

**Cortical multi-attribute
auditory discrimination deficits
and their amelioration in dyslexia**

Riikka Lovio



Cognitive Brain Research Unit
Cognitive Science
Institute of Behavioural Sciences
University of Helsinki, Finland

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Supervisors

Professor Teija Kujala
Cognitive Brain Research Unit
Cognitive Science
Institute of Behavioural Sciences
& Cicero Learning
University of Helsinki, Finland

Professor Risto Näätänen
Cognitive Brain Research Unit
Cognitive Science
Institute of Behavioural Sciences
University of Helsinki, Finland

Department of Psychology
University of Tartu
Tartu, Estonia

Center of Integrative Neuroscience
University of Aarhus
Aarhus, Denmark

Reviewers

Professor Pirjo Korpilahti
Department of Behavioural Sciences and Philosophy
Institute of Social Sciences
University of Turku, Finland

Dr. Maria Uther
Head of Department and Reader in Cognitive Psychology
Department of Psychology
University of Winchester
Winchester, Hampshire, United Kingdom

Opponent

Dr. Torsten Baldeweg
Developmental Cognitive Neuroscience Unit
UCL Institute of Child Health
London, United Kingdom

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ABSTRACT

Dyslexia is a highly heritable neurobiological disorder defined as a persistent difficulty in learning to read. Phonological processing skills, associating letters to sounds, and word retrieval are deficient in many children with dyslexia. Poor reading accuracy and slow reading speed are, in turn, characteristic for adults with dyslexia.

Intact processing of even minor differences in speech sounds is essential for language development and reading skills. Speech perception requires sound discrimination and phoneme identification, despite the variation in their acoustical features. Accurate phonological representations are also important for learning the connection between sounds and letters. Difficulties in auditory processing are common in individuals with dyslexia. Cortical auditory processing can be investigated by recording the electroencephalography (EEG). The detection of changes in the regularities of the auditory input gives rise to neural activity in the brain that is seen as a mismatch negativity (MMN) response of the event-related potential (ERP) recorded by EEG. As the recording of MMN requires neither a subject's behavioural response nor attention towards the sounds, it is suitable for studies of even young children. Despite its advantages over behavioural measures, a major obstacle to the use of the MMN method has been the relatively long duration of its recording. However, the multi-feature MMN paradigm with several types of sound changes was recently developed in order to obtain a comprehensive profile of auditory sensory memory and discrimination accuracy in a short recording time.

The present thesis investigated cortical multi-attribute auditory processing in dyslexia and the efficacy of intervention on reading-related skills and cortical speech sound discrimination. Moreover, the feasibility of the multi-feature paradigm for dyslexia research, and studies in children was tested for the first time. In this thesis, the multi-feature paradigm was found to be well suited for studies investigating central auditory processing in dyslexia and in children. The results showed that cortical auditory processing is aberrant in dyslexia. In children at risk for dyslexia, auditory processing seems to be deficient even at the initial phase of sound encoding. Furthermore, these children also showed a widespread pattern of abnormal cortical

auditory discrimination processes. Adults with dyslexia, in turn, have difficulties in discriminating sound frequency and duration features in a complex auditory environment. Early intervention can influence the developmental path of dyslexia, however. The results of this thesis show that even a short intervention with audio-visual letter-sound exercises improves children's reading-related skills and cortical discrimination of vowel contrasts.

TIIVISTELMÄ

Lukivaikeus on vahvasti perinnöllinen neurobiologinen häiriö, jota määrittää pysyvä vaikeus lukemaanoppimisessa. Fonologinen prosessointi, kirjain-äänne –vastaavuuksien oppiminen sekä sanahaku ovat usein poikkeavia lapsilla, joilla on lukivaikeus. Lukemisen virheet ja hitaus ovat puolestaan lukivaikeudelle tyypillisiä piirteitä aikuisuuteen saakka.

Normaali kielenkehitys ja lukemaanoppiminen edellyttävät puheessa tapahtuvien muutosten tarkkaa käsittelykykyä. Puheen havaitseminen vaatii äänten hienojakoista erottelukykyä ja foneemien tunnistamista akustisten piirteiden vaihtelusta huolimatta. Vahvat fonologiset edustukset ovat tärkeitä myös kirjain-äänne –vastaavuuksien oppimisessa. Kuulotiedon käsittelyn vaikeudet ovat yleisiä lukivaikeudessa. Kuulotiedon esitietoista käsittelyä voidaan tutkia aivosähkökäyrää mittaamalla. Ääniympäristöstä poikkeavien äänien havaitsemisesta syntyvä hermosolujen aktivoituminen näkyy aivosähkökäyrässä tapahtumasidonnoisena MMN-jännitevasteena (engl. mismatch negativity). Koska MMN:n rekisteröiminen ei edellytä tutkittavalta tehtävän tekemistä tai ärsykkeiden aktiivista kuuntelemista, sen avulla voidaan tutkia sensorisen kuulotiedon käsittelyä jo pienillä lapsilla. Vaikka MMN-tutkimuksella onkin huomattavia etuja verrattuna behavioraalsiin menetelmiin, sen yleistymistä laajempaan käyttöön on jarruttanut MMN-rekisteröinnin suhteellinen hitaus. Vastikään kehitetyillä koeasetelmilla voidaan kuitenkin rekisteröidä lyhyessä ajassa useiden äänten piirteiden prosessoinnin profiilit.

Tässä väitöskirjassa tutkittiin esitietoista kuuloprosessoinnin profiilia lukivaikeudessa sekä kuntoutusmenetelmän vaikutuksia lukuvalmiustaitoihin ja puheäänissä tapahtuvien muutosten esitietoiseen erotteluun. Lisäksi monipiirreparadigman soveltuvuutta lukivaikeus- ja lapsitutkimuksiin tutkittiin ensimmäistä kertaa. Väitöskirjan tulokset osoittavat, että monipiirreparadigma soveltuu sensorisen kuulotiedon käsittelyn tutkimukseen lukivaikeudessa ja lapsilla. Väitöskirjan tulosten mukaan sensorinen kuulotiedon käsittely on poikkeavaa lukivaikeudessa. Lapsilla, joilla on riski lukivaikeuteen, kuulotiedon sensorinen käsittely poikkeaa jo äänitiedon peruskäsittelyssä. Lisäksi näillä lapsilla kuulotiedon esitietoinen

erottelutarkkuus on heikompaa niin kielellisten kuin ei-kielellisten ääntenpiirteiden osalta. Aikuisilla, joilla on lukivaikeus, on puolestaan vaikeuksia muodostaa muistijälkeä äänen taajuudelle ja kestolle ääniympäristön ollessa haasteellinen. Lukivaikeuden kehityskulkuun voidaan kuitenkin vaikuttaa aikaisella kuntoutuksella. Väitöskirjan tulosten mukaan jo lyhytkestoinen audiovisuaalinen kirjain-äänne – yhteyksien harjoittelujakso kohentaa lasten lukemiseen liittyviä taitoja ja esitietoista vokaalierottelua.

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LIST OF ORIGINAL PUBLICATIONS

I Kujala, T., Lovio, R., Lepistö, T., Laasonen, M., & Näätänen, R. (2006). Evaluation of multi-attribute auditory discrimination profile in dyslexia with the mismatch negativity. *Clinical Neurophysiology*, *117*, 885–893.

II Lovio, R., Pakarinen, S., Huotilainen, M., Alku, P., Silvennoinen, S., Näätänen, R., & Kujala, T. (2009). Auditory discrimination profiles of speech sound changes in 6-year-old children as determined with the multi-feature MMN paradigm. *Clinical Neurophysiology*, *5*, 916–921.

III Lovio, R., Näätänen, R., & Kujala, T. (2010). Abnormal pattern of cortical speech feature discrimination in 6-year-old children at risk for dyslexia. *Brain Research*, *1335*, 53–62.

IV Lovio, R., Halttunen, A., Lyytinen, H., Näätänen, R., & Kujala, T. (2012). Reading skill and neural processing accuracy improvement after a 3-hour intervention in preschoolers with difficulties in reading-related skills. *Brain Research*, *1448*, 42–55.

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ABBREVIATIONS

ANOVA	analysis of variance
EEG	electroencephalogram
ERP	event-related potential
fMRI	functional magnetic resonance imaging
FIQ	full-scale intelligence quotient
F0	fundamental frequency
Hz	Hertz
IQ	intelligence quotient
MEG	magnetoencephalography
MMN	mismatch negativity
MMNm	magnetic mismatch negativity
p	probability
PIQ	performance intelligence quotient
RAN	Rapid naming test
SD	standard deviation
SOA	stimulus onset asynchrony
SSG	Semisynthetic Speech Generation method
VIQ	verbal intelligence quotient
WAIS-R	Wechsler Adult Intelligence Scale – Reviser
WISC-III	Wechsler Intelligence Scale for Children, 3 rd edition

1 INTRODUCTION

From early on, a child is exposed to a rich sound environment created by the surrounding culture and spoken languages. Small children are keen on hearing their close ones sing and play with rhymes and words. In this early interaction, the basis for the upcoming language development is born which then continues stepwise towards fluent communication, with spoken and written language skills. However, depending on the genetics and the environmental influences, children receive varying possibilities and abilities related to communication. One of these skills is reading, which some children learn as early as at the age of three whereas some other children struggle with fluent reading and writing and continue to do so into adulthood. Over the past decades, there has been a growing interest in trying to understand why some children, despite normal intellectual abilities, have difficulties in reading acquisition. As reading is a basic skill, important both in everyday life, as well as for success at school, problems in this area may not only affect the child's prerequisites for academic achievements but also cause severe problems for self-esteem and behaviour.

Nowadays, there are several theories trying to explain the underlying causes of reading problems. These theories also guide the attempts to help these children. The earlier the child gets adequate help, the easier it is to prevent further problems related to reading. In the present set of studies, electrophysiological methods were used to determine auditory discrimination skills in dyslexic adults and children at risk for dyslexia. Furthermore, behavioural and electrophysiological methods were used to determine whether a short intervention could alleviate reading-related problems even before the school start. Moreover, the feasibility of the multi-feature MMN paradigm for dyslexia research and studies in children was tested for the first time.

1.1 Clinical characteristics and the brain basis of dyslexia

Dyslexia is a neurobiological disorder that is defined as a persistent difficulty in learning to read that is not explained by sensory or cognitive deficits, lack of

motivation, or lack of adequate reading instruction and schooling (Shaywitz, 2003). Current diagnostic criteria (Siegel, 1992; Waber et al., 2000) no longer require a discrepancy between reading abilities and intelligence quotient (IQ) scores but rather reading problems while the IQ is within normal limits (>80). Problems in central auditory processing of the sounds of language, phonological processing, is seen as one of the core features of dyslexia (Bradley & Bryant, 1978; Snowling et al., 2000; Gabrieli, 2009). Learning to read requires explicit phonological awareness, the understanding of how spoken words are composed of different sounds that relate to letters and syllables. Younger children with dyslexia often have problems in operating with sounds within words and with word segmentation (Snowling et al., 2000). Learning the alphabet or letters and associating letters to phonemes is often hard and word retrieval can be slow (Lyytinen et al., 2007). Older children who can read have, in turn, problems with unfamiliar words (Wimmer & Schurz, 2010; Wimmer et al., 2010). This impairment is evident when asked to read nonsense words that are decoded on the basis of grapheme-to-phoneme mapping principles. Even children who improve in their reading accuracy often continue to read very slowly. In addition to working memory problems, which are often present in dyslexic individuals (Siegel & Ryan, 1989; Swanson, 1993; Vargo et al., 1995), dyslexia affects reading comprehension later on as the focus switches from learning to read to reading to learn.

Both the function and structure of the brain areas involved in reading and language processes are atypical in individuals with dyslexia. Neuroimaging studies have revealed reduced or absent activation of the left temporo-parietal cortex, which is normally activated when individuals perform tasks that require phonological awareness for print (Rumsey et al., 1992; Shaywitz et al., 1998; 2002; Temple et al., 2003; Blau et al., 2010). This brain area is hypothesized to support the cross-modal interaction of auditory and visual processes during reading (Hoeft et al., 2007). Furthermore, atypical activations in dyslexia are also found in the left occipito-temporal regions associated with visual analysis of letters and words (Shaywitz et al., 2002; Kronbichler et al., 2006; Hoeft et al., 2007; Maurer et al., 2011), left middle and superior temporal gyri associated with receptive language (Hoeft et al., 2007), auditory sensory thalamus, the medial geniculate body (MGB), associated with attending to phonemes (Díaz et al., 2012), and left prefrontal regions associated with verbal working memory (Hoeft et al.,

2007). Moreover, dyslexic children do not show activation in the left prefrontal cortex during auditory perception of rapidly changing non-speech stimuli that is seen in typically developing children (Temple et al., 2003).

The functional abnormalities overlap with structural variations reported in dyslexia. Structural imaging studies using voxel-based morphometry (VBM) have demonstrated grey matter reductions in individuals with dyslexia in bilateral temporo-parietal and left occipito-temporal cortical regions and in the cerebellum bilaterally (for reviews, see Eckert, 2004; Richardson & Price, 2009; for meta-analysis studies, see Linkersdörfer et al., 2012; Richlan et al., 2012). Recent diffusion tensor imaging (DTI) studies, in turn, have revealed weaker than normal white matter tracks in left temporo-parietal regions of dyslexic adults (Klingberg et al., 2000, for a review, see Vandermosten et al., 2012a). Furthermore, reduced fractional anisotropy in the left arcuate fasciculus, in particular in the segment that directly connects posterior temporal and frontal areas was shown in dyslexic adults (Vandermosten et al., 2012b). This fractional anisotropy was demonstrated to have a specific relation to performance on phoneme awareness and speech perception (Vandermosten et al., 2012b). Weaker white matter tracks were suggested to reflect a lower degree of myelination in dyslexic individuals (Vandermosten et al., 2012b). White-matter connectivity in the corpus callosum was, in turn, greater than normal in dyslexic adults (Dougherty et al., 2007). This was suggested to reflect a too strong projection between hemispheres and an atypical reliance on right-hemisphere regions for reading in dyslexia (Gabrieli, 2009). Recently, these findings have lead to hypotheses that dyslexia is a disorder of network connections in the brain (Vandermosten et al., 2012b).

1.2 Risk factors for dyslexia

Genetics plays an important role when risk for dyslexia is evaluated. Dyslexia is highly heritable, as 54-75 % of children who have a parent or a sibling with dyslexia also become dyslexics (Pennington & Gilger, 1996). Several candidate risk genes have been identified (Taipale et al., 2003; Hannula-Jouppi et al., 2005; Paracchini et al., 2006; Galaburda et al., 2006). These genes are important for neural migration and brain development, which suggests that dyslexia may be a consequence of atypical neural

migration in the developing brain (Gabrieli, 2009). Reduction in glucose levels within the brain during childhood could also be one of the factors leading to phonological difficulties in dyslexia (Roeske et al., 2011). A risk haplotype that may lead to a reduced expression of a gene important for glucose levels in neurons was recently found in dyslexic children. The risk haplotype was associated with aberrant preattentive speech sound discrimination performance in these children (Roeske et al., 2011).

There are several early behavioural indicators related to the risk for dyslexia. The prospective studies have provided ways to successfully identify, already at a relatively early age, those children who face the risk of delays in reading acquisition at school age (Scarborough, 1990; Lyytinen et al., 2004). As early as at the ages of 8 and 19 months, canonical utterances were of lower proportion and syllable structures less complex in children with familial risk for dyslexia (Smith et al., 2010). Furthermore, at the age of 2 years, the maximum sentence length was shorter in children at risk for dyslexia, and had a predictive correlation on developing reading skills (Lyytinen et al., 2004). Articulation accuracy is also poorer at the age of 2.5 years in the risk group (Turunen, 2003). Moreover, inflectional morphology at the age of 3 years (Lyytinen et al., 2004), phonological awareness (Puolakanaho et al., 2004), and letter-knowledge at the age of 4-7 years (Lyytinen et al., 2007), verbal short-term memory, and the rapid serial naming at the age of 5 years (Lyytinen et al., 2004; 2007), and the perception of phonemic duration at the age of 6 years (Lyytinen et al., 2007), differentiate the risk children from children without the risk and have predictive correlation on upcoming reading skills.

Complexity of the orthography exacerbates some symptoms of dyslexia (Landerl et al., 2012), however. Phoneme deletion and rapid naming (RAN) are strong concurrent predictors of developmental dyslexia, while verbal short-term memory and general verbal abilities play a comparatively minor role (Landerl et al., 2012). The impact of phoneme deletion and RAN-digits was stronger in complex than in less complex orthographies (Landerl et al., 2012). In Finnish children, the measures of letter naming, rapid naming, morphology, and phonological awareness have the strongest predictive links to later reading skills (Torppa et al., 2010).

1.3 Central auditory processing in dyslexia

Intact processing of even minor differences in speech sounds is essential for language development and reading skills. A child's language was suggested to develop on a specific setting of phonological prototypic representations that depend on the language context (Kuhl, 1992). For perceiving speech, one has to both discriminate sounds, and to identify phonemes, despite the variation in their acoustical features. For example, the speaker, background noise, and speech rate varies in everyday communication. Accurate and strong phonological representations were also suggested to be important for understanding and learning the connection between sounds and letters (Liberman, 1973).

Dyslexia was suggested to be a heterogeneous group of conditions, which could be divided into subtypes (Boder, 1973; Castles & Coltheart, 1993). For example, Boder (1973) suggested three subgroups of dyslexia (see also e.g., Castles & Coltheart, 1993; Borsting et al., 1996; Cohen et al., 1992; Fried et al., 1981; Wolf & Bowers, 1999; Wolf et al., 2002). The first group would include individuals that have problems in phonological processing and grapheme-phoneme conversion, called dysphonetics, the second group would include those that have difficulties in sight vocabulary, called dyseidetics, and the third group would be a combination of those that have problems in both processes, called dysphoneidetics. There is still no agreed classification of the possible subtypes of dyslexia. However, many individuals with dyslexia have phonological problems (Snowling et al., 2000; Ramus et al., 2003), and at least a subgroup of individuals with dyslexia have auditory processing problems (Ramus et al., 2003; for a review, see Hämäläinen et al., 2012). Both behavioural and neural-level evidence of auditory processing deficits in dyslexia exist. In particular, difficulties in discriminating sounds are very common (for a review, see Farmer & Klein, 1995; Studdert-Kennedy & Mody, 1995). Dyslexic individuals seem to perceive single auditorily presented sounds normally (Tallal, 1980). However, the identification of different sound stimuli is impaired (Farmer & Klein, 1995; Haggerty & Stamm, 1978; McCroskey & Kidder, 1980). Dyslexic individuals need a longer time interval between two sounds in order to hear them as separate sounds (McCroskey & Kidder, 1980).

Moreover, dyslexic children have difficulties in evaluating whether the sounds they hear come at the same time or not (Laasonen et al., 2000).

Many studies have also found dyslexics to be less sensitive for detecting amplitude envelope onset (rise time) or its correlate sound strength (amplitude) modulations (for a review, see Hämäläinen et al., 2012), which are behaviourally closely associated with the perceptual experience of speech rhythm and stress (Morton et al., 1976). In line with this, perception of stress patterning in speech in dyslexic adults (Leong et al., 2011), and perception of musical beat patterns in dyslexic children (Huss et al., 2011; Goswami et al., 2012) were recently shown to be altered. Dyslexic individuals are also poorer in auditory frequency discrimination (e.g. DeWeirdt, 1988; Baldeweg et al., 1999; Ahissar et al., 2000; Amitay et al., 2002; for a review, see Hämäläinen et al., 2012) and have elevated just noticeable differences for frequency (McAnally and Stein, 1996; Hari et al., 1999). Their detection of tones in narrowband noise, and the perception of the direction of sound sources moving in virtual space, and that of the lateralized position of tones based on their interaural phase differences are also impaired (Amitay et al., 2002).

Even duration discrimination is impaired at fast stimulation rates in adults and in children with dyslexia (Thomson & Goswami, 2008; Goswami et al., 2011; Banai & Ahissar, 2004; for a review, see Hämäläinen et al., 2012). Also infants at risk for dyslexia are poorer in perceiving stimulus-duration differences (Richardson et al., 2003). Furthermore, dyslexic individuals show less well separated and broader phonemic categories than normal readers (e.g. Godfrey et al., 1981). Poor phonological processing skills are also reported in tasks involving pseudo-word repetition (Brady et al., 1983; Kamhi & Catts, 1986; Snowling et al., 1986). Moreover, dyslexic individuals perform worse than normal on pseudo word repetition in noise (Ahissar et al., 2006), and have decreased decoding of spectral cues of the speech in noise (Sperling et al., 2005; Ziegler et al., 2009). They even perform poorly in auditory tasks involving backward masking (Ramus et al., 2003).

The auditory problems in dyslexia seem to be expressed at the early auditory sensory-memory stage of information processing (for reviews, see Bishop, 2007; Kujala, 2007). Both cortical auditory discrimination of changes in speech sounds (Schulte-Körne et al., 2001) and tones are altered in dyslexia (Baldeweg et al., 1999;

Kujala et al., 2003; for a review, see Hämäläinen et al., 2012). There are also studies showing altered sensory encoding (for a review, see Lyytinen et al., 2005) and brainstem timing for sound features (e.g. Banai et al., 2009). All in all, these deficits reflect impairments in both explicit (awareness) and implicit (preattentive) operations on phonological and auditory representations as well as altered auditory processing at the stage of sound encoding and brainstem timing.

Several theories have tried to explain these phonological and auditory processing deficits in dyslexia. According to the phonological-deficit theory of dyslexia, individuals with dyslexia have a specific phoneme-awareness impairment which affects their auditory memory, word recall, and sound association skills when processing speech (Ramus, 2003; Mody et al., 1997; Snowling et al., 2000; for a review, see Vellutino et al., 2004). The rapid-auditory processing deficit model suggests that the phonological deficit is related to a more widespread difficulty in temporal processing (Stein & Talcott, 1999; Tallal, 1980; for a review, see Stein 2001). As speech is composed of fast sequences of brief stimuli, such a deficit would impair speech perception (Tallal & Percy, 1973). Another theory, the Cerebellar deficit hypothesis, postulates that a mildly dysfunctional cerebellum can cause articulation problems, which then lead to phonological problems. In addition, as the cerebellum is involved in skill automatisations, it would alter automatisations of reading and writing processes in individuals with dyslexia (Nicolson et al., 2001). The magnocellular model, in turn, suggests that dyslexia results from a neurodevelopmental abnormality of the magnocellular system, which causes auditory, visual and sensory processing deficits in dyslexia (Galaburda et al., 1994; Stein & Walsh, 1997).

Moreover, it has also been suggested that the problems of dyslexic individuals are more pronounced in tasks requiring sensory integration than in those limited to one modality (Laasonen et al., 2000). Furthermore, a specific deficit in audiovisual integration was suggested to be a proximal cause for the reading deficit in dyslexia (Blau et al., 2010; Blomert, 2011; Mittag et al., 2013; Widmann et al., 2012). This cross-modal binding deficit of letters and speech sounds is suggested to interfere with and/or slow down the incremental tuning of auditory and multisensory cortex for the fast integration of unique audiovisual orthographic–phonological objects. This would negatively influence and/or delay the tuning of the fusiform cortex for letters and words

(Blomert et al., 2011). The binding deficit would not only be a proximal cause for reading deficits in dyslexia but also explain the lack of reading fluency in dyslexia (Blomert et al., 2011).

At least three theories emphasize attentional deficits as one of the dysfunctional areas associated with dyslexia (for a review, see Shaywitz & Shaywitz, 2008). According to the attentional sluggishness hypothesis, the attentional mechanisms that underlie switching from processing one object to processing another are inefficient in dyslexia. Individuals with dyslexia have a longer “attentional blink” which alters their ability to identify a second target that is presented in a time window of 200-400 ms after the first target (Hari & Renvall, 2001). This prolongation might then affect the development of cortical representations (Hari & Renvall, 2001; Lallier et al., 2010). Recently, it was further suggested that sluggish multisensory attention shifting impairs the sublexical mechanisms that are critical for reading development (Facoetti et al., 2006; 2008; 2010; Ruffino et al., 2010), whereas “Impaired-anchoring” is suggested as a specific type of altered attention hypothesis (Ahissar, 2007). According to this hypothesis, specific anchors guide the perceptual interpretation of subsequent stimuli, and contribute to the ability to retain and explicitly retrieve recently presented stimuli. The deficits of dyslexic individuals would reside in the dynamics that link perception with sensory memory through the implicit formation of stimulus-specific anchors rather than due to poor long-term representations for phonemes. The double deficit hypothesis of dyslexia considers naming speed problems as a second core deficit independent of a phonological deficit in dyslexia (Bowers & Wolf, 1993; Wolf, 1997; Wolf & Bowers, 1999). Attention, executive functioning and general speed of processing are seen as important areas involved in rapid naming rather than viewing rapid naming as only phonological in nature.

Recently, the temporal sampling framework (TSF), was proposed as a novel causal framework for developmental dyslexia (Goswami, 2011). In this framework, the core deficit in dyslexia is considered to be phonological. A specific deficit in temporal sampling of speech by neuroelectric oscillations that encode incoming information at different frequencies would explain the perceptual and phonological difficulties with syllables, rhymes and phonemes found in individuals with dyslexia (Goswami, 2011).

The proposed auditory phase locking deficit was also suggested to have implications for the efficient functioning of other sensory systems (Goswami, 2011).

1.4 Dyslexia interventions

Despite the growing knowledge of symptoms and predicting factors of dyslexia, there are still relatively few attempts of early preventive interventions. Intervention programs have so far mostly been designed for and also tested with school children. Research on cortical plasticity highlights that the training should be extensive and intensive as well as adaptive and highly motivating, in order to produce learning induced changes (Merzenich et al., 1996). In the dyslexia remediation studies conducted so far, auditory training, involving listening exercises designed to improve the function of the central auditory system, has been one of the predominant approaches. With the improved technology, computer-based programs become available and are promising in dyslexia remediation.

For example, FastForWord Language program (FFW, Scientific Learning Corporation, Oakland, CA) is designed to train temporal processing, speech perception, and language comprehension skills in children who have specific language impairment (SLI) or dyslexia. At least 13 studies have reported positive effects of the FFW training on language, phonological awareness and/or reading skills (for a review, see Loo et al., 2010). For example, 8-12 year-old dyslexic children improved their receptive and expressive language, rapid naming, real word reading, pseudo-word decoding, and passage comprehension after an 8-week training period with this program (Temple et al., 2003). However, the FFW has not been reported to improve children's spelling skills.

Earobics (Houghton Mifflin Harcourt Publishing Company) is designed for the training of phonological awareness and auditory-language processing. The few studies that have assessed the use of the Earobics as a training program, have reported a positive effect on phonological awareness, but the evidence on the efficacy of the program in improving reading and spelling skills is still limited (Russo et al., 2005; Warrier et al., 2004; Hayes et al., 2003).

Some intervention programs are instead designed to train audio-visual matching instead of auditory training only. In fact, recent studies of dyslexia highlight the importance of combining auditory and visual training in attempts at improving reading skills (Kujala et al., 2001; Törmänen et al., 2009; Brem et al., 2010; Snowling & Hulme, 2012; for a review, see Loo et al., 2010). The Audilex (Karma, 1999) is one of these programs and includes audiovisual training without linguistic material, with the exercises requiring matching sound elements that vary in pitch, duration, and intensity with the visually presented material. In the study of Kujala et al. (2001), dyslexic children improved their reading skills after 14 training sessions of about 10 minutes twice a week during a period of 7 weeks with the Audilex. Furthermore, it has been suggested that audio-visual training that focuses in particular on the pairing of letters with sounds would support the acquisition of reading and spelling skills as it supports phonological awareness (Lyytinen et al., 2009). For example, an audio-visual program that included matching exercises of consonant-vowel syllables that the child both heard and saw, improved both reading and spelling skills in children with dyslexia (Veillet et al., 2007).

The GraphoGame intervention program (Lyytinen et al., 2007) trains both phoneme awareness and letter knowledge. The exercises progress from grapheme–phoneme relations to the stage of phonological recoding and decoding, covering the basic areas needed for fluent and accurate reading. In the study by Saine et al., (2010), school-beginning children with deficits in the core reading-related skills (letter knowledge, phonological awareness, or rapid automatized naming) were divided into two groups. One of the groups was exposed to regular phonics-based remedial reading training whereas the other group also played the GraphoGame as a part of the training. Both groups were performing the exercises in 4 weekly sessions of 45 min over a period of 28 weeks in Grade I. The follow up of the training effects showed that the children in the GraphoGame group had reached the average level of the mainstream children by the end of Grade 2 in the word-level reading fluency.

The effects of dyslexia interventions have been studied both with behavioural and brain-imaging methods. For example, at the same time as the children's oral language and word reading improved by playing The FastForWord Language program, functional magnetic resonance imaging (fMRI) measurements showed that their brain activity also

increased in the left temporo-parietal cortex and left inferior frontal gyrus, bringing activation in these regions closer to that of normal-reading children (Temple et al., 2003). Increased activation was also seen in the right-hemisphere frontal and temporal regions and in the anterior cingulate gyrus, which was suggested as reflecting an additional compensatory activation (Temple et al., 2003). In line with this, greater right prefrontal activation during a reading task that demanded phonological awareness, was recently shown to predict future reading gains in dyslexia together with right superior longitudinal fasciculus white-matter organization (Hoeft et al., 2011). Furthermore, the audiovisual Audilex training without linguistic material that improved dyslexic children's word reading, also caused neurofunctional changes in the auditory cortex (Kujala et al., 2001). The learning of letter-speech sound correspondences with GraphoGame, in turn, resulted in an initial sensitization to print in specific areas within the occipito-temporal cortex in young non-reading children (Brem et al., 2010).

1.5 Auditory event-related potentials (ERPs) used in dyslexia research

1.5.1 ERPs reflecting acoustic feature processing

The auditory event-related potentials (ERPs) have recently become a popular means of determining auditory impairments in dyslexia as they provide an accurate way of monitoring the timing and changes of the synaptic communication of the neurons involved in central auditory processing (Coles & Rugg, 1995). ERPs can be non-invasively recorded from the scalp using the electroencephalogram (EEG). Auditory ERPs are transient voltage changes in the EEG caused by, and time-locked to, acoustic or cognitive events.

The long-latency auditory ERPs start with the exogenous components that reflect the transient detection of the physical stimulus features. These components are obligatorily elicited by all stimuli, and mainly reflect the physical features of the stimuli. The endogenous components, in turn, reflect also cognitive processes (Näätänen, 1992). The exogenous and endogenous components are generated in the auditory cortex and related cortical areas.

In adults, the obligatory long-latency components are the P1, N1, P2, and N2. The P1 peaks at about 50 ms, and the N1 at 100 ms from stimulus onset. The P1 is generated in the primary auditory cortex (Liegeois-Chauvel et al., 1994), and the N1 in the temporal lobes (Näätänen & Picton, 1987). The P2 peaks at 175-200 ms and, depending on stimulus duration, may be followed by the N2 (Kushnerenko et al., 2001; for a review, see Näätänen, 1992). These responses were suggested to reflect sound detection and the encoding of physical stimulus features (Näätänen & Picton, 1987; Näätänen & Winkler, 1999). Their amplitude and latency strongly depend on the physical features of the stimulus input (Wunderlich & Cone-Wesson, 2006). For example, N1 amplitude diminishes with a decreasing stimulus intensity.

The studies on the exogenous ERPs in childhood are limited in number but the children's exogenous ERP waveform is known to be quite different from that of adults. In children, the waveform is typically dominated by the P1 response, which usually peaks at 100 ms, and is followed by a broad negativity at about 200 ms (N2) (Sharma et al., 1997; Čeponiene et al., 2001, 2002), and often by the N4 response (Čeponiene et al., 1998, 2001; Cunningham et al., 2000; Ponton et al., 2000). The P1 and N2 components were suggested to reflect auditory sensory processing of tones in 4- to 9-year-olds (Čeponiene et al., 2002). The N1 and P2 components, in turn, start to emerge with adult-like latencies at approximately 9 years of age, with the amplitudes increasing and latencies decreasing with age until the early adulthood (Ponton et al., 2000, 2002). However, when long ISIs are used, these components can be seen at even earlier ages (Čeponiene et al., 2002).

1.5.2 MMN

The endogenous mismatch negativity (MMN) ERP component (Näätänen et al., 1978) has been widely used in studies investigating auditory and speech perception as it reflects early cortical stages of sound discrimination (for a review, see Näätänen et al., 2007). The MMN is elicited by any discriminable change in a sequence of repetitive speech or non-speech sounds, or by a sound violating an abstract rule or regularity in the preceding auditory context (Näätänen et al., 2001). The MMN normally peaks at 100-250 ms after change onset. The amplitude of the MMN is larger and the latency

shorter, the larger the deviance magnitude is (Sams et al., 1985; Tiitinen et al., 1994; Kujala & Näätänen, 2001; Rinne et al., 2006; Pakarinen et al., 2007). Furthermore, the MMN is correlated with behavioural discrimination abilities. Large amplitude, short latency MMNs are associated with accurate discrimination, and low amplitude, long latency MMNs with poor discrimination skills (Kujala et al., 2001; Lang et al., 1990; Novitski et al., 2004; for a review, see Kujala & Näätänen, 2010).

According to Näätänen (1990), repetitive sounds form a memory trace based on the regularities of the preceding auditory context. The MMN reflects a pre-attentive memory-based comparison process where each incoming sound is compared with this memory trace (Näätänen & Winkler, 1999; Näätänen & Alho, 2005). The MMN is elicited when an incoming sound does not match with the physical or temporal attributes of the memory trace (Kujala et al., 2007; Näätänen et al., 2001). Several studies have shown that although the MMN operates at the sensory memory level (Näätänen & Winkler, 1999), it is also affected by long-term sound representations such as those formed for the native phonemes (Dehaene Lambertz, 1997; Näätänen et al., 1997). Extensive exposure to a certain language facilitates the processing of the acoustic changes that are linguistically relevant in that language (Dehaene-Lambertz et al., 2000; Huotilainen et al., 2001). This is reflected as an enhanced MMN for these changes. For changes of native-language phonemes, the MMN often predominates in the left hemisphere (Alho et al., 1998; Näätänen et al., 1997; Shtyrov et al., 2000). For non-speech changes, the MMN is lateralized to the right hemisphere (Levänen et al., 1996; Paavilainen et al., 1991; Sorokin et al., 2010).

The MMN is composed of two components, the first component generated in the left and right supratemporal auditory cortices and the second one in the frontal lobes (for reviews, see Näätänen, 1992; Näätänen & Alho, 1995; Rinne et al., 2000; Näätänen & Rinne, 2002). The exact source locations vary depending on the sound feature to be discriminated and, therefore, these source locations were suggested to reflect activity directly related to sensory-memory traces (Giard et al., 1995; Molholm et al., 2005). In addition to sound discrimination, the process generating the MMN has been proposed to play an important role in initiating involuntary attention switch to changes in auditory environment (Escera et al., 1998; 2000). This may be reflected in the second MMN component, one that is generated in the frontal lobes (Näätänen & Alho, 1995; Näätänen

& Rinne, 2002; Opitz et al., 2002), and by P3a following the MMN (Escera et al., 2000).

The MMN is well suited for studies addressing central auditory processing in clinical groups and children because it is elicited even without the subject's attention towards the sounds or without a task related to the sounds (Näätänen, 1979, 1985; Näätänen et al., 1978). The advantage of the MMN is that it is considerably less affected by vigilance or task-related artifacts than behavioral measures. The MMN can even be used for investigating subjects with communication problems or with limitations in performing behavioural discrimination tasks. These features have made it popular for investigating sound discrimination in various patient groups (for a review, see Näätänen, 2003; Näätänen et al., 2012), for example specific language impairment (e.g., Kraus et al., 1996), dyslexia (e.g., Baldeweg et al., 1999), and autism (e.g., Lepistö et al., 2005; for a review, see Kujala et al., 2013). MMN responses have also been recorded from infants (Alho et al., 1990) and fetuses (Huotilainen et al., 2005) by using magnetoencephalography (MEG) which detects the magnetic field produced by the active neurons in the fetal brain tissue from above the mother's abdomen.

However, the MMN has usually been recorded with the so-called oddball paradigm, which requires long recording sessions. As the signal-to-noise ratio is affected by vigilance, paradigm improvements have been welcome (Kujala et al., 2007). In order to obtain a more comprehensive view on cortical discrimination within a tolerable recording time, the new multi-feature MMN paradigm was developed ("Optimum-1"; Näätänen et al., 2004). With this paradigm, the MMN can efficiently (see Fig 1., p. 39) be recorded in about 15 min for five different types of sound changes. In the traditional oddball paradigm, there are normally 80-90 % repetitive standard sounds, with the rest of the sounds being deviants. In the new paradigm, 50 % of the stimuli are standards and 50 % deviants. Each of the deviants differs from the standard in one acoustic feature only and the deviants alternate with the standard sounds, with every second sound being a standard and every second a deviant. The new paradigm is based on the assumption that each sound strengthens the memory trace for the standard stimulus for those features that it shares with the standard. The multi-feature paradigm yields similar or even slightly larger MMN responses for changes in sound duration, frequency, intensity, location (Näätänen et al., 2004; Pakarinen et al., 2007), and for sounds

including a short gap (Näätänen et al., 2004). Hence, the multi-feature paradigm enables one to determine the profile of discrimination abilities.

As MMN studies investigating speech-sound discrimination are popular, recently a new variant of the multi-feature paradigm was developed for this purpose (Pakarinen et al., 2009). In this paradigm, semi-synthetic consonant-vowel syllables are used as standards whereas the deviants include vowel, vowel-duration, consonant, frequency (F0), and intensity changes. In adults, the MMNs recorded with this multi-feature paradigm were very similar to those obtained with the traditional oddball paradigm (Pakarinen et al., 2009).

1.5.3 P3a

The MMN process is usually followed by the P3a, which is an ERP component that can be elicited by any unexpected physical stimulus change, even when the stimuli are not actively attended. The P3a peaks at 200-300 ms from stimulus onset (Squires et al., 1975). The amplitude of the P3a response varies with the magnitude of stimulus change (for a review, see Escera et al., 2000), and it is especially large for novel, surprising sounds. It has been associated with an orienting response (Nieuwenhuis et al., 2011), and involuntary attention shifting elicited by perceivable sound changes (Escera et al., 2000; for a review, see Escera et al., 2007). The P3a has several neural sources including prefrontal, temporal, and parietal cortices, as well as the posterior hippocampus, parahippocampal gyrus, and cingulate gyrus (for reviews, see Escera et al., 2000; Näätänen, 1992; Yago et al., 2003).

An abnormally large P3a response is related to a lowered threshold for involuntary attention switch, as unattended information reaches the consciousness more easily (for a review, see Escera et al., 2000). Enhanced P3a responses were shown in patients with closed-head injuries (Kaipio et al., 1999), in chronic alcoholics (Polo et al., 2003), and in children with attention deficit/hyperactivity disorder (Gumenyuk et al., 2005), whereas patients with prefrontal (Knight, 1984), temporo-parietal (Knight et al., 1989), and posterior hippocampal lesions (Knight, 1996) have diminished P3a responses.

1.5.4 ERP findings reflecting acoustic feature processing in dyslexia

Studies investigating the P1, N1, P2, N2, and N4 responses in individuals with dyslexia have reported rather inconsistent results. The studies have shown both normal, diminished, and increased exogenous ERP amplitudes as well as differences in the ERP latencies and sources for speech and non-speech stimuli in adults and children with dyslexia as well as in children at familial risk for dyslexia. Diminished P1-N1 peak-to-peak response amplitudes and longer P1 peak latencies for word stimuli were found among children with spelling problems (Byring & Järvillehto, 1985). In contrast, no differences in obligatory responses were found by Yingling et al. (1986). Poorly reading girls had larger P2 and N2 amplitudes but no differences in their N1 for a large pitch change compared to poorly reading boys or control children (Bernal et al., 2000). However, in 9-year old dyslexic children, the N1 response was larger than normal to stimuli with short within-pair-intervals and long rise time (Hämäläinen et al., 2007). Moreover, the magnetic counterpart of the N1 (N1m) was abnormally strong in the left supratemporal auditory cortex for speech-sound onsets (Helenius et al., 2002a) and spoken words presented in sentence context in adults with than without dyslexia (Helenius et al., 2002b).

Several studies report dyslexia-related hemispheric variation of the exogenous components. The N1 amplitude for speech-related stimuli was larger over the right than the left hemisphere in adults and children with dyslexia, whereas in their normally reading age-mates, a reversed asymmetry was observed (Fried et al., 1981; Rosenthal et al., 1982). Children with dyslexia were also shown to have larger responses over the left than right hemisphere at the P1 and P2 time windows for tone pairs with long within pair intervals (255 ms) than their controls but not for tone pairs with short within pair intervals (10 ms) for which they showed equal amplitudes over both hemispheres (Khan et al., 2011). This was suggested to indicate that individuals with dyslexia process basic auditory information abnormally when the tones are within the temporal window of integration. Recent MEG studies show that the sources of N1m (Heim et al., 1999; 2003a) and P1m (Heim et al., 2003b), the magnetic counterparts of P1 and N1, are different in dyslexic than in normal reading individuals. The N1m source in the temporal areas to speech sounds seems to be more symmetrical in adults with dyslexia than in control adults whose N1m source is anterior in the left to that in the right

hemisphere (Heim et al., 2003a). The P1 sources seem to be more symmetrical in children with dyslexia than in normal reading children whose P1m source was located anterior in the right to left hemisphere (Heim et al., 2003b).

Even newborns at risk for dyslexia have a tendency for right hemispheric predominance for early speech sound processing whereas a reversed asymmetry is present in controls (Pihko et al., 1999; Leppänen et al., 1999; Molfese et al., 2000; Guttorm et al., 2001). Van Herten et al. (2008) found that the P1 and P2 peaks were delayed for standard word stimuli in children at risk for dyslexia at the age of 17 months. Moreover, hemispheric group differences were observed for the N2 amplitude and the P1 latency. While the N2 peak amplitude was similar in size for the left and right hemispheres in the control group, in the at-risk group it was larger for the right than left hemisphere. The P1 occurrence, in turn, was delayed in the left hemisphere in the at-risk group. In addition, larger P1 and P2 amplitudes for deviant words were found in the control but not in the at-risk group. Conversely, only at-risk children showed enlarged N4 amplitudes for the deviant relative to the standard stimuli.

Even the very early stages of central auditory processing seem to be strongly associated with upcoming reading skills. Based on ERP responses to speech sounds within 36 hours of birth, those infants who were diagnosed as having dyslexia at the age of 8 were identified with over 81 % accuracy (Molfese et al., 2000). Newborn event-related potentials (ERPs) of children with and without familial risk for dyslexia are also associated with receptive language and verbal memory skills between 2.5 and 5 years of age (Guttorm et al., 2005) as well as phonological skills, rapid naming, and letter knowledge at the age of six (Guttorm et al., 2010). Moreover, the early obligatory responses for pitch changes in tones are associated with phonological processing at the age of 3.5 years, as well as with reading speed and reading accuracy in the 2nd grade of school (Leppänen et al., 2010). Furthermore, Banai et al. (2009) even showed a correlation between the timing of subcortical auditory processing and phonological decoding skills.

1.5.5 MMN in dyslexia

The MMN studies have indicated impairments in discriminating both speech and non-speech sounds in dyslexia. Several studies suggested diminished MMNs for sound frequency changes in dyslexic adults (Baldeweg et al., 1999; Kujala et al., 2003; Renvall & Hari, 2003). Baldeweg et al. (1999) found that MMNs to frequency changes (15-, 30-, and 60-Hz deviation) of 50 ms long 1000 Hz pure tones but not to duration changes (40-, 80-, 120-, and 160-ms deviation) of 200 ms long tones were abnormally small in amplitude in dyslexic subjects. The MMN area also was markedly reduced and the MMN onset and peak latencies longer for the frequency contrasts in adults with dyslexia than those in controls. Further evidence of such a neurophysiological deficit was given by the finding of a similarly specific impairment in discriminating tone frequency, but not tone duration, in a separate behavioural discrimination task. The MMN scalp topography for frequency changes was also abnormal in adults with dyslexia as the MMN amplitude was significantly smaller over the left hemisphere in dyslexic than in control subjects (Kujala et al., 2003). In agreement with this, MMNm (the magnetic counterpart of MMN) fields to frequency changes in tones were diminished in the left hemisphere of dyslexic subjects (Renvall & Hari, 2003).

Furthermore, dyslexic adults also have pre-attentive difficulties in the processing of rapid temporal patterns. For example, the MMNs for tone pattern deviations, in which two segments of identical frequency but of different duration were exchanged, were smaller in the dyslexic group (Schulte Körne et al., 1999). In agreement with these results, attenuated MMN amplitudes were also found for tone order reversals in tone-pairs, when an additional third tone followed the pairs after a 10 ms silent gap (Kujala et al., 2003). This was suggested to reflect temporal discrimination problems and increased backward-masking in the auditory cortex of dyslexic individuals.

In dyslexic children, the cortical discrimination of consonant changes in syllables was impaired (Schulte-Körne et al., 1998; Sharma et al., 2006). The MMN for frequency change in tones did not differ between dyslexic teenagers and controls, whereas the MMNs elicited by the syllable deviant (da/ vs. /ga/) were diminished in

dyslexic individuals (Schulte-Körne et al., 1998). A similar finding was also reported in adults with dyslexia by the same research group (Schulte-Körne et al., 2001).

Smaller MMNs to a consonant change in a stream of syllables (/ba-/da/) were also found in dyslexic than in non-dyslexic children, the group difference being more pronounced in the left than right hemisphere (Heim et al., 1999). Interestingly, the cortical discrimination of tone frequency and consonant changes in syllables (/ba/ vs. /da/) was altered only in a subgroup of dyslexic children (Lachmann et al., 2005). Whereas the MMNs for frequency and consonant changes did not differ between controls and dyslexic children, who were impaired in non-word reading (or both non-word and frequent word reading), the MMNs were diminished in the dyslexic group which had difficulties in frequent word reading but not in non-word reading. Both groups, in turn, showed altered cortical sound reception as reflected in diminished N250 response amplitudes to tones and syllables compared with those of controls. These results were suggested to indicate that different diagnostic subgroups of dyslexics have different patterns of auditory processing deficits.

The MMNs for a duration change in harmonical tones were enhanced in amplitude, but delayed in latency in dyslexic children (Corbera et al., 2006). Furthermore, the MMN laterality for duration changes in tones was abnormal in dyslexic children. In the dyslexic group, the MMN peak responses were larger over the left than right hemisphere, whereas the opposite pattern was found in controls (Huttunen et al., 2007). Children with dyslexia did not show enhanced MMNs to native-vowel prototypes either in comparison to responses to atypical vowels as controls did (Bruder et al., 2011). They even lacked crossmodal effects in an audiovisual letter-speech sound oddball paradigm (Froyen et al., 2011). Furthermore, whereas MMN amplitudes were larger to syllable changes in combination with written syllables than with scrambled images in fluent readers, dyslexic readers showed no difference between syllables vs. scrambled image condition (Mittag et al., 2013). MMNs to consonant and frequency changes also peaked later in dyslexic than fluent readers (Mittag et al., 2013).

Pre-school children at familial risk for dyslexia also differed from their peers without such a risk with regard to their MMNs to frequency and phoneme changes (Maurer et al., 2003). The MMNs were smaller for frequency changes in tones in the at-risk than in the control group (Maurer et al., 2003). Moreover, the MMN to consonant deviance (/ba/

vs. /ta/ and /da/) in syllables tended to be less lateralized to the left hemisphere in the at-risk than in the control group (Maurer et al., 2003). As early as at the age of 6-months, infants with a familial risk for dyslexia showed reduced MMNs to varying /t/ durations in a pseudoword /ata/ (Leppänen et al., 2002) and to a frequency change in tones (Leppänen et al., 2010). An abnormal hemispheric ERP pattern was also observed.

Taken together, several MMN studies suggest that the problems in dyslexia are expressed even at the early auditory sensory-memory stage of information processing (for reviews, see Bishop, 2007; Kujala, 2007; Schulte-Körne & Bruder, 2010; Leppänen et al., 2012; Hämäläinen et al., 2012). Furthermore, the altered change detection process reflected in the MMN was associated with later reading-related skills. The newborn MMNs for a frequency change were associated with phonological skills and letter knowledge prior to school age and with the phoneme duration perception, reading speed and spelling accuracy in the 2nd grade of school (Leppänen et al., 2010). Moreover, in 9-year-old children, the MMN amplitudes to the native-vowel prototype correlated with more advanced reading and spelling skills (Bruder et al., 2011). In dyslexic adults, in turn, the MMNs for frequency changes were associated with the degree of impairment in phonological skills, as reflected in reading errors of regular words and non-words (Baldeweg et al., 1999).

1.5.6 P3a in dyslexia

There are only few studies that have investigated P3a in dyslexia. In adults with dyslexia, the P3a tends to be smaller in amplitude for pitch changes (Kujala et al., 2003) in unattended auditory stimulus sequences. In dyslexic children, the P3a amplitude is reduced and the latency delayed for a duration change of tones (Corbera et al., 2006). The P3a amplitude is also diminished for a frequency change in sinusoidal tone pairs (Hämäläinen et al., 2008).

Moreover, reduced P3a was found in response to sounds incongruent with an asynchronously presented visual symbol in comparison with congruent sounds in dyslexic children when they were performing a symbol-to-sound matching task (Widmann et al., 2012). Enlarged P3a to novel sounds was, in contrast, found for novel sounds in dyslexic adults in an active listening condition (Rüsseler et al., 2002). These

results suggest that attention shifting, as indicated by the P3a (Escera et al., 2000; Squires et al., 1975), is abnormal at least in a subgroup of dyslexic individuals, which is in agreement with the notion that some dyslexic subjects suffer from attentional problems (Willcutt & Pennington, 2000; Willcutt et al., 2000; Carrol et al., 2005).

1.5.7 Intervention, language-related deficits and ERPs

There are so far only a few studies that have investigated effects of remediation programs on reading and spelling skills and concurrent changes in neural processes as reflected by auditory ERPs. In the study by Kujala et al. (2001) the non-speech audio–visual computer program Audilex (Karma, 1999) improved auditory discrimination of infrequent order reversals in a group of dyslexics. This was reflected in increased MMN amplitudes in the Audilex group, which did not occur in the control group. The MMN amplitude change also correlated with the improvement in reading performance. In a recent study by Huotilainen et al. (2011) the same audio–visual training modestly improved the discrimination of duration and frequency changes as reflected in increased MMN amplitudes in 5-year-old children born with an extremely low birth weight and having reading-related difficulties. However, their reading-related skills did not significantly improve by the training.

In the MEG study by Pihko et al. (2007), the effectiveness of a phonological intervention program was assessed in bilingual preschool children with specific language impairment (SLI). Auditory evoked magnetic fields were measured before and after the intervention for phoneme changes in syllables. Also a behavioural discrimination test of these phoneme changes was performed. The phonological training group manifested changes of brain activity in both hemispheres and slightly improved in the behavioural discrimination test. Effects of the intervention were observed both in sound encoding (P1m) and sound discrimination (MMNm) as the strength of the P1m responses, and the MMNm for the syllable deviant increased in the training group. Together, these studies suggest that ERPs provide an excellent tool for investigating possible cortical changes caused by reading-related remediation programs.

2 THE AIM OF THE STUDY

The present thesis addressed cortical multi-attribute auditory discrimination in dyslexia and the effects of intervention on reading-related skills and speech sound discrimination. Furthermore, the feasibility of the multi-feature MMN paradigm for dyslexia research and studies in children was tested for the first time.

Study I aimed at determining the pattern of cortical auditory discrimination in adults with dyslexia, more specifically, whether they have difficulties in the discrimination of frequency, duration, intensity, and location changes as well as a short gap in tones, and if so, whether these auditory deficits are affected by stimulus duration or paradigm complexity. By comparing the MMNs obtained with the multi-feature paradigm and oddball paradigm, the feasibility of the new, time-effective paradigm for evaluating auditory impairments in dyslexia was addressed. It was hypothesized that adults with dyslexia would have deficits in frequency discrimination of shorter but not longer sound stimuli. Furthermore, the multi-feature paradigm was hypothesized to be more challenging than the oddball paradigm for the sensory memory of dyslexic individuals.

The goal of **Study II** was to determine the feasibility of the multi-feature paradigm for investigating auditory discrimination of vowel, vowel-duration, consonant, frequency, and intensity changes in syllables in 6-year-old normally developing children. To this end, it was determined whether the MMNs elicited with the new multi-feature paradigm were similar to those in the oddball paradigm. If the MMNs elicited in the two paradigms were similar, then the more time-efficient multi-feature paradigm could be applied in future studies to determine auditory discrimination profiles in children.

Study III aimed at gaining a comprehensive view on the possible ERP markers associated with dyslexia even before school age. Sound encoding and sound discrimination critical for speech perception were investigated with the new multi-feature paradigm in children at risk for dyslexia. Also the oddball paradigm was used in order to determine whether the multi-feature paradigm yields results consistent with

those obtained with the oddball paradigm. The children at risk for dyslexia were hypothesized as having difficulties in sound encoding and particularly in sound discrimination of vowel, vowel-duration, consonant, and frequency contrasts.

Study IV wished to determine whether an intervention game developed for strengthening phonological awareness by letter-sound association training has a remediating effect on reading skills and central auditory processing in 6-year-old children with difficulties in reading-related skills. The effectiveness of the intervention was evaluated by testing reading-related skills and by recording auditory ERPs with the multi-feature MMN and oddball paradigms before and after the training period. Reading-related skills and phonetic discrimination accuracy were hypothesized to improve in the intervention group as these were actively trained in the intervention game.

3 METHODS

3.1 Subjects

The subjects were adults with dyslexia (**Study I**), 6-year-old children without indications of dyslexia (**Study II**), children with familial risk for dyslexia having reading-related difficulties (**Study III**), and children with reading-related difficulties with or without a familial risk for dyslexia (**Study IV**). The clinical groups in **Studies I & III** were compared with an age-matched control group. All the subjects were monolingual Finnish-speakers.

In **Study I**, all the adult dyslexic subjects described reading problems according to the ICD-10 (World Health Organization, 1993) and had a performance worse than -1 SD below the mean of the age-matched normative data (Virsu et al., 2003) on at least three of the reading-skills tests.

The children (**Studies II, III, & IV**) underwent a rigorous assessment related to developing reading skills. The children tested were thereafter selected to **Studies II, III, & IV** based on the history of reading-related difficulties in their families and children's performance on reading-related tests:

In **Study II**, none of the children had two or more test results 1 SD or more below the normative mean in reading-related tests. In tests without normative data, the children were not expected to be able to read or write, even though many of them did.

In **Study III**, the criterion for the dyslexia risk was to have at least the mother or the father and one additional close relative with a history of reading-related problems and a performance worse than 1 SD below the mean in at least two of the reading-related tests. The criteria for the control group was not to have relatives with reported history of developmental disorders and to have no more than one test result 1 SD below the normative mean in reading-related tests, to be able to write his/her own name, and to name at least 17 letters.

In **Study IV**, the at-risk children from **Study III** and additional children who were not able to read and who had performance on at least one reading-related task more than 1 SD below the expected, were chosen for the training period.

A more detailed description of the subjects is given in Table 1. An informed written consent was obtained from the adult subjects (**Study I**) and parents (**Studies II, III, & IV**), and a verbal assent from the children. The studies were approved by the Ethical Committee of the former Department of Psychology, the University of Helsinki.

Table 1. Characteristics of the subjects

	N	Male/Female ratio	Mean age in years (range)	Mean PIQ (SD)	Mean VIQ (SD)	Mean FIQ (SD)
Study I	9 adults with dyslexia	6/3	33 (23-41)	108 (14)	109 (11)	109 (11)
	11 control adults	9/3	29 (20-41)	115 (10)	113 (9)	115 (10)
Study II	17 children	7/10	6.4 (6.2-7.1)	115 (12.3)	-	-
Study III	10 children at dyslexia risk	7/3	6.7 (6.1-7.3)	107 (6)	-	-
	9 control children	6/3	6.5 (6.2-7.2)	114 (16)	-	-
Study IV	16 children in the intervention group	10/6	6.6 (6-7.3)	102 (11)	-	-
	13 children in the control training group	8/5	6.5 (6.1-6.9)	107 (15)	-	-

* PIQ was assessed with WISC-III in child (Wechsler, 1991) and with WAIS-R in adult (Wechsler, 1981) subjects.

3.2 Reading skills and reading-related skills

In **Study I**, the adult subjects were tested with several reading-skill tests. In phonological tests, the subjects were asked to either discriminate non-words, or to form words from speech sounds. The non-word span was tested with a task to repeat non-word lists, and naming speed with Rapid Alternating Stimulus Naming (RAS; Wolf, 1986). In a test of reading accuracy, the subject had to read a text, and in a word segmentation speed test (Lindeman, 1998) to mark word boundaries as fast and accurately as possible. Reading comprehension test included questions on a fiction and a non-fiction text (for 6th graders), presented one-by-one (Lindeman, 1998). The subject could read the text as many times as required without time constraints. The word segmentation speed test and reading comprehension test for children (Lindeman, 1998) were previously shown to be applicable even to adults with dyslexia when compared to adult norms (Laasonen, 2002).

In **Studies II-IV**, the children were assessed with phonological tests: Phonological Processing (NEPSY; Korkman et al., 1997), Phonological Processing (Diagnostic Tests 1; Poskiparta et al., 1994), and Repetition of Non-words (NEPSY; Korkman et al., 1997). In these tasks, the child operated with sounds within words, segmented words

into parts and repeated non-words after the play recorder. The naming speed was assessed with Rapid Alternating Naming Test (RAN; Ahonen et al., 2003), and digit span (forward and backward) with WISC-III (Wechsler, 1991). Their reading was assessed with Reading Fluency (Lukilasse; Häyrynen et al., 1999) and with a test called Reading Syllables and Non-words where children read syllables and non-words. Children's letter knowledge and writing skills were assessed with tests as follows: Letter Knowledge, Letter Recognition (**Studies III & IV**), Writing Words and Non-words, and Writing Syllables and Non-words. In these tasks, children were asked to name the Finnish alphabets, to recognize Finnish letters from other symbols, and to write down syllables, easy Finnish words, and non-words. In **Study IV**, Phonological processing (Poskiparta et al., 1994), Reading Syllables and Non-words, Letter Knowledge, Letter Recognition, Spelling Words and Non-Words, and Spelling Syllables and Non-Words were administered twice to the children who participated in the training period. Analysis of variance (ANOVA), paired-samples t-test, and one-tailed Spearman test were used for statistical analysis of the behavioural data.

3.3 Intervention

In **Study IV**, 29 children successfully completed a computer game training period of 3 weeks (5-20 min training per session, total of 3 hours) in the child's preschool or at the child's home. The intervention game GraphoGame (Lyytinen et al., 2007) was played by 16 children, and the control number-knowledge game by 13 children. Both games were matched in terms of game type, visual appearance, and motivational aspects.

In GraphoGame, the player makes a choice from orthographic items (letters) that match speech sounds (phonemes) delivered concurrently. The letters are presented in falling balls each containing a stimulus. The child's task is to find and click with the mouse on the visual target that matches the auditory stimulus he/she hears from the headphones. The game proceeds via several levels depending on the child's learning. Firstly, the child gets to practice with the most frequent letter-sound (grapheme-phoneme) pairs, thereafter moving to less frequent and more complex graphemes, monosyllabic words, and pseudowords. As the player progresses through the levels, both the number of alternative orthographic items (distracters) and their rate of falling

increase. The control game consists of arithmetic exercises instead. The player trains number knowledge, size and quantity estimations, ordering of numerals, and basic addition and subtraction. As the GraphoGame, the control game also proceeds via several levels, depending on the child's learning. The player gets to more advanced levels only if she/he responds with high accuracy at the present level. In both games, correct performance is rewarded with visual "stickers" that are collected as well as by verbal encouragement produced by the game.

3.4 Event-related potential recordings

3.4.1 Experimental conditions and stimuli

ERPs were recorded with multi-feature and oddball paradigms in all studies (Fig. 1). In **Study I**, the standard sounds were harmonical tones composed of 500, 1000 and 1500 Hz sinusoidal tones of 100 ms (3 multi-feature and 3 oddball blocks) or 50 ms (3 multi-feature and 3 oddball blocks) duration. In the multi-feature condition, the deviant sounds differed from the standards by frequency ($\pm 6\%$), duration (-35 ms with the 100 ms standards and -17 ms with the 50 ms standards), intensity (± 5 dB), location (presented 0.65 ms earlier to the right, or left ear), or by including a gap (10 ms within the 100 ms standards and 5 ms within the 50 ms standards). In the oddball condition, the frequency and duration deviants were the same as in the multi-feature paradigm whereas the rest of the deviant stimuli were replaced with standard stimuli.

In **Studies II-IV**, the standard sounds were semi-synthetic consonant-vowel (CV) syllables, /pi:/ in a half of the blocks, and /te:/ in the other half of the blocks. There were 4 blocks that were multi-feature paradigm sequences and 4 blocks with oddball sequences. The fundamental frequency (F0) of the syllable was 101 Hz and duration 170 ms. In the multi-feature condition, the deviant syllables differed from the standards by the vowel (/pe:/ and /ti:/), vowel-duration (-70ms; /pi/ and /te/), consonant (/ti:/ and /pe:/), syllable frequency ($\pm 8\%$), or intensity (± 7 dB). In the oddball condition, vowel and vowel-duration deviants were the same as in the multi-feature paradigm whereas the rest of the deviant stimuli were replaced with standard stimuli. In all studies, the

order of the stimulus blocks was counterbalanced and the stimulus-onset asynchrony (SOA) was 500 ms.

Oddball paradigm

S S S **D₁** S S S **D₂** S S S S S **D₁** S S S ...

Multi-feature paradigm

S **D₃** S **D₁** S **D₄** S **D₂** S **D₅** S **D₄** S **D₁** S **D₅** S ...

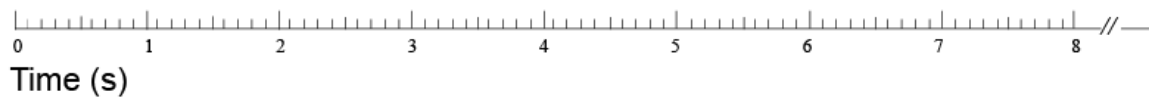


Figure 1. Illustration of the multi-feature (a) and oddball (b) paradigms. S denotes standard tone/syllable and D1-5 deviant types. D1 and D2 were either frequency and duration deviants (**Study I**) or vowel and vowel-duration deviants (**Studies II-IV**) which were used in both paradigms. D3-D5 were intensity, gap and location deviants (**Study I**) or consonant, frequency (F0) and intensity deviants (**Studies II-IV**), which were used in the multi-feature paradigm only (Adapted from Näätänen et al., 2004).

All the experiments were carried out in an electrically shielded and sound-attenuated room. The stimuli were presented through headphones with an intensity of 55 dB (SPL) (**Study I**) or through two loudspeakers that were positioned behind the subject, who heard the stimuli as coming from the back midline space at an intensity of 60 dB (SPL) (**Studies II-IV**). All the subjects were watching a silent movie during the recordings.

3.4.2 Data acquisition and analysis

The electroencephalogram (EEG) was recorded with electrodes placed according to the International 10-20 system (Jasper, 1958). In **Study I**, the electrodes were placed at F3, Fz, F4, C3, Cz, C4, Pt3, Pz, T3, and T4 and in **Studies II-IV**, at F3, Fz, F4, C3, Cz, C4 scalp sites. In all the studies, electrodes were also placed at the left and right mastoids and the reference at the tip of the nose. Vertical and horizontal eye-movements were monitored as well, with electrodes placed below and at the outer corner of the right eye.

The ERPs were separately averaged for each standard and deviant type, filtered, and baseline-corrected. The details of data acquisition and analysis are presented in Table 2.

The electrodes and the windows for the ERP latency and amplitude quantifications were chosen based on the guidelines by Picton et al. (2000) and by visual inspection of the waveforms. The grand-mean peak P1, N2 and N4 latencies were identified from the waveforms for the standards at F3 (**Study III**) and Fz (**Study IV**). The windows for the latency identification were at 50-150 ms (P1), 150-300 (N2), and 300-400 ms (N4) from standard-stimulus onset. The MMN (**Studies I-IV**) and P3a (**Studies I & IV**) responses were quantified from the difference waveforms obtained by subtracting the ERPs elicited by standard stimuli from those elicited by deviants. These difference waveforms were separately created for each deviant type. In **Study I**, the MMN latency and amplitude were quantified at Fz at 100-250 ms and those for P3a at Cz at 200-350 ms from deviant stimulus onset from the individual difference waveforms. The amplitude values were measured with a 50 ms window centered at the individual peaks. In **Study II**, the MMN latency and amplitude were quantified from the difference waveforms at Fz at 200-330 ms, in **Study III** at the F3 at 200-400 ms, and in **Study IV** at the Fz at 200-400 ms. The window for the P3a was 300-500 ms from deviant-stimulus onset (**Study IV**). The individual mean amplitudes were integrated over 50 ms around the grand-mean peak latencies.

Table 2. The details of the data acquisition and analysis

	Study I-II	Studies III-IV
Sampling rate	500 Hz	500 Hz
EEG recording bandpass	0.1–100 Hz	0.1–100 Hz
Artefact rejection	$\pm 75 \mu\text{V}$	$\pm 75 \mu\text{V}$
Epoch duration	-100–600 ms	-100–600 ms
Filtering bandpass	1.5–20 Hz	1–20 Hz

T-tests were used to determine whether the responses significantly differed from zero. Differences in the ERP amplitudes and latencies between the groups (**Studies I, III, and IV**), between the multi-feature and oddball paradigms (**Studies I - IV**), and between the measurement times before and after the training period (**Study IV**) were analyzed with the analysis of variance (ANOVA) for repeated measures. The

Greenhouse-Geisser correction was applied to determine the sources of the significant main effects and interactions. Unless otherwise mentioned, all results presented in the Results section are significant with p-values less than .05.

4 RESULTS AND DISCUSSION

4.1 Multi-feature MMN paradigm as a research tool

In **Study I**, the MMNs for frequency and duration changes in harmonical tones were comparable in amplitude in the multi-feature and the oddball paradigms in the adult control group. The dyslexic adults had, in turn, significantly smaller MMNs for frequency and duration changes when they were presented with the multi-feature than the oddball paradigm. This suggests that dyslexic adults have more difficulties in detecting changes in sound streams with than without variation, as the auditory context in the multi-feature paradigm is more complex than in the oddball paradigm.

In **Study II**, normally developing children had significant MMNs for vowel, vowel-duration, consonant, frequency (F0), and intensity changes in syllables presented with the multi-feature paradigm (Fig. 2). Furthermore, the responses for vowel and vowel-duration changes were comparable to the ones recorded with the oddball paradigm as no significant differences between the responses between the two paradigms were observed (Fig. 3). These results suggest that the multi-feature paradigm is suitable for studies in children.

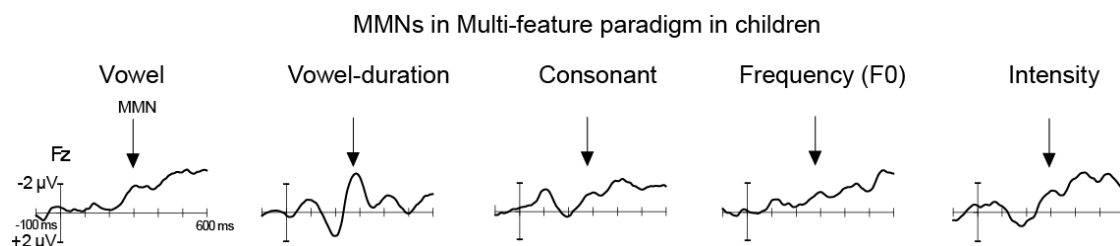


Figure 2. Deviant-minus-standard difference waveforms for ERPs elicited by vowel, vowel-duration, consonant, frequency (F0) and intensity deviants at the Fz scalp location in the Multi-feature paradigm in normally developing children.

MMNs in Multi-feature and Oddball paradigms in children

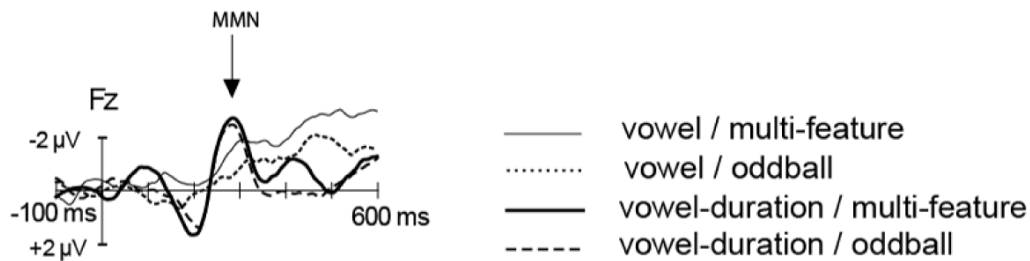


Figure 3. Deviant-minus-standard ERP difference waveforms for vowel and vowel-duration deviants at Fz loci in the Multi-feature and Oddball paradigms in normally developing children.

In **Study III**, the MMNs recorded with the two paradigms did not significantly differ from each other, either in the control group or the group at risk for dyslexia. However, in **Study IV**, the MMN amplitudes were larger in general in the multi-feature than in the oddball paradigm. Taken together, these results suggest that the multi-feature MMN paradigm produces either similar or even a better MMN signal than the oddball paradigm in adults and in children and is therefore suitable for clinical studies.

4.2 Cortical auditory processing in dyslexia

4.2.1 Obligatory ERPs

Obligatory ERPs were investigated in **Study III** including children at risk for dyslexia. The amplitude of the P1 waveform for syllables was nearly significantly smaller in the at risk children than in their controls, particularly over the right hemisphere (group main effect ($F(1,17) = 3.52, p < .08$) (see Fig. 4). Furthermore, the group waveforms (Fig. 4) suggest amplitude differences of the N2 and N4 responses between the groups although these differences were not statistically significant. These results are in agreement with previous studies that have also suggested deficits even at the stage of establishing sound presentations in children at risk for dyslexia (Guttorm et al., 2001; Van Herten et al., 2008; Leppänen et al., 2012). The processing speed of sound feature encoding, in turn,

was comparable in children at risk for dyslexia and controls as no latency differences in the standard-sound ERPs were found between the groups.

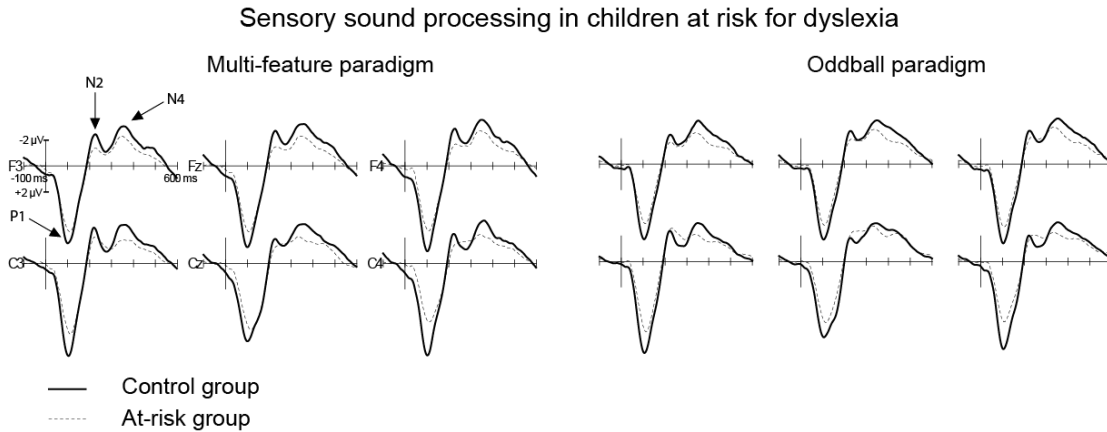


Figure 4. Grand mean ERP waves for the standard syllables at the F3, Fz, F4, C3, Cz, and C4 scalp loci in the multi-feature and oddball paradigms in children at risk for dyslexia and controls.

4.2.2 MMN

In **Study I**, the MMN recorded with the multi-feature paradigm was significantly diminished for a tone frequency change and enhanced for a location change in adults with dyslexia (Fig. 5). In contrast, there were no significant group differences in the MMN amplitudes recorded for the frequency change in the oddball paradigm (Fig. 5). The longer stimuli (100 ms vs. 50 ms) did not seem to facilitate frequency discrimination as no tone duration x group interaction was found. The results obtained with the multi-feature paradigm suggesting impaired frequency discrimination in adult dyslexics are in agreement with previous studies (Baldeweg et al., 1999; Kujala et al., 2003; Renvall & Hari, 2003), whereas the results obtained with the oddball paradigm are not.

The failure to replicate the frequency discrimination impairment in dyslexia in an oddball condition could have been caused by use of the spectrally rich stimuli used in the present study, whereas the previous studies used sinusoidal tones (Baldeweg et al., 1999; Kujala et al., 2003; Renvall & Hari, 2003). As a rich spectral sound structure facilitates frequency discrimination (Tervaniemi et al., 1999), it may have improved

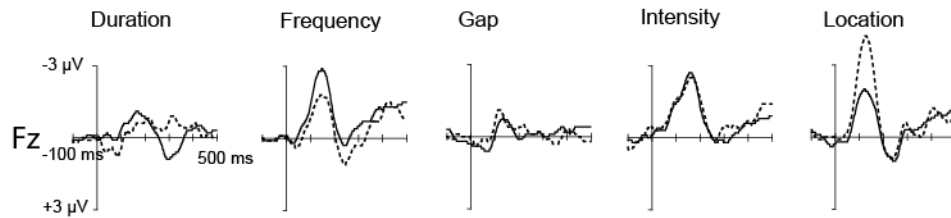
frequency discrimination in dyslexic subjects, thereby abolishing group differences in the oddball condition. The high degree of variation in multi-feature condition, in turn, might have caused the diminished frequency MMN in dyslexic subjects.

Stimulus parameters had, in turn, an effect on the location discrimination, as the MMNs for sound location changes were enlarged for the 50 ms tones but not for the 100 ms tones in the dyslexic group compared to controls in the multi-feature paradigm. This suggests that dyslexic adults are superior to their controls in discriminating location of short but not of long tones. The enhanced MMN for sound location changes of 50 ms sounds in the dyslexic subjects is a novel finding (Fig. 5). Previously, in a behavioral study by Amitay et al. (2002), the dyslexics were poorer in discriminating sound locations produced with interaural phase differences of 500 Hz sinusoidal 500 ms sounds compared to controls. Again, different stimulus parameters in these two studies may be the reason for the discrepant results (e.g., pure tones vs. spectrally rich tones, short vs. long sound duration).

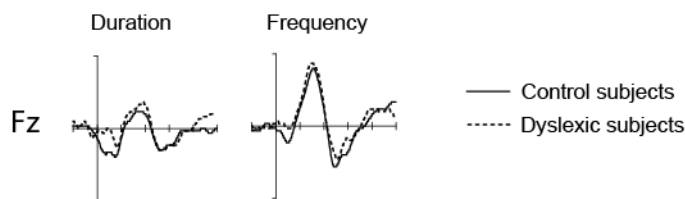
Cortical auditory discrimination in adults with dyslexia

50-ms Stimulus Duration

Multi-feature paradigm

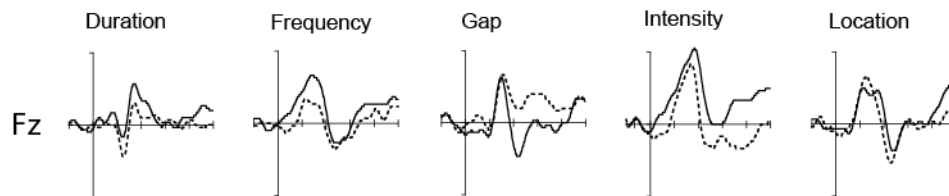


Oddball paradigm



100-ms Stimulus Duration

Multi-feature paradigm



Oddball Paradigm

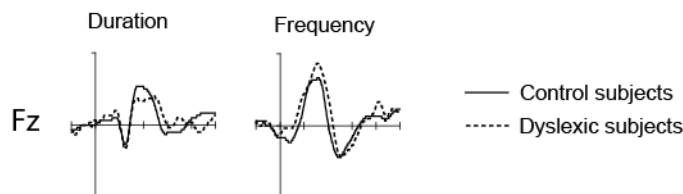


Figure 5. Deviant-minus-standard ERP difference waveforms for the 50 ms (top) and 100 ms stimuli (bottom) in the Multi-feature and Oddball paradigm in adults with dyslexia and controls.

In **Study III**, children at risk for dyslexia had diminished MMN amplitudes for the vowel, vowel-duration, and consonant changes compared to the controls (Fig. 6). These

results are in agreement with previous studies (Schulte-Körne et al., 1998; Leppänen et al., 2002; Sharma et al., 2006), and indicate deficient pre-attentive phoneme processing in dyslexia. The results are compatible with the contention that dyslexia is associated with a difficulty in establishing accurate phonological representations (Snowling et al., 2000). Furthermore, the MMNs for intensity changes were also diminished in the at-risk group. This suggests that even the discrimination of non-linguistic changes and changes involving no rapid transitions are impaired in children at risk for dyslexia. As sound intensity, how the sound energy changes in amplitude over time, is crucial information for syllabic segmentation, impairments in intensity discrimination could lead to word segmentation difficulties often present in young dyslexic children (Snowling et al., 2000).

In contrast to the results from the study with adult subjects (**Study I**) and previous studies showing altered frequency processing in dyslexia (Baldeweg et al., 1999; Kujala et al., 2003, 2006b; Renvall & Hari, 2003; Maurer et al., 2003; Leppänen et al., 2010), there were no significant differences between the children at risk for dyslexia and controls in the MMNs for the frequency change. However, there are also other studies that have reported similar MMNs to a frequency change in dyslexic children and their controls (Schulte-Körne et al., 1998; Corbera et al., 2006). As suggested before, it may be that there is only a subgroup of dyslexic children that have difficulties in frequency discrimination (Ramus et al., 2003; Lachmann et al., 2005). Furthermore, it has been suggested that the frequency discrimination skills might not be adult-like until the ages of 7-9 (Jensen & Neff, 1993). If these skills are still developing in 6-year-old children, it may be difficult to find group differences.

Cortical auditory discrimination in children at risk for dyslexia

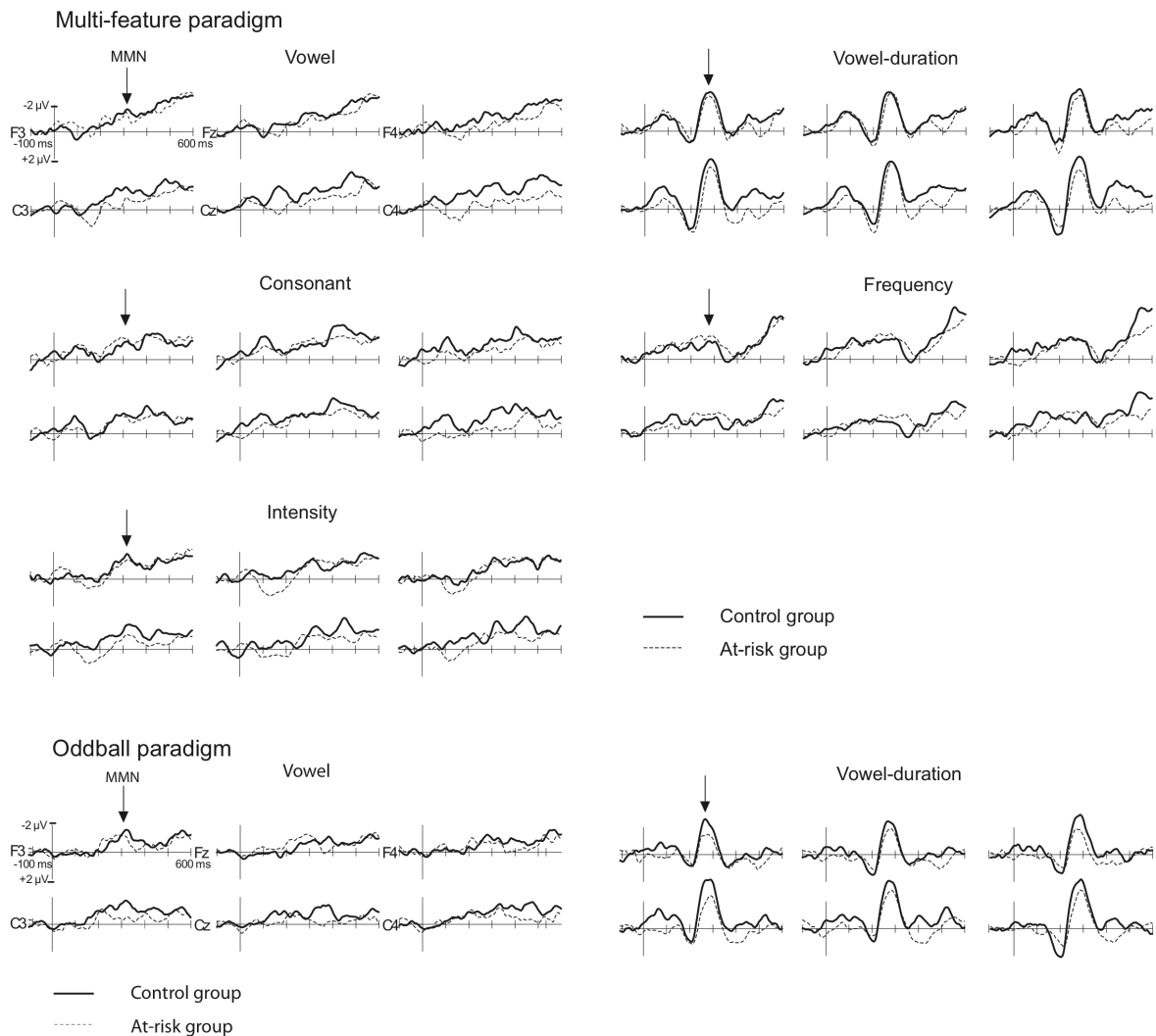


Figure 6. Deviant-minus-standard ERP difference waveforms at the F3, Fz, F4, C3, Cz, and C4 scalp location in the multi-feature and oddball paradigms in children at risk for dyslexia and controls.

MMN abnormalities in the at-risk group were also seen in the scalp topography. Whereas the MMN amplitudes were smaller in the at-risk than in the control group for the vowel deviant in all electrode loci, and for the vowel-duration and intensity deviants over the lateral scalp loci, the MMN for the consonant deviant was diminished in amplitude over the right hemisphere in the at risk group. These results are in agreement with previous studies suggesting altered neural generators for speech sound processing in dyslexia. Even though the present study shows group differences in the MMN

topography for several sound features, the results do not indicate a special left-hemisphere dysfunction in at-risk children suggested by previous studies (Shaywitz et al., 1998; Renvall & Hari, 2003; Temple et al., 2003). However, there are also imaging studies that show differences between dyslexic subjects and normal readers in both hemispheres (Eden et al., 1996; Klingberg et al., 2000; Maurer et al., 2011). For instance, reduced word-specific activation in dyslexic 5th grader's fMRI data occurred bilaterally in middle temporal regions and in the left posterior superior sulcus (Maurer et al., 2011). Moreover, as only a limited number of electrodes were used, it is difficult to interpret exactly which brain areas contributed to the results.

The latency comparisons (**Studies I and III**) indicated no significant group differences. This suggests that the speed of cortical auditory discrimination in adult dyslexics and at risk children is comparable to their controls.

4.2.3 P3a

In **Study I**, there were no significant amplitude or latency group effects on the P3a. However, amplitude differences could be seen in the grand-mean difference waves (Fig. 5). Moreover, there were fewer significant P3a responses in dyslexic than control subjects. These results are in agreement with previous studies that have suggested to some extent impaired involuntary attention shifting to sound changes as indicated by the P3a in dyslexia (Kujala et al., 2003; Corbera et al., 2006; Hämäläinen et al., 2008). Even though attentional problems often co-occur with dyslexia (Carroll et al., 2005), it is possible that only a subsample of individuals participating in **Study I** had attentional problems.

The P3a responses were not analyzed in **Study III** as there were no clear P3a deflections seen in the group difference waveforms for all the deviants. A small P3a deflection can only be seen for the vowel-duration change, which also elicited the largest MMNs compared to the other deviants (Fig. 6). These results suggest that involuntary attention did not shift to vowel, consonant, frequency, and intensity changes in syllables in either of the child groups. The results are in agreement with **Study II** and a previous adult study that used the same syllable stimuli (Pakarinen et al., 2009).

4.3 Intervention effects

In **Study IV**, the brief training period with audio-visual intervention improved central skills needed for successful reading-skill acquisition. Although there appears to be a difference in the group averages before the training period (Figs. 7 and 8), no statistically significant differences were found. The children who played the intervention game improved in all the reading-related skills tested, while the children in the control group improved only in few (Fig. 7). Letter Knowledge, Phonological Processing and Reading Syllables and Non-Words were skills that developed in both groups, whereas the children in the intervention group also improved in recognizing letters belonging or not belonging to Finnish, and learned to write syllables, non-words, and words, effects that were not present in the control group. These results are in agreement with previous studies with GraphoGame (Brem et al., 2010, Saine et al., 2010; Lyytinen et al., 2007) that report improved reading-related skills after audio-visual letter-sound association training.

Children's reading-related performance

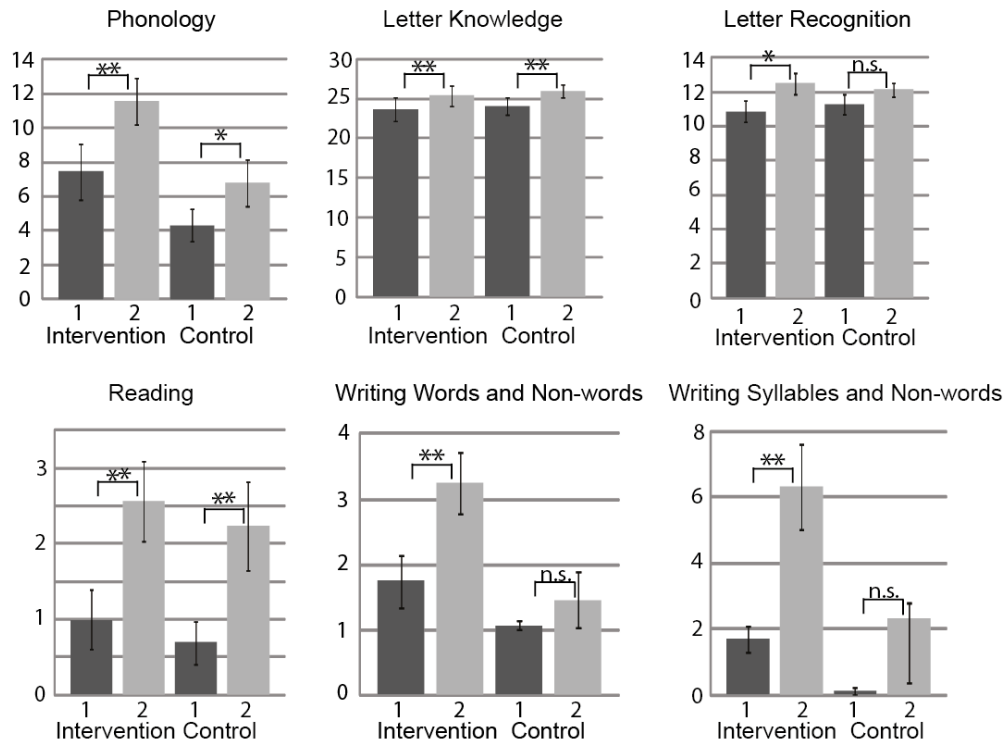


Figure 7. Test scores in Phonological processing, Letter Knowledge, Letter Recognition, Reading syllables and non-words, Writing words and non-words, and Writing syllables and non-words before and after the training period (1=before, 2=after) in the intervention and control groups. Significant differences before and after the training are marked with asterisks, * $p < .05$, ** $p < .01$, *** $p < .001$ (matched pairs test).

Reading improvements were paralleled by functional changes in the brain, reflected in the increased MMN amplitudes for the vowel and vowel-duration changes in the intervention group. The training effects were best reflected in the vowel MMN (Fig. 8). Moreover, there was a significant correlation between the increase in the MMN amplitude and improvements in Letter Knowledge and in Letter Recognition. This result indicates a close relationship between the passive cortical discrimination of vowel changes and the active letter processing ability. As expected, MMN amplitudes for frequency and intensity changes, in turn, were not increased by the intervention as they were not features actively trained in the games.

5 GENERAL DISCUSSION

5.1 Multi-feature MMN paradigm in dyslexia research

As indicated by the compatible (**Studies II and III**) or even larger (**Study IV**) MMN amplitudes for vowel and vowel-duration changes in the multi-feature paradigm than those in the oddball paradigm in children, it can be concluded that the multi-feature paradigm produces either a compatible or even a better MMN signal than the oddball paradigm in children. This suggests that the multi-feature paradigm is well suited for studies in children.

The results from **Study I** showed that the MMN amplitudes for frequency and duration deviants were diminished in adults with dyslexia compared to those of their controls in the multi-feature but not in the oddball paradigm. This indicates that the multi-feature paradigm is more sensitive than the traditional oddball paradigm in tapping auditory impairments in dyslexic adults. In line with this, the multi-feature paradigm also provides a more sensitive measure than the oddball paradigm for detecting auditory discrimination deficits in schizophrenia (Thönnesen et al., 2008). Furthermore, a paradigm with continuously changing ('roving') standard stimuli was suggested to characterise the abnormal processes underlying cognitive impairments in schizophrenia more appropriately than the oddball paradigm (Baldeweg et al., 2004). Taken together, these results suggest that responses measured with more challenging paradigms than the oddball paradigm more appropriately characterise the central auditory processes underlying cognitive impairments in adults.

Furthermore, the results from **Study I** are to some extent in agreement with the anchoring-deficit hypothesis of Ahissar (2007), which predicted that the MMN process would be more abnormal in dyslexic subjects under conditions that tax the formation of the memory trace. In agreement with Ahissar's (2007) hypothesis, it seems to be more difficult for dyslexic individuals to form a memory trace for the standard sound-frequency and duration in the multi-feature paradigm that includes more variation than the oddball paradigm. In line with this, children with better results in Auditory Memory

Span test have a higher incidence of the MMN in multi-feature paradigm (Bauer et al., 2009).

However, in contrast to the results from the adult study, children at risk for dyslexia processed vowel and vowel-duration contrasts in a deficient way in both paradigms and not only in the multi-feature paradigm. Possibly, the at-risk children did not similarly benefit from the simple acoustic context of the oddball paradigm as did the adult dyslexic subjects. It would be worth studying, whether the ability to discriminate sound features is more severely altered in the early childhood than later in life in dyslexia. Consistent with this, younger SLI children were poorer in sound discrimination than older SLI children (McArthur & Bishop, 2004). This was suggested to reflect an immature development of auditory cortex in SLI, such that the adult level of auditory discrimination performance is attained several years later than normal. Furthermore, an impaired N1 tuning for print was shown to play a major role for dyslexia at the beginning of learning to read whereas other aspects of visual word form processing remained impaired after several years of reading practice (Maurer et al., 2011). This was suggested to reflect how neural deficits associated with dyslexia are plastic and change throughout the development and reading acquisition (Maurer et al., 2011).

In conclusion, the results from this thesis suggest that the multi-feature paradigm is an attractive tool for future studies that address auditory processing in children and clinical groups. This is consistent with recent studies in which the multi-feature paradigm with tones was successfully used to investigate healthy newborns (Sambeth et al., 2009), 2-3- year-old toddlers (Putkinen et al., 2012), and with individuals with Asperger syndrome (Kujala et al., 2007), schizophrenia (Thönnesen et al., 2008), post-traumatic stress disorder (Menning et al., 2008), central auditory processing disorder (Bauer et al., 2009), and epilepsy (Korostenskaja et al., 2010). The multi-feature paradigm with syllables, in turn, has been successfully applied to study healthy newborns (Partanen et al., 2013), and children with the Asperger syndrome (Kujala et al., 2010). Recently, new versions of the multi-feature paradigm have been developed (Thönnesen et al., 2010; Shtyrov et al., 2010; Sandmann et al., 2010; Partanen et al., 2011; Pakarinen et al., 2012), for example one with pseudo-words (Partanen et al., 2011).

5.2 Altered cortical auditory processing in dyslexia

As indicated by a tendency for diminished amplitudes of the obligatory ERPs, the processing of auditory information in children at risk for dyslexia differs from the typical path even at the early stages of sound feature encoding. It could be assumed that these difficulties contribute to the phonological problems in dyslexia as deficits in sound feature encoding may weaken the development of phonological representations. However, it is unlikely that atypical sound feature encoding alone is sufficient to lead to dyslexia but rather is a risk factor causing cumulative effects on those processes that are critical for learning to read. Moreover, since the exact functional correlates of the childhood P1, N2 and N4 responses are still poorly understood, further studies in normally developing children and in children at risk for dyslexia at different ages are needed before these findings can be used as markers of dyslexia risk.

As reflected in the diminished MMN amplitudes, the adults and children at risk for dyslexia have a deficient way of discriminating non-speech and speech sound changes. Adults with dyslexia show deficits in discriminating frequency and duration differences in a demanding auditory context including variation. However, their discrimination of intensity changes and gap seems to be unaffected and the processing of location even enhanced. Children at risk for dyslexia showed a widespread pattern of deficits, which was manifested in the compromised processing of vowel, vowel-duration, consonant and intensity but not frequency contrasts. The failure to replicate frequency-discrimination impairment in adults in the oddball paradigm and in children at risk for dyslexia in the multi-feature paradigm may be caused by different stimulus types (simple tones in previous studies vs. spectrally rich tones and syllables in the present ones), different magnitudes of the sound changes, and experimental parameters. These differences may at least partially explain the inconsistencies that concern the findings on auditory processing deficit in dyslexia. Therefore, future studies in dyslexia should longitudinally investigate, with the help of multi-feature paradigm, how individuals with dyslexia differentiate different magnitudes of different sound feature contrasts, such as frequency and duration, in both tone and speech contexts at different ages. Knowledge of these processes could, in the long run, help in designing remediation programs.

The great heterogeneity of the symptoms in dyslexia or heterogeneity of the disorder (Boder, 1973; Castles & Coltheart, 1993; Borsting et al., 1996; Cohen et al., 1992; Wolf & Bowers, 1999; Wolf et al., 2002; Kirby et al., 2003; Ramus et al., 2003; Papadopoulos et al, 2009; Araújo et al., 2010) may also be factors leading to varying findings on auditory processing deficits in dyslexia. Recent studies report auditory processing deficits in ca. 39 % of individuals with dyslexia (Hämäläinen et al., 2012), and it has been suggested that only a sub-group of dyslexic individuals has a pitch discrimination deficit (Bailey & Snowling, 2002; Banai & Ahissar, 2004). The majority of the children at risk for dyslexia in **Study III** may have been children that do not pose difficulties in frequency discrimination while having a deficient way of processing other sound differences. As suggested by Lachmann et al. (2005), different subgroups of dyslexic children may have different kinds of auditory problems. In their study, frequency and consonant processing was altered only in a subgroup of dyslexic children who had problems in frequent word reading. As the children in **Study III** were investigated before the school start, it was not possible to know how many of them do become dyslexics later on, and what kind of reading problems they may suffer from.

The present thesis supports the view that one of the developmental pathways leading to dyslexia involves compromised low-level auditory-processing skills. It is also one of the potential areas on which to focus in order to prevent upcoming reading problems. However, advances in the EEG analysis techniques are needed in order to be able to increase the signal-to-noise ratio and thereby enable interpretations and actions at an individual level.

5.3 Intervention effects on reading-related skills and cortical processes

Training grapheme-phoneme associations with GraphoGame (Lyytinen et al., 2007) for only 3 hours was sufficient for causing reading-related improvements, as the children who played the intervention game made progress in all the reading-related skills tested. Previous remediation studies have tended to include extensive amounts of training, resulting in a conclusion that a 5-18 hour training period over several weeks is needed in order to gain maximal effects (Ehri et al., 2001). The present results show that even a

short carefully targeted intervention that is adaptively administered and motivating for the child can induce significant changes.

As in many intervention studies, also the control group improved in reading-related skills (e.g., Rouse & Krueger 2004; Given et al., 2008; Törmänen et al., 2009). This may at least partially be caused by the children's sensitive developmental stage at the age of six. Reading-related skills are actively learned in Kindergarten, at home and even independently, and the improvements can be fast (Aro, 2006; Lyytinen et al., 2006). Letter knowledge is thought to be the most important basic skill needed for learning to read a shallow orthography such as Finnish, and it was this skill that developed in both groups. However, the intervention group learned not only to recognize letters but also improved in recognizing letters belonging or not belonging to Finnish. Moreover, only the intervention group improved in the spelling skills. Only few previous studies investigating the effects of auditory or audiovisual remediation reported improved spelling skills together with improved reading-skills (for a review, see Loo et al., 2010). In the present study, the children learned to write syllables, non-words, and words. In Finnish, reading and spelling skills seem to develop hand-in-hand. When a child learns to read a word he/she also learns to write it (Aro, 2006). These results may therefore indicate a generalized training effect.

The phonological processing task, in which the child was asked to remove and change the phonemes of the words, shows whether the child has developed a sensitivity to attend to small segments of speech sound (here phonemes) and to manipulate these in his/her mind. This metaskill is a prerequisite and a predictor of the emerging reading ability (Bradley & Bryant, 1978), and also a skill which is developing at the age of six (Wagner et al., 1994). The children were expected to improve in syllable reading, since the intervention trains association between graphemes and phonemes, which is the core of the decoding skill in transparent orthography (Lundberg et al., 1980; Lyytinen & Lyytinen, 2004; Ziegler & Goswami, 2005). Indeed, the intervention group improved in both phonological processing skills and in reading short syllables and words. Also the control group improved in these skills, although the improvement in phonological processing was stronger in the intervention than control group. Unfortunately, the reading test included only few syllables and words, and the effects of the intervention may have been stronger had more items been used as in the spelling tasks.

The reading improvements were also paralleled by functional changes in the brain. The training effects were best reflected in the vowel MMN in the intervention group as the MMN amplitudes for the vowel change showed a large increase over time in the intervention group. The training-induced enhancement of the MMN amplitude presumably indicates an increased accuracy of cortical auditory representations for vowels (Kraus et al., 1995; Näätänen et al., 2002; for a review, see Näätänen & Kujala, 2010). The MMN amplitude for the consonant change showed no increase, however. Even though consonants were trained as much as vowels in the intervention game, the consonant stimuli in the multi-feature paradigm were probably too difficult to discriminate in order to reflect training-induced improvements. Finnish stop consonant changes have elicited small and even unreliable MMN amplitudes in healthy adults (Pakarinen et al., 2009) and in children (**Studies II and III**). The consonant change from /t/ to /p/ and vice versa maybe the most challenging one in Finnish since the acoustic difference is very small and the Finnish clusile consonants are very weak. Another explanation is that the training period was too short for consonant-related learning to proceed sufficiently. In future remediation studies, it would be of interest to include several magnitudes of duration, vowel and consonant contrasts in order to optimize the deviant parameters so that they are as sensitive as possible to detect training induced plastic cortical changes.

The functional changes in the brain even correlated with the behavioural measures in the present study. The vowel-MMN amplitude enhancement correlated with the improvement in the Letter Knowledge and the change in the Letter Recognition test scores. These results support the idea that cortical auditory discrimination is causally connected to reading-related skills (for reviews, see Bishop, 2007; Kujala, 2007).

One of the novel findings in **Study IV** was that the MMN peak latency was shorter for the vowel change in both groups after the training period compared to the MMN latencies before the training period, and that the training effects were also seen in the P3a response. Both the intervention and control games facilitated faster performance as the children were expected to respond to the stimuli as quickly as possible. Therefore, the shorter MMN peak latency may reflect a general improvement in reaction speed. As the behavioral results of this study showed improved phonological processing skills in both groups, the shorter MMN peak latency for vowel changes may also indicate

improvement in vowel discrimination in both groups. The increased P3a response could either (1) follow this improved discrimination accuracy or (2) reflect general improvement in involuntary attention shifting (Escera et al., 2000) as both games also demanded a strong attentional engagement from the child. The children stayed focused as the play-like contexts and immediate rewards were highly motivating for the children. Getting on-line feedback on an improving performance motivates the child to continue competing against himself/herself in order to get even better results. It could be assumed that the training improvements seen in both groups partly depend on attention, as it is an important factor in facilitating neural changes (Kujala & Näätänen, 2010). In line with this, recent studies with computerized visuospatial working memory tasks with similar designs as the games in **Study IV** have improved performance not only in visual but also in verbal working memory tasks (for a review, see Klingberg, 2010). These improvements were also accompanied by changes in brain activity in frontal and parietal cortex (for a review, see Klingberg, 2010).

Taken together, the results from the reading-skill related tests and neurophysiological measures are consistent and indicate improvement caused by the GraphoGame intervention: (1) The intervention group improved in all reading-related skills but the control group only in some of them, (2) There were group differences in reading-related test results after but not before the intervention, (3) The MMN results indicated greater improvements in central auditory processing in the intervention than in the control group, (4) There was a correlation between the vowel-MMN amplitude change and the change in the Letter Knowledge and Letter Recognition test scores. Therefore, the behavioural and MMN results suggest that the effects of training were associated with the improved phonological discrimination which is considered one of the most typical bottlenecks affecting reading acquisition. The results support the idea that when the cortical memory representations for phonemes become stronger also the behavioral phonological processing skills and letter knowledge improve as letter knowledge shows a high degree of overlap with phonological awareness in the orthographically highly consistent Finnish. These improvements lead, in turn, to improved reading and spelling skills.

In future, the remediation efficacy of a short audio-visual training period should be separately determined with larger samples, at different ages, and for different dyslexia

subgroups in order to investigate the possible benefits of the intervention more profoundly. Moreover, long-term effects of this kind of a short intervention should be followed up as the mechanisms and processes that lead to permanent improvements in reading-related skills are still quite unknown. An extensive training period with GraphoGame in Grade 1 was previously shown to help children with reading-related difficulties reach the average level in reading fluency by the end of Grade 2 (Saine et al., 2010). Here the follow-up was not possible for ethical reasons, as both groups were given both games after the training period.

5.4 Clinical implications

As a consequence of early deficits in central auditory processing of sound changes, a child at-risk for dyslexia receives atypical quality of sound information from the environment. This abnormal sound quality is likely to affect the experience dependent phonological representations in the brain that are essential for learning to read. Furthermore, at least in a subgroup of dyslexics, the early auditory deficits persist until adulthood and continue to affect fluent reading. These concerns illuminate the importance of the early detection and intervention of these deficits. In future, the MMN may provide a means for early detection paralleled by behavioural techniques. With the multi-feature MMN paradigm, early multi-attribute cortical auditory profiles can be measured time-efficiently even from infants and young children. As soon as the stimulus parameters are optimised and the signal-to-noise ratio is sufficiently high, auditory deficits could be diagnosed at an individual level. Based on the individual auditory profile, in turn, an optimally targeted auditory training or assistive listening device (see e.g., Hornickel et al., 2012) could be designed for each individual.

The training of sound-letter-associations that strengthens phonological representations is one of the ways that help children in the process of learning to read. Musical training, in turn, may also be useful in early dyslexia intervention as it strengthens the entire integrated auditory system (Kraus, 2012), e.g., improves pitch processing not only in music but also in speech (Besson et al., 2007), and even improves the experienced mood (Särkämö et al., 2008). In line with this, training with

musical audio-visual matching was previously shown to be effective in dyslexia remediation (Kujala et al., 2001).

5.5 Conclusions

The present thesis investigated cortical multi-attribute auditory discrimination in dyslexia and the effects of intervention on reading-related skills and speech sound discrimination. Moreover, the feasibility of the multi-feature MMN paradigm for dyslexia research and studies in children was tested for the first time. The results show that the multi-feature paradigm is well suited for studies investigating auditory processing in dyslexia and in children. Furthermore, the results show that cortical auditory processing is compromised in dyslexia. In children at risk for dyslexia, auditory processing diverges from the typical path even at the initial phase of sound encoding. In addition, these children have a widespread pattern of deficient cortical auditory discrimination processes. Adults with dyslexia, in turn, have difficulties in anchoring to sound frequency and duration features in a complex auditory environment. The developmental path of dyslexia can be influenced by early intervention, though. Even a short intervention with audio-visual letter-sound exercises improves children's reading-related skills and cortical discrimination of vowel contrasts.

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7 ORIGINAL PUBLICATIONS