestions have been made of different developmental trajectory of the perceptual abilities of children with language related difficulties (McArthur and Bishop, 2004; Wright and Zecker, 2004). Similar changes in perceptual abilities during development have been found using non-linguistic stimuli as well (Stefanics et al., 2011).

1.1.5. Maturation of ERP components

During development, brain physiology slowly changes because of, for example, myelination and changes in synaptic density, affecting also auditory brain responses (Bishop et al., 2007; Johnstone, Barry, Anderson, and Coyle, 1996; Moore and Guan, 2001; Ponton et al., 2000, 2002). In early infancy, broad ERP waveforms are typical, but already by the age of six months the auditory ERPs are well defined (see e.g. Leppänen et al., 2002). By pre-school and school-age, childhood ERPs are dominated by obligatory responses P1 and N250 with peaks around 100 and 250 ms, respectively (Čeponienė et al., 2002; Hämäläinen et al., 2013). Around 9 years of age, the most prominent auditory ERP components in adulthood, N1 and P2, begin to emerge, while P1 and N250 diminish (Hämäläinen et al., 2007; Ponton et al., 2000; Ruhnau et al., 2011). However, these changes do not purely follow the chronological age, because also (auditory) environment, i.e., sounds surrounding us, shapes the system, e.g., through exposure to music (Partanen et al., 2013). The auditory mismatch response (MMR), a component reflecting change detection process, which is detectable from a very early age, is also affected by developmental changes and acquires the waveform similar to that of an adult mismatch negativity (MMN) by school-age with a negative deflection for a deviating sound around 150–200 ms (Cheour et al., 2000, 2001; Csépe, 1995; Leppänen et al., 2004; Lohvansuu et al., 2013; Näätänen et al., 2005, 2007). Late discriminative negativity (LDN) reflecting a cognitive-level preattentive processing of the deviant stimuli has been suggested to diminish in amplitude with age (Čeponienė et al., 2004; Cheour et al., 2001; Kraus et al., 1993).

1.2. Research questions

We studied auditory event-related potentials (ERPs) of school-aged children to pseudo-words differing in phonemic length, i.e., varying in the duration of a silent gap between syllables which determines the perception of a consonant duration as short or long. Stimuli were presented in unattended condition. Group differences were investigated between three groups: reading disabled children with a familial risk for dyslexia (RDFR), typically reading children with a familial risk for dyslexia (TRFR), and typically reading control children with no familial risk for dyslexia (TRC). Based on the previous studies reviewed above, we expected to see group differences between the RDFR group and typically reading groups to phonemic length contrasts. In the RDFR group the smaller amplitudes for the change detection responses whereas larger responses for the obligatory responses were expected. Previous studies have also suggested that auditory ERP amplitudes could be associated with reading and spelling skills as well as phonological skills. However, the associations could have a different direction in the three groups. Therefore, the associations between ERPs and outcomes in phonemic length discrimination, reading accuracy, reading fluency, and writing accuracy tasks were also investigated for deeper understanding of brain activation differences between groups.

2. Material and methods

2.1. Participants

Data were collected in the Jyväskylä Longitudinal Study of Dyslexia (JLD; for reviews see Lyytinen et al., 2001, 2004, 2008) when the children were at a mean age of 9.41 years (SD .34; range 8.18 - 10.23). The ERP data of 139 children (73 girls, 66 boys) were included in this study.[1] The children had no neurological disorders and their performance IQ was at least 80, as tested with the Wechsler Intelligence Scale for Children – Third Edition (WISC-III: Wechsler, 1991). The hearing levels of the children were measured with an audiogram and determined normal with the average hearing threshold (average of the both ears) being at or below 25 dB (BSA). The children were grouped into three groups according to their reading performance at the end of 2nd grade at the age of 9 years and their family risk status. Familial risk for dyslexia was defined when at least one parent had a diagnosis of dyslexia and at least one other close relative was reported to have reading disability (see Leinonen et al., 2001). The children were determined to have a reading disability if their reading performance outcome at the end of 2nd grade fell below the 10th percentile of the performance of the JLD control children (N = 89) on at least three of four measures of reading/writing accuracy, at least three of four measures of reading speed, or two reading accuracy, and two reading speed tasks (for details see Eklund et al., 2013). Otherwise, child's reading skills were considered to be typical. The data of 58 typically reading control children with no familial risk for dyslexia (TRC), 51 typically reading children with a familial risk for dyslexia (TRFR), and 30 children with a familial risk for dyslexia and reading disability (RDFR) were included in the current study. No significant group differences were found between the groups in age or performance IQ (see Table 1).

2.2. Behavioral measures

Phonemic length discrimination, reading accuracy, reading fluency, and writing accuracy were assessed at the end of 2nd grade. The phonemic length discrimination task consisted of 22 two-, three- and four-syllable pseudo- and non-word pairs. Children were asked to determine whether words in the pair were identical or not. Reading accuracy was determined by a composite score based on reading accuracy in three- and four-syllable word (20 items) and non-word list reading tasks (20 items), whereas a composite score for reading fluency comprised of the average reading times of the abovementioned word and non-word lists. Writing accuracy was defined by a composite score of the accuracy of writing performance in four-syllable non-word dictation tests (altogether 12 items). (For details on the tests see Pennala et al., 2010; Puolakanaho et al., 2007).

2.3. Stimuli

Two naturally produced pseudo-words were used as stimuli: the short /ata/, with a total duration of 300 ms, and the long /at:a/, with a total duration of 460 ms (Fig. 1). For both stimuli, the duration of the first part of the stimulus, including the initial glottal stop and the vowel /a/, was 72 ms, and the duration of the second part, comprising of the explosion of the /t/ and the final vowel /a/, was 133 ms. The short and the long stimuli differed only in the length of the silent gap, the voiceless stop of 95 ms or 255 ms, respectively, between the initial vowel and the following stop consonant. The stimuli were presented to the participants with an interstimulus interval (ISI) of 610 ms at an intensity of 75 ± 0.5 dB(A) via a loudspeaker located approximately 1 meter above the participant's head. The intensities of the stimuli were measured with a Brüel & Kjær sound level meter (type 2235) at the estimated head position of the participant.

2.4. Procedure

During the experiment, four passive oddball experiments (each lasting 20–25 min) and one equal probability (EQ) experiment (ca. 35 min) were conducted. The results of the consonant quantity stimuli from two speech oddball experiments are reported in the current paper (the results considering stop consonant change stimuli are reported elsewhere, and the results from the experiments with paired non-speech stimuli using frequency and rise time change were reported in Hämäläinen et al., 2008). The speech stimuli analyzed in this study

[1] Out of 164 children participating in EEG measurements altogether 25 participants were excluded from this study: 12 children whose EEG data were noisy and/or had inadequate number of accepted epochs (≤60), 3 children with reported reduced hearing, 4 children with performance IQ lower than 80, 3 children with ADHD, 1 children with Asperger's syndrome, 2 children with other neurological reason (one with distended cerebral ventricles and one with exceptional findings in EEG).

Table 1
Means (standard deviations) and group comparisons (post-hoc Tukey) for behavioral measures.

	Means (standard deviations)			
	RDFR (N = 30)	TRFR (N = 51)	TRC (N = 58)	Group comparisons
Gender (boys/girls)	(13/17)	(25/26)	(28/30)	
Age	9.39 (.39)	9.44 (.34)	9.39 (.31)	RDFR = TRFR = TRC
Performance IQ	100.37 (11.59)	101.06 (11.23)	105.76 (12.35)	RDFR = TRFR = TRC
PLD (d' prime)	1.82 (.92)	1.98 (.63)	2.25 (.58)	RDFR < TRC*
Reading accuracy	−3.22 (2.55)	−.39 (1.27)	.00 (1.00)	RDFR < TRFR***, RDFR < TRC***
Reading fluency	−3.67 (3.29)	−.40 (.82)	.00 (1.00)	RDFR < TRFR***, RDFR < TRC***
Writing accuracy	−1.98 (1.60)	−.10 (.99)	.00 (1.00)	RDFR < TRFR***, RDFR < TRC***

Note. IQ, intelligence quotient; PLD, phonemic length discrimination. *$p < .05$, ***$p <$ .001 (2-tailed).

were presented in two oddball paradigms (Fig. 1): first with the short /ata/ as a standard (80%, 1010 trials) and the long /at:a/ as a deviant (10%, 125 trials); and second with the long /at:a/ as a standard (80%, 1010 trials) and the short /ata/ (10%, 125 trials) as a deviant (results for the other two deviants in the above paradigms, short /apa/ and long /ap:a/ (10%, 125 trials each), are reported elsewhere). The experiments were carried out in this order for each child. During the experiment, participants watched a silenced video or played a computer game and were instructed not to pay any attention to the sounds.

2.5. EEG recording

The EEG was recorded with Ag-AgCl electrodes using 128-channel Geodesic Sensor Nets (Electric Geodesics Inc.). The EEG was referred to the Cz electrode and recorded with the sampling rate of 500 Hz and the bandpass filter of 0.1–100 Hz. Electro-oculogram (EOG) was recorded with electrodes located above, below, and lateral to both eyes. During the experiment, impedances for the majority of the electrodes were kept below 50 kΩ. For the few electrode locations where the impedances were higher, the quality of the EEG was visually ensured. Individual EEG channels with excessive electric or other extra-cerebral noise were marked and later interpolated.

2.6. Preprocessing of the EEG data

EEG data were preprocessed using BESA software. The raw EEG data were filtered offline with a highpass filter of 0.53 Hz (forward 6 dB) and a notch filter of 50.0 Hz and re-referred to an average reference. Eye blinks in the data were corrected before averaging with an individual eye blink correction algorithm, implemented in BESA, using principal component analysis (PCA; Ille et al., 2002). ERPs to each stimulus type were obtained by averaging EEG epochs of the time window of −300 to 1060 ms around the stimulus onset and baselined to −50 to 0 ms. Channels with multiple artifacts throughout the data were omitted from the averaging and interpolated later (see below). EEG epochs with peak-to-peak deflections of over 200 μV within the epoch time window or transient peaks over 115 μV were also excluded from the averaging. For the standard stimuli, only the responses to the pre-deviant standard stimuli (preceding either of the deviants) were included in the average. Participants having at least 60 good epochs per stimulus type in the oddball experiments were included in the analyses (the average number of accepted epochs (standard deviations) and percentages, respectively, for the RDFR group were 95.1 (14.4) and 76.08 % for the deviant and 189.2 (28.7) and 75.68% for the standard stimuli; for the TRFR group 96.2 (12.6) and 76.96% for the deviant and 190.6 (23.7) and 76.24% for the standard stimuli; for the TRC group 93.6 (11.6) and 74.88% for the deviant and 186.3 (24.2) and 74.52% for the standard stimuli). The amount of accepted epochs did not differ statistically between the groups. After averaging, a lowpass filter of 35 Hz (zero-phase 12 dB) was applied, and the data for the channels previously omitted from the averaging were interpolated using a spherical spline interpolation method (Perrin et al., 1989). The average number (standard deviation) and percentage of the interpolated channels, respectively, for the RDFR group were 11.23 (4.60) and 8.77%; for the TRFR group 8.51 (5.40) and 6.65%; for the TRC group 9.72 (4.93) and 7.59%.

2.7. Statistical analyses

2.7.1. Permutation tests

Individual averaged ERPs were analyzed with BESA Statistics 1.0 for between and within group stimulus related differences. Permutation tests with channel and time point clustering for paired comparisons for the responses (2 standards, 2 deviants) and groups (RDFR, TRFR, TRC) were carried out. Number of permutations was set to 1000 for each contrast, channel cluster distance to 3 cm, analysis time window to 50–900 ms, and cluster alpha level to 0.05 (for further information

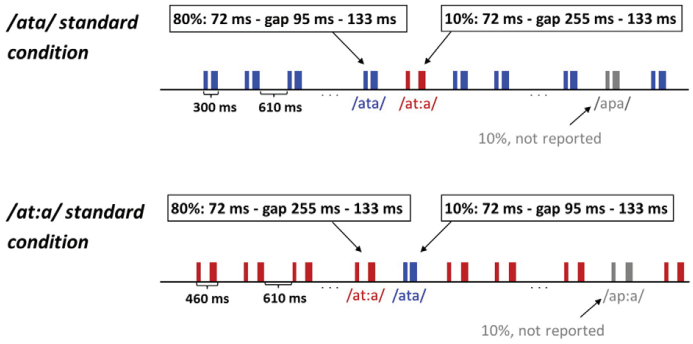

Fig. 1. Schematic illustration of the experiments and stimuli.

on the permutation testing, see Bullmore et al., 1999; Ernst, 2004; Maris and Oostenveld, 2007).

2.7.2. Correlation analysis

Brain responses in time window showing significant group differences were correlated within the groups channel by channel with phonemic length discrimination, reading and writing accuracy, and reading fluency measures using Matlab (for details regarding these measures, see Pennala et al., 2010). Significant correlations were plotted as topographic maps separately for each group using EEGLAB toolbox (see Fig. 7). Furthermore, significance of the differences in the correlation topographies between the groups was tested using Matlab (for further information on correlation testing, see McNemar, 1969).

2.7.3. Phase-locking analysis

In order to further examine the group differences for all stimuli across the whole analysis time window, phase locking values were calculated, using the coherence module in Besa Research 6.0, across the trials for each child. The data were first transformed to 26 channels corresponding to the 10–10 system. No offline filters were applied to the raw EEG data before the time-frequency calculations. Frequencies between 2 and 46 Hz were examined with 1 Hz frequency resolution and 50 ms time resolution. A complex demodulation method built in BESA was used to examine the inter-trial phase locking (ITPL) values. Differences between groups in ITPL were examined in paired comparisons using BESA Statistics 1.0.

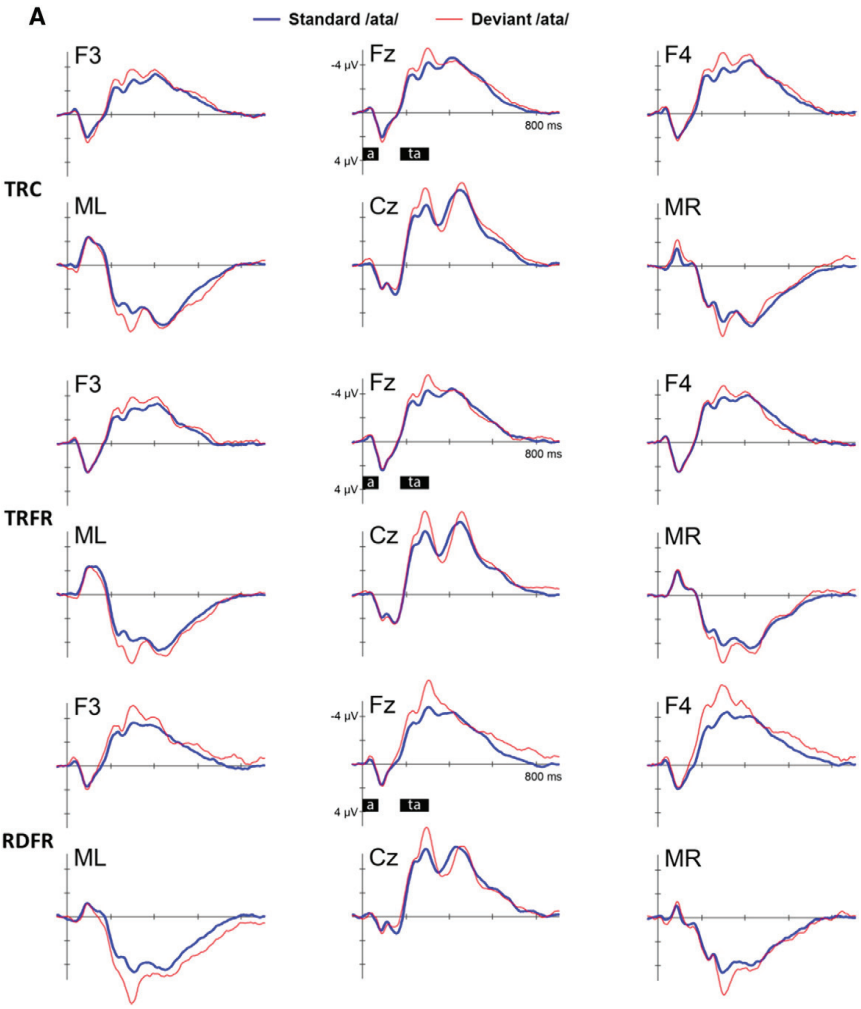

Fig. 2. Grand average ERP waveforms for the stimuli with a short (A) and for long (B) consonant length in the three groups: children with a familial risk for dyslexia and reading disability (RDFR, N = 30), typically reading children with a familial risk for dyslexia (TRFR, N = 51), and typically reading controls (TRC, N = 58). Vertical tick marks represent 2 μV and horizontal tick marks 200 ms (negativity up).

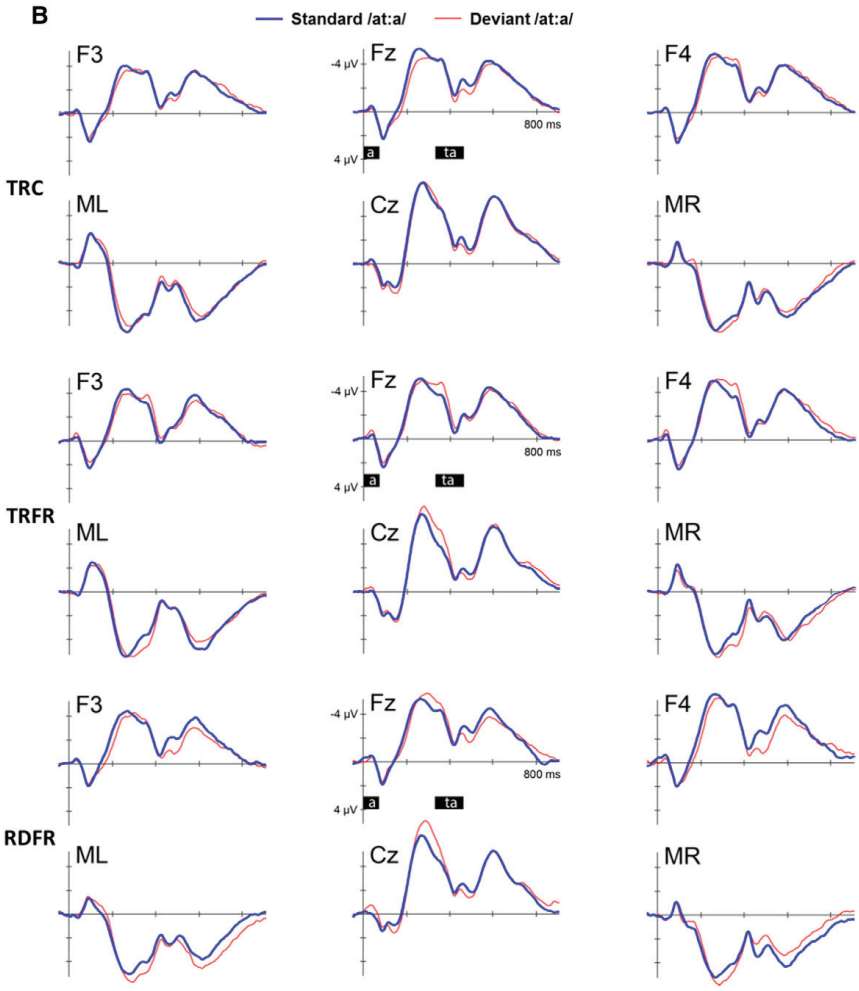

Fig. 2 (*continued*).

2.7.4. Source analysis

The source localization was carried out for the grand average ERP waveforms of the groups to reveal the approximate areas generating the activity for the short /ata/ deviant stimulus, which showed most significant group differences in permutation tests (see Results). A time window of 264–324 ms showing the most significant group differences between the RDFR (N = 30), TRFR (N = 51), and TRC (N = 58) was used for dipole fitting. For the source localization analysis the RDFR group was divided into 3 equally sized groups on the basis of their reading accuracy performance (N = 10 for each) to explore the effect of the stronger ERP amplitudes correlating with better reading accuracy within the RDFR group. A realistic approximation head model for 8–10-year-old children, available in the BESA software, was used with brain-to-skull conductivity ratio of 30 (Hoechstetter et al., 2010). The time window used showed a stable topography for the source analysis.

3. Results

3.1. Within group comparisons

3.1.1. Deviant /ata/ vs. standard /ata/

Within all groups, the response to the deviant /ata/ was statistically significantly stronger (more negative at frontal and central areas and more positive at occipital, parietal, and temporal areas, if not mentioned otherwise) in amplitude than response to the standard /ata/ (see Figs. 2A and 3). In the TRC group, the response to deviant /ata/ was stronger frontocentrally at the time window of 136–338 ms and at temporal-parietal-occipital area at 158–364 ms (p = .001 and p = .017, respectively). In the TRFR group, two clusters were significant between responses: one beginning with central distribution and shifting to bilateral temporal sites at 126–618 ms, being weaker in positivity between 126–290 ms, and another at temporal-parietal-occipital area

between 88–372 ms, being weaker in positivity between 375–440 ms ($p < .00001$ and $p = .003$, respectively). In the RDFR group, responses to deviant /ata/ were stronger frontocentrally at 88–450 ms and at 494–900 ms ($p < .00001$ and $p = .002$, respectively), and bilaterally at temporal-parietal-occipital site at 108–448 ms and moving from right to left between 572–900 ms ($p = .002$ and $p = .001$, respectively). Based on the timings and topographies, these differences most likely occurred in several different components, including MMN, and, for the TRFR and RDFR groups, also LDN response at the later time window. The response at the time window of the earliest differences at 88–167 ms (before the onset of the second /ta/ syllable of the short /ata/) is due to a violation of a context effect created by a longer SOA when the longer /at:a/ was the standard stimulus. The consecutive time window from 170 ms onwards is likely to reflect afferent activation for the earlier second syllable /ta/ onset when the longer /at:a/ was the standard stimulus. Later on, from ca. 270 ms the deviant-standard response differences reflect overlapping effects of change detection (MMN) and N250. Similar effects also explain comparable deviant-standard response differences in relation to a shorter SOA when short /ata/ was the standard stimulus (see Fig. 1).

3.1.2. Deviant /at:a/ vs. standard /at:a/

Within all groups, the responses to the deviant /at:a/ differed from the responses to the standard /at:a/ (see Figs. 2B and 3): in the TRC group frontocentral activation between 124–280 ms was more negative for the standard ($p = .011$). In the TRFR group, responses were stronger for the deviant as compared to the response to the standard stimulus at frontocentral area, being more negative at 266–424 ms, and occipital site, being more positive at 278–670 ms ($p = .002$ and $p = .010$, respectively). In the RDFR group, centrally distributed activation between 256–520 ms was more negative for the deviant stimulus, and frontally distributed activation between 146–264 ms was more negative for the standard stimulus ($p = .003$ and $p = .049$, respectively).

3.2. Between group differences

Responses to the deviant /ata/ in the RDFR group differed statistically significantly from responses of the other groups, TRFR and TRC, for several channel clusters and time windows (see Figs. 4 and 5). The RDFR group showed significantly more negative and more right-lateralized responses as compared to the TRC group at the frontal area between 132–900 ms after stimulus onset and more positive at occipital site between 50–378 ms ($p = .001$ and $p = .038$, respectively). When compared to the TRFR group, the RDFR group showed significantly larger responses towards negative voltages at frontocentral area at 50–900 ms and more positive responses at occipital site at 56–380 ms and at 486–830 ms ($p < .00001$, $p = .043$ and $p = .005$, respectively). No statistically significant group differences were found for responses to the other stimuli.

3.2.1. Phase-locking and source analysis

Larger ERP responses could be due to better phase-locking of the single trials to the stimulation. Therefore, we also examined the inter-trial phase locking values in each group, but did not find statistically significant differences between any of the groups. Another cause for differences in the ERP amplitudes could be due to the underlying source structure of the ERPs. Equivalent current dipole fitting to the grand average data revealed that the source locations between the TRC and TRFR groups were the same near left and right auditory cortices (see Fig. 6). However, when examining the source locations of the subgroup of RDFR children who had the largest amplitudes ($N = 10$), a right hemisphere source location was found approximately 20 mm posterior to of the sources in all the other groups, including other children of the RDFR group ($N = 20$) with amplitudes close to those of the TRC group. Source in the left hemisphere, in the subgroup of RDFR children who had the largest amplitudes ($N = 10$), was close to that of the other groups.

3.3. Short deviant /ata/ and correlations to behavior

The time windows showing group differences were selected for correlation calculations. Amplitude values around N250/MMN peak (294 ms ± 30 ms) and LDN time window (600 ms ± 50 ms) were averaged across time. The averaged amplitudes were correlated to behavioral measures within groups in each measured channel. Significant correlations ($ps < .05$) are seen plotted as a topographic map for each group in Fig. 7. Statistical significances of within group correlation differences were also tested between groups. Fig. 8 shows scatterplots of the correlations from a representative channel. As can be seen, the correlation coefficient is overall clearly larger for the children with dyslexia as compared to the other groups and the correlations are not produced by outlying cases (one participant from the RDFR group was excluded as an outlier in reading fluency).

3.3.1. Phonemic length discrimination

At the N250/MMN time window in the RDFR group, right frontocentral and occipital brain responses to the deviant /ata/ showed correlations with speech perception (phonemic length discrimination) scores ($ps < .05$), but only the correlations at the frontal area differed from the other groups ($ps < .05$). Significant correlations within at-risk and dyslexic groups were found at the LDN time window as well as at frontocentral and occipital brain areas, but those were not significantly different between groups.

3.3.2. Reading accuracy

The brain processing of consonant length at the right frontocentral and occipitoparietal areas at the N250/MMN and LDN time windows was found to be associated with reading accuracy, but in the RDFR group only. The frontal correlations of the RDFR group were significantly different from the correlations in the other groups ($ps < .05$).

3.3.3. Reading fluency

Significant correlations between brain measures and reading fluency were found only for the N250/MMN time window. Correlations of the RDFR group at the frontal area and correlations of the TRFR group at the occipital area differed significantly from those of the TRC group ($ps < .05$).

3.3.4. Writing accuracy

Brain measures at the N250/MMN time window at the right frontal and occipital brain areas showed significant correlations with writing accuracy scores in the RDFR group ($ps < .05$), but only correlations at the frontal area differed significantly ($ps < .05$) from the correlations of the other groups. At the LDN time window at right frontal area, the TRC group showed correlations significantly different from the other groups ($ps < .05$).

4. Discussion

In the current study, consonant quantity perception was investigated in school-aged children with and without familial risk for dyslexia and with and without reading disorder using electroencephalography (EEG). Enhanced ERPs were found for shortening of the pseudo-word stimuli (/ata/ presented among /at:a/ in an oddball/ MMN paradigm) in dyslexics with familial risk for dyslexia (RDFR) as compared to both typically reading groups (TRFR and TRC). Group differences were not found for lengthening of the consonant duration (see Fig. 2). Visual inspection of topographic maps (Fig. 3) and source localization analysis (see Fig. 4) revealed that a subgroup of the RDFR group with highest reading performance had the largest brain responses and that the source of their ERPs was located more posteriorly at the right auditory

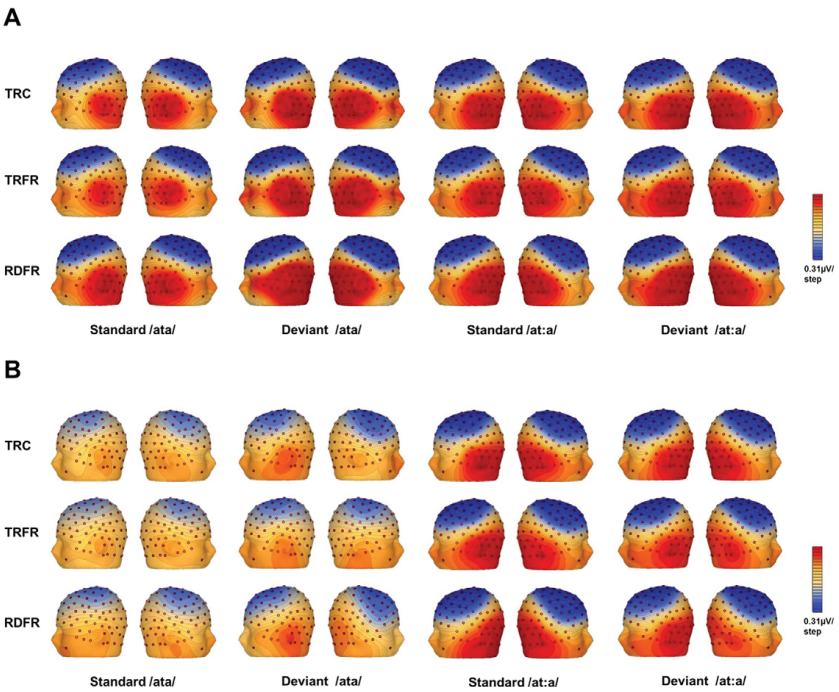

Fig. 3. Topographic maps for responses to all stimuli at 294 ms (A) and at 600 ms (B) by groups: children with a familial risk for dyslexia and reading disability (RDFR, N = 30), typically reading children with a familial risk for dyslexia (TRFR, N = 51), and typically reading controls (TRC, N = 58).

areas as compared to the all other participants. Further, correlations between brain responses to the speech sounds and reading and writing accuracy, reading fluency, as well as behavioral discrimination of phonemic length were assessed. The correlations showed that the responses within the dyslexic group (RDFR) to short deviant /ata/ at N250/MMN time window were associated with phonemic length discrimination (Figs. 7 and 8), as well as reading and writing accuracy: the stronger the potential, the better performance in behavioral tasks. Associations in the other two groups were less systematic. These findings suggest that different brain areas are involved in processing of these tasks in the different groups.

Previously, mainly diminished brain event-related responses in dyslexic children or in children at familial risk for dyslexia for any change in auditory stimulus train have been reported (Schulte-Körne et al., 1998; Maurer et al., 2003; Lachmann et al., 2005; Lovio et al., 2010; Sharma et al., 2006). Instead, in the current study we found atypically large

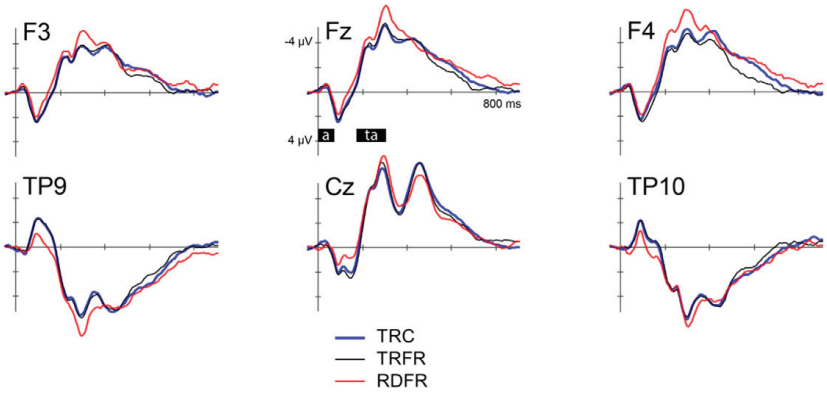

Fig. 4. Grand average ERP waveforms for the responses to the short deviant /ata/ stimulus in the three groups: children with a familial risk for dyslexia and reading disability (RDFR, N = 30), typically reading children with a familial risk for dyslexia (TRFR, N = 51), and typically reading controls (TRC, N = 58). Vertical tick marks represent 2 μV and horizontal tick marks 200 ms (negativity up).

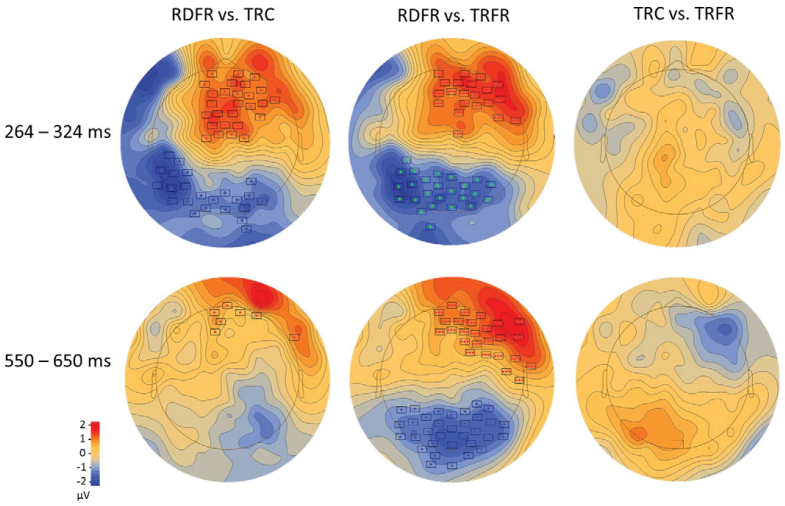

Fig. 5. Group difference topographies between children with a familial risk for dyslexia and reading disability (RDFR, N = 30), typically reading children with a familial risk for dyslexia (TRFR, N = 51), and typically reading controls (TRC, N = 58) for the deviant /ata/ stimulus response at 264–324 ms (N250/MMN) and 550–650 ms (LDN) time windows. Statistical clusters marked with rectangles differ significantly between the groups.

and enhanced response for shortening of the consonant length in pseudo-word stimuli in the dyslexic group. A few studies reporting enhanced ERPs in dyslexics to auditory stimuli also exist. For example, Hämäläinen et al. (2013) found enhanced N250 responses in 6.5-year-old kindergarten children with later dyslexia as compared to at-risk and control groups. In their study, though, the enhancement occurred for lengthening of consonant duration, whereas in the current study, this was found only for the shortening, which was not studied in the study by Hämäläinen et al. (2013). Furthermore, the enhanced responses in their study were associated with poorer reading accuracy and slower reading speed later at the 2nd grade. In adult dyslexics, parents of the children of the current study, enhanced N100m responses to first /a/ syllable of the pseudo-word /ata/ have been reported in active discrimination condition (Helenius et al., 2002). However, because of the differences in experimental design (e.g., in instructions (active/passive), stimulation rate, and presentation), the results are not fully comparable with our findings. In their study, Helenius et al. (2002) did not examine associations to behavioral measures, and therefore it remains unknown whether participants with the largest amplitudes were the best discriminators and readers within the adult dyslexic group. The enhanced responses in the current study could be due to larger cortical area activating to stimulation reflected also in the different source location at the right hemisphere for the sub-group of children with largest responses within the RDFR group.

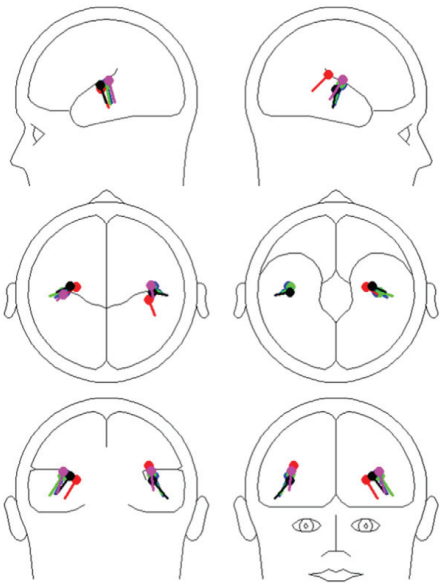

Fig. 6. Source localization for the short deviant /ata/ at a time window of 264–324 ms. Dipoles for groups are denoted with different colors as follows: red = the most accurate readers of the RDFR group (N = 10), black = the intermediate readers of the RDFR group (N = 10), pink = the poorest readers of the RDFR group (N = 10), green = TRFR group (N = 51), and blue = TRC group (N = 58).

4.1. Correlations of brain responses to reading related skills

Interestingly, it was found that, within the dyslexic group, those with the largest N250/MMN responses were the best in behaviorally discriminating phonemic length and they were also the most accurate readers and writers within the dyslexic group (Figs. 7 and 8). To our knowledge, no such result has been reported previously. We speculate it could reflect a compensatory mechanism in some individuals with dyslexia, in whom the auditory and speech perception network is organized differently leading to improved speech perception, reading, and writing skills. This is supported by our earlier finding, that within partly overlapping population of dyslexics tested three years before, the enhanced brain responses were related to poorer performance in reading at the 2nd grade (Hämäläinen et al., 2013).

Many studies show anomalies in children with dyslexia in their brain functionality and anatomy. For example, dyslexics have been suggested to have more symmetrical hemispheres in general, as well

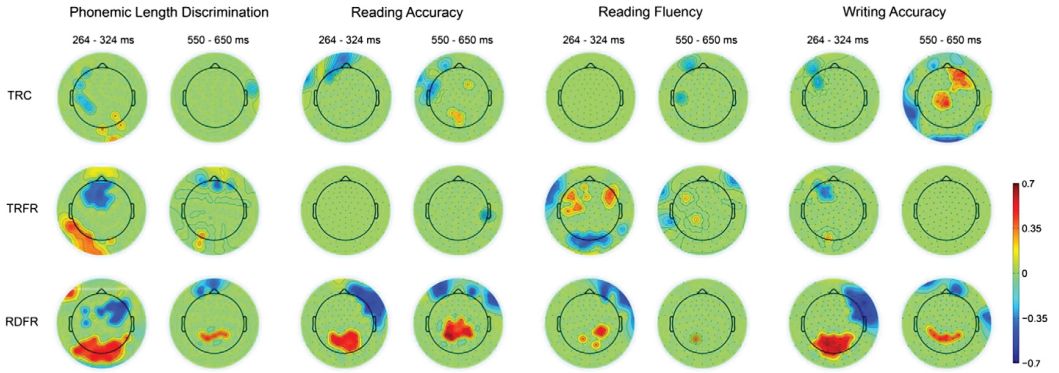

Fig. 7. Significant correlations ($p < .05$) indicated by blue (negative) and red (positive) for responses to the short deviant /ata/ stimulus (averaged over the time windows of 264–324 ms (N250/MMN) and 550–650 ms (LDN)) with phonemic length discrimination, reading accuracy, reading fluency, and writing accuracy measures. One participant from the RDFR group was excluded as an outlier in reading fluency.

as symmetrical specific brain structures such as plana temporale in the posterior Sylvian fissure, which might affect the brain activation originating from these areas involved in speech and language processing (Binder et al., 1996; Galaburda et al., 1978, 1985; Illingworth and Bishop, 2009; Leonard and Eckert, 2008; Sun et al., 2010). Regardless of the commonly reported reduced asymmetry, also asymmetry has been reported: adults with familial risk and earlier history of clinically diagnosed dyslexia, but whose reading skills were later compensated, showed leftward asymmetry of planum temporale (Chiarello et al., 2006; Leonard et al., 1993).

Leonard et al. (1993) studied compensated adult dyslexics as well as their first or second-degree unaffected relatives. They found that the relatives had less cerebral anomalies and better scores in phonological awareness as compared to compensated dyslexics, yet more anomalies and lower scores than in the control group. This was interpreted to mean that all anomalies in the brain are linked to certain processing or perceptual strategies, of which some would be compensable by alternative strategies, while multiple and bilateral anomalies would be more difficult to compensate. Source localization analysis of the current data revealed that, for the subgroup of the best reading dyslexics with the largest EEG responses, the source was located about 20 mm more posterior at the right auditory areas as compared to the others in the RDFR, TRFR, and TRC groups. This suggests a *more* asymmetrical brain response pattern between the hemispheres in the anterior-posterior direction in the subgroup of dyslexics, possibly reflecting compensation mechanisms. Using fMRI during a same-different word identification test, Kovelman et al. (2012) found greater activation in the right temporoparietal neocortex in dyslexic children as compared to typical readers who suppressed this region, suggesting atypical reliance on right posterior cortex in phonological processing in dyslexics. Kovelman et al. (2012) suggested that this is due to a compensatory mechanism in dyslexics related to their impaired phonological processing. Some reading studies have also reported hyperactivation of right temporal and parietal regions, which has been interpreted as an enhanced compensatory neural mechanism due to the reading process being more demanding for dyslexic children (Shaywitz and Shaywitz, 2005; Simos et al., 2002). Also, hyperactivation in the left inferior frontal gyrus in dyslexic group has been reported and assumed to reflect increased effort related to phonological coding (Georgiewa et al., 2002). In the current study, discrimination performance as well as reading and writing accuracy showed significantly differing correlations (the larger the amplitudes the better the scores) in the dyslexic group at the right frontal areas as compared to other groups. These areas have been found to be involved in reading in dyslexics and assumed to compensate for the underachievement of corresponding left temporal and parietal areas (Pugh et al., 2000; Shaywitz and Shaywitz, 2005).

An important point, when comparing the present study with the earlier studies in children of the same age, is that the stimuli used in several of those studies substantially differ from those used in the present study. Although speech sounds have been used, stimulus sets have typically consisted of CV syllables differing in consonant quality rather than in consonant quantity, which was the modification in the current study. However, using the same pseudo-word stimuli /ata/ and /at:a/ and partly the same sample as in the current study, enhanced responses have been observed for the quantity change, at an earlier age before reading instruction and acquisition (Leppänen et al., 2002; Hämäläinen et al., 2013). These findings refer to the fact that the complexity/type of the stimuli and experimental design highly affect the observed group differences between dyslexics and good readers. Further, the severity of dyslexia phenotype and the age of the participants with dyslexia also seem to affect the results, as well as the fact that in some cases there is a familial, i.e. genetic, background, and in others there is not. It should also be noted that there is considerable overlap in the responses of children with dyslexia and typical readers and that not all dyslexic children display an atypical response. These differences should be taken into consideration when comparing studies.

4.2. Maturation

Although our finding of the enhancement of the N250/MMN in the dyslexic group deviates from the main line of findings of group differences in children of the same age, the morphology of the brain event-related potentials as a whole is very similar as in the previous studies (Bishop et al., 2007; Čeponienė et al., 2002; Ponton et al., 2000, 2002). In line with earlier studies of children at early school-age, the predominent ERP components in the current study were P1, a positive deflection around 100 ms, and N250, a negative deflection around 250 ms, for all groups and in response to all stimuli. With the relatively short ISI of 610 ms, N1 was not yet clearly visible at the frontal area, but the TRC and the TRFR groups showed significantly larger amplitudes to all stimuli around 100 ms as compared to the RDFR group, which could suggest a more immature activation of the supratemporal source of the N1 in the RDFR group (see Figs. 2 and 4). In addition, the TRC and TRFR groups showed smaller amplitudes at the N250 time window as compared to the RDFR group (see Figs. 2 and 4). These group differences seen between the RDFR group and the other two groups indicate a

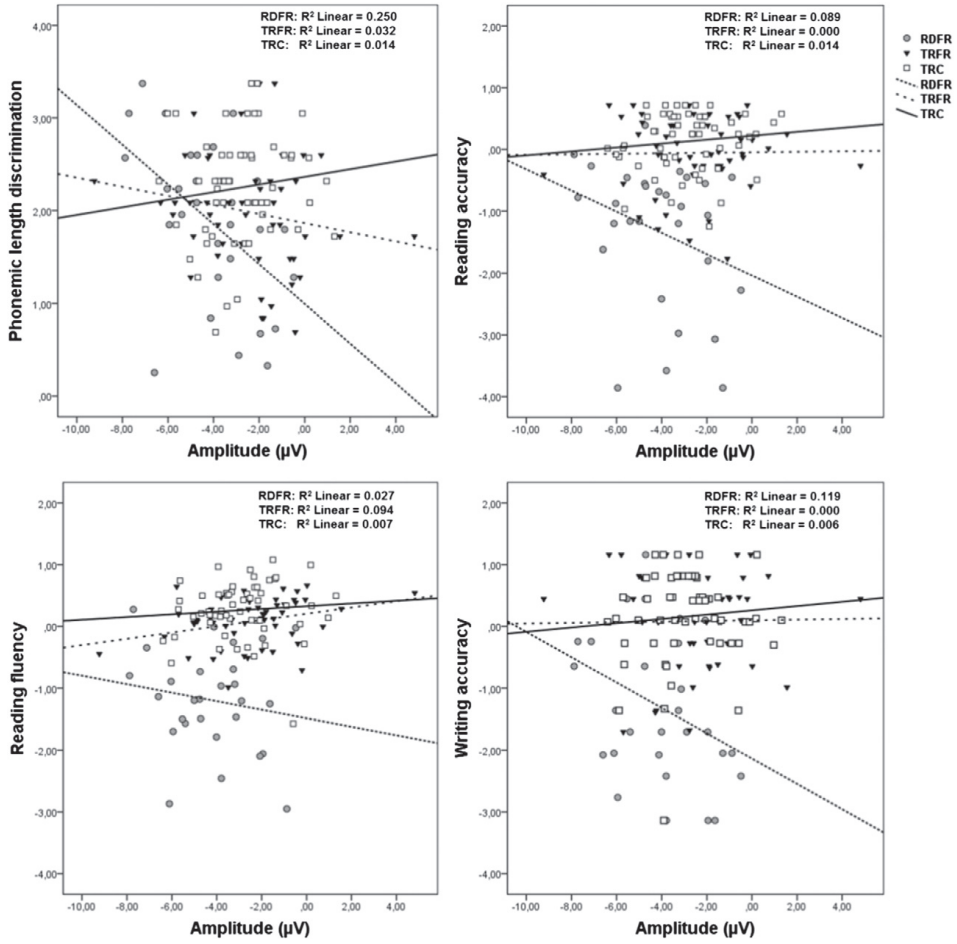

Fig. 8. Scatter plots of average amplitude (μV) of responses to the short deviant /ata/ between 264–324 ms at the channel 123 (near F4) and phonemic length discrimination, reading accuracy, reading fluency, and writing accuracy scores in the three groups: children with a familial risk for dyslexia and reading disability (RDFR, N = 30), typically reading children with a familial risk for dyslexia (TRFR, N = 51), and typically reading controls (TRC, N = 58). One participant from the RDFR group was excluded as an outlier in reading fluency.

possible slower maturation and differential brain development in dyslexic group, although earlier studies suggest that no clear developmental lag exist in children with reading difficulties at the behavioral level (Felton et al., 1990; Francis et al., 1996; Shaywitz et al., 1999). Unlike in the RDFR group, in the TRC and TRFR groups relative diminishing of the N250 (see Fig. 4) during maturation may already have begun, as well as emerging of the supratemporal subcomponent of the N1 (Hämäläinen et al., 2007; Ponton et al., 2000; Ruhnau et al., 2011). Late discriminative negativity (LDN) was seen in all groups emerging at around 550 ms for the short deviant stimuli and after 700 ms for the long deviant stimuli (in both cases at about 400 ms after the stimulus deviancy). This finding is in line with earlier findings in children of this age (e.g., Cheour et al., 2001; Čeponienė et al., 2004).

It might be possible that the above group differences arise because of a larger change detection processing (MMN) being embedded in the brain responses of the RDFR group within these time windows. However, the N250 response to the other short stimuli as well, i.e., to the standard /ata/, was smaller in amplitude in the TRC and TRFR groups in comparison to the RDFR group, and the response to the deviant /ata/ was clearly larger in all groups when compared to the response to the standard stimuli with a short gap (see Fig. 2A). This indicates that the larger response in the RDFR group cannot purely be due to the chance detection process, although, in the current study, the identification of the MMN for the consonant length change was difficult with confidence, because the short deviant /ata/ and the short standard /ata/ were presented in different conditions, most likely causing some differing context effects. However, it is likely that the change detection processes contributes to the responses after 150 ms after the stimulus deviancy.

4.3. Conclusion

In this study, we found that the subgroup of dyslexic children who had enhanced brain responses performed better in phonemic length discrimination and reading and writing accuracy, but not in reading

fluency, when compared to the other dyslexics who did not have enhanced brain responses. We also discovered that the brain responses of those dyslexic children with the largest amplitudes for the pseudo-word with a short consonant length originated from a more posterior area of the supra-temporal cortex in comparison to the other groups. The best readers within the dyslexic group have probably developed alternative strategies which employ compensatory mechanisms substituting their possible earlier deficit in phonological processing and might therefore be able to perform better in phoneme length discrimination and reading and writing accuracy tasks. However, it seems that for reading fluency possible compensatory mechanisms are not that easily built and, as usually has been seen, dyslexic children remain slow, although become rather accurate readers during their adult life.

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III

INFANT BRAIN RESPONSES AT 6 MONTH PREDICT READING AT 14 YEARS

by

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