Fixing fluency: Neurocognitive assessment of a dysfluent reading intervention

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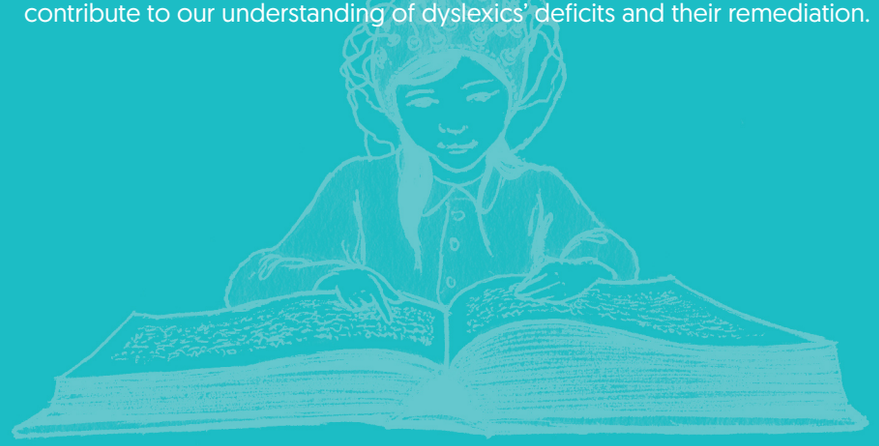
Fixing Fluency

NEUROCOGNITIVE ASSESSMENT OF A DYSFLUENT READING INTERVENTION

The ability to read is essential to attain society's literacy demands. Unfortunately, a significant percentage of the population experiences major difficulties in mastering reading and spelling skills. Individuals diagnosed with developmental dyslexia are at severe risk for adverse academic, economic, and psychosocial consequences, thus requiring clinical intervention. To date, there is no effective remediation for the lack of reading fluency, which remains as the most persistent symptom in dyslexia. This thesis aims at identifying factors involved in the failure to develop a functional reading network as well as factors of treatment success in addressing the notorious 'fluency barrier' in dyslexia.

The present work combines a theoretical framework of dyslexia based on the multisensory integration deficit with recent advances in our knowledge of the brain networks specialized for reading. This thesis uses a longitudinal design including both behavioral and neurophysiological measures in dyslexics at 3rd grade of school. Between measurements, we provide an intervention aimed at improving reading fluency by training automation of letter-speech sound mappings. The studies presented in this thesis contribute to our understanding of dyslexics' deficits and their remediation.



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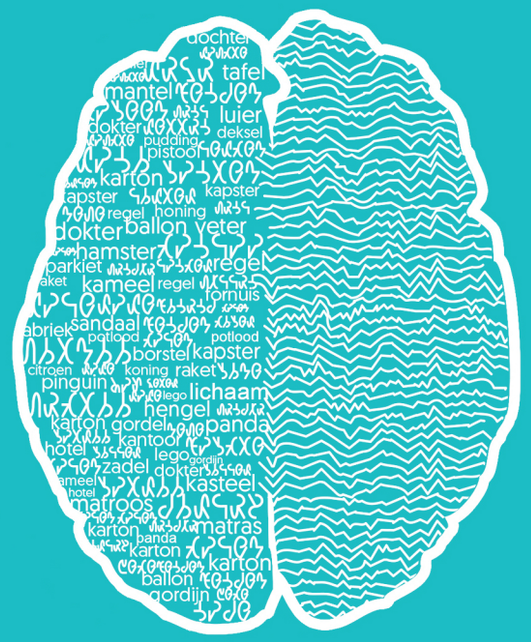

Gorka Fraga González

FIXING FLUENCY: NEUROCOGNITIVE ASSESSMENT OF A DYSFLUENT READING INTERVENTION

Gorka Fraga González

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Chapter 1

General Introduction

1.1 General Introduction

In the information society, reading has become an essential skill to fulfill social, academic and economic demands. Despite its relevance, we are still not able to explain why a small but significant percentage of the population diagnosed with developmental dyslexia fails to attain typical levels of reading abilities in absence of other cognitive or neurological impairments (Snowling, 2013). To date, there is no effective remediation for the lack of reading fluency, which remains as the most persistent symptom in dyslexia. A recent theoretical account for dyslexia proposes a failure to integrate letters and speech sounds as the core deficit underlying reading dysfluency (Blomert, 2011; Froyen, Willems, & Blomert, 2011). This approach is based on growing and converging evidence from behavioral and neuroimaging studies (Aravena, Snellings, Tijms, & van der Molen, 2013; Blau et al., 2010; Froyen, Bonte, van Atteveldt, & Blomert, 2009). The latter also provide new insights on typical and impaired reading development taking into account the role of connectivity within large scale neural networks.

Our research aims at identifying factors involved in the failure to develop a functional reading network as well as factors of treatment success in addressing the notorious 'fluency barrier' in dyslexia. The present work, together with the thesis of Gojko Žarić (Maastricht University), is part of a larger project entitled 'Fluent reading acquisition neurocognitively decomposed: the case of dyslexia - HCMI 10-59' funded by the Netherlands Initiative Brain and Cognition, a part of the Organization for Scientific Research (NWO) under grant number 056-14-015. This project is the result of a collaborative effort between the University of Amsterdam (UvA), IWAL/Rudolf Berlin Center (RBC) and Maastricht University (UM). The UvA contributed with its expertise on cognitive psychophysiology of development and dyslexia. The RBC (founded in 2012) aims at integrating fundamental and applied research in the field of learning disabilities. The project is the result of a long-term cooperation between the programme group Developmental Psychology of the UvA and IWAL (clinical center for dyslexia). The IWAL/RBC were essential in the recruitment, screening and training of dyslexic participants and provided substantial expertise in the cognitive assessment and treatment of dyslexia. Finally, the late professor Leo Blomert from UM played a fundamental role in the design of this project, and the expertise of the co-investigator from Maastricht Brain Imaging center (UM, Gojko Žarić and Milene Bonte) was essential in the design, preprocessing and analysis of our EEG data.

The present project combines a theoretical framework of dyslexia based on the multisensory integration deficit with recent advances in our knowledge of the reading network. The present thesis uses a longitudinal design including both behavioral and neurophysiological measures in dyslexics at 3rd grade of school. Between measurements, we provide an intervention aimed at improving reading fluency by training automation of letter-speech sound mappings. In the first study, we use brain

potentials analysis during visual word recognition to examine neural responses to print in dyslexics and typical readers. That study aims at finding neural markers that are related to reading speed performance in dyslexics. A second study evaluates the behavioral effects of training letter-speech sound integration in dyslexics with a special focus on gains in reading speed. In a third study, we examine neural changes after the training, particularly in dyslexics that showed larger improvements in reading fluency. Finally, we use graph theoretical analysis on resting-state data to examine the global organization of functional brain networks in dyslexics and typical readers.

In this introductory section, we present a brief overview of the cognitive processes that develop with reading acquisition and the brain networks that support them. This is followed by an overview of the most relevant cognitive and neural deficits reported in dyslexic readers. Finally, remediation in dyslexia is reviewed together with neurocognitive intervention studies.

1.2 Fluent Reading Acquisition

Reading involves visual decoding of learned alphabetic symbols to access word meanings and pronunciations. In alphabetic orthographies, reading acquisition starts with learning an alphabetic script code in which the elements of spoken language - speech sounds or phonemes- are associated to the letters or clusters of letters - graphemes- that represent them. Learning this code involves having knowledge of the different spelling patterns and the ability to distinguish the separate phonemes that constitute the pronunciation of a word (phonemic awareness). Efficiently establishing letter-speech sound associations is thus essential to connect the spelling of written words to their pronunciation and meaning. This ultimately enables sight word learning, that is, automatic and accurate word reading from memory (Ehri, 2005).

The study of reading fluency and its development has only gained importance in the field in the recent years, as opposed to reading accuracy which has typically received more attention from practitioners and research (Pikulski & Chard, 2005). Some elements that comprise a working definition of reading fluency are accuracy, reading rate and prosody (Kuhn & Stahl, 2003; Torgesen & Hudson, 2006). Another important characteristic of fluent reading is its effortlessness. This means that performance that can be sustained over time, generalized across texts and that it remains fluent after long periods without reading practice (Hudson, Lane, & Pullen, 2005). One additional consequence of effortless reading is the inability to suppress word decoding, as this becomes an automatic response to alphabetic stimuli (Dehaene, 2009; Noble & McCandliss, 2005).

There is general consensus that the development of reading fluency takes place through a series of stages. As mentioned before in this section, after learning the alphabetic code, readers progressively become more able to link specific parts of words (e.g. graphemes) to speech sounds. Subsequently, it becomes possible to decode new words by consciously attending and decoding all the sounds within

them. This leads to a final consolidated stage in which, through repeated exposure, larger patterns of letters are instantly recognized until the attainment of rapid word identification or sight word reading (Ehri, 2002). In this stage-like process, the reader does not go through one stage at the time; for instance, some words may be processed automatically while others require effortful decoding of each sound within (Share, 1995). Furthermore, efficient word processing may require the reader to proceed through all the stages with every single word (Perfetti, 1992). In addition to decoding skills, other theoretical frameworks have also stressed the role of comprehension in reading fluency acquisition (Chall, 1996).

The development towards fast word recognition is thus associated with extensive experience and it is largely based upon underlying phonological processes (Perfetti & Liu, 2005). In relation to this, the self-teaching hypothesis proposes that phonological decoding of new words allows the reader to autonomously generate word-specific orthographic representations, which would eventually enable fast word recognition (Share, 1995, 2004). Additionally, contextual information is suggested to be used to learn the exceptions in cases where letter-speech sound irregularities only allow partial decoding (Share, 1995).

The view of phonological decoding as a basis for fluent reading is in line with general models of skill acquisition. Accordingly, skill learning is the result of interactions between metacognitive and associative mechanisms (Chein & Schneider, 2005; Siegler, 2005). With growing experience, the associative mechanism develops an implicit and fast analogue of the initial slow, effortful - metacognitive - version of the skill (Crowley, Shrager, & Siegler, 1997). Similarly, the development of fully automated letter-speech sound associations in a way that they enable to attain fluent reading, takes much longer than the acquisition of a passive knowledge of them (Blomert, 2005; Sprenger-Charolles, Colé, & Serniclaes, 2006). In relation to this, while reading accuracy approaches ceiling levels already after the first year of instruction, reading fluency continues to develop moderately over the years (Vaessen & Blomert, 2010; Wimmer & Hummer, 1990). Finally, in addition to efficient word decoding, the increasing role of anticipatory processing in reading fluency has been suggested (Wood, Flowers, & Grigorenko, 2001). This relates to anticipation at both the level of phonemic decoding and at the word identification level by which familiarity of preceding or successive words can facilitate processing. This idea emphasizes that with increasing fluency, reading becomes more characterized by integrative, i.e., anticipatory, processing rather than by item-by-item recognition (Wood et al., 2001).

In brief, reading fluency develops in qualitatively distinct stages and largely relies on processes of which the acquisition of efficient linkage of letters to speech sounds is a fundamental element. The final stage of this process results in instant word identification in proficient readers.

The Reading Network

Literacy has emerged relatively late in the history of human evolution, thus it appears unlikely that any specific brain circuitry is 'hardwired' to subserve the cognitive functions required for reading. Instead, the cultural 'recycling' hypothesis argues that naturally evolved systems for visual and auditory processing become specialized with acquisition of reading abilities. These systems include distinct cortical networks, primarily located at the left hemisphere, and their mutual interaction to enable effortless and fast word decoding.

Neuroimaging studies, mainly using functional magnetic resonance imaging (fMRI), have identified three main brain systems involved in reading; two posterior and one anterior system that develop with reading expertise (see Figure 1.1). The first posterior system is located at more dorsal regions encompassing parieto-temporal areas related to letter-speech sound association. This system includes the superior temporal sulci which has been proposed as an audiovisual integration site (Calvert, 2001). Importantly, the superior temporal sulci showed sensitivity to bimodal letter-speech sound pairs in skill readers (van Atteveldt, Formisano, Goebel, & Blomert, 2004). In addition, the activity of unimodal auditory areas at the superior temporal gyrus/planum temporale seem to be modulated by letters as a consequence of feedback from multimodal areas (van Atteveldt et al., 2004; van Atteveldt, Roebroeck, & Goebel, 2009).

Most relevant to this thesis is the second posterior system, which is situated at more ventral locations and includes regions of the occipito-temporal cortex. Within this region an area located lateral to the middle section of the fusiform gyrus has been related to print processing with strong reproducibility across subjects and multiple script types (Cohen et al., 2000; Dehaene & Cohen, 2011). This area is referred to as the Visual Word Form Area (VWFA) and it is suggested to specialize for fast word recognition with reading expertise (Schlaggar & McCandliss, 2007). Neural responses of the VWFA become stronger to words in a given script than to other visual stimuli (e.g. faces, objects) only after learning the specific script code (Baker et al., 2007; Szwed, Qiao, Antoinette, Dehaene, & Cohen, 2013). In addition, the responses are much smaller and less word-specific in illiterate compared to literate individuals and they seem to increase with reading fluency (Dehaene et al., 2010).

The VWFA is connected to auditory and audiovisual processing areas of the parieto-temporal system by the inferior longitudinal fasciculus (Vandermosten, Boets, Wouters, & Ghesquière, 2012; Yeatman, Dougherty, Ben-Shachar, & Wandell, 2012). Additionally, some studies also suggest a ventral route linking occipital areas to more anterior regions via the inferior fronto-occipital fasciculus (Epelbaum et al., 2008; Vandermosten et al., 2012). These structural connections are consistent with the functional role attributed to the VWFA. There is general agreement that its main function of the VWFA is to facilitate efficient word identification and to link orthographic stimuli to phonological and

lexical information. However, the details on how these functions take place in the visual areas and the specific contribution of the other language systems remains an open question.

A theoretical account has proposed that specific orthographic coding is developed at the VWFA with increasing reading expertise (Dehaene, Cohen, Sigman, & Vinckier, 2005). Accordingly, reading acquisition would result in an bottom-up hierarchy of tuned neuronal circuitry for letters, bigrams, morphemes and short words in visual areas (Dehaene et al., 2005). This account is supported by studies examining the functional organization of the left ventral occipito-temporal cortex and suggesting a posterior-to-anterior hierarchy of responses to stimuli with increasing complexity, e.g., from letters to bigrams (Vinckier et al., 2007). Moreover, VWFA specific responses to a learnt script are also reported when the task, presumably, does not involve naming or activation of systems related to naming (Dehaene et al., 2010; Pegado et al., 2014). Additional support comes from an orthographic training study suggesting a dissociation between top-down modulation of the VWFA after the initial learning stages and bottom-up tuning responses emerging afterwards (Perrone-Bertolotti et al., 2014). Alternatively, to the 'orthographic coding' or tuning account, other authors have emphasized the role of top-down interactions between visual areas and other language systems (Price & Devlin, 2011). This interactive account posits that, in expert readers, bidirectional connections are established between a more generic circuitry in visual areas and other language systems, facilitating effective top-down predictions by for instance, phonological information (Price & Devlin, 2011). This account is supported by an fMRI study using a naming task and showing similar activation levels for pictures and words, and greater responses when visual and spoken forms were presented (Taylor, Rastle, & Davis, 2014). In addition, word-specific responses were found stronger in a phonological task compared to a visual discrimination task in a passing viewing paradigm (Mano et al., 2013). These findings, together with additional studies underscoring the task-dependency of VWFA responses (e.g., Okumura, Kasai, & Murohashi, 2015; Vogel, Petersen, & Schlaggar, 2014) appear to favor an interactive account of visual specialization. Importantly, however, the influence of top-down processes on VWFA activity is also accounted for and is not incompatible with the 'orthographic coding' framework (Dehaene et al., 2010; Perrone-Bertolotti et al., 2014; Yoncheva, Zevin, Maurer, & McCandliss, 2010). Thus, the discussion relates to whether there is a circuitry selectively tuned to orthography at the VWFA or the apparent tuning mostly reflects top-down predictions supported by the special pattern of connectivity of the VWFA to other language areas.

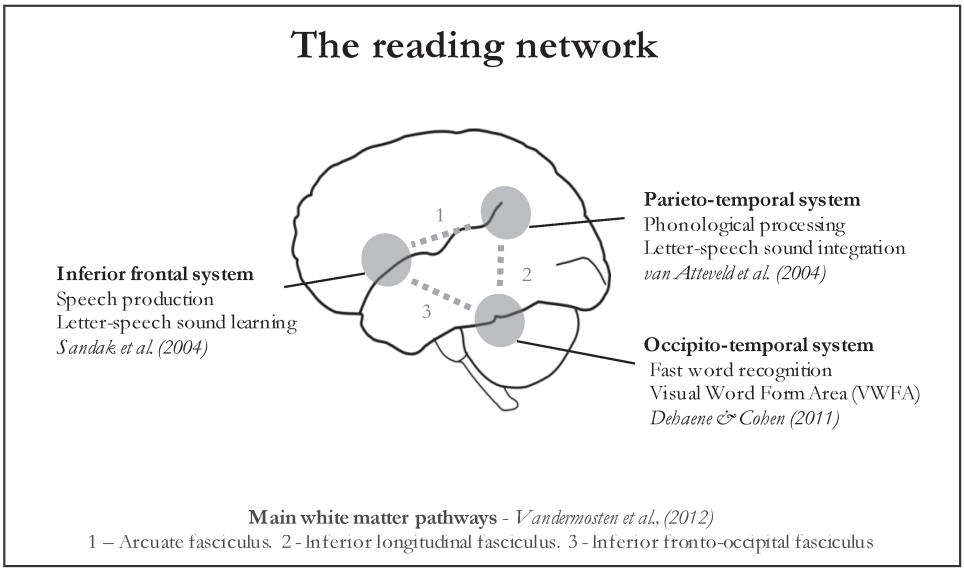

Figure 1.1. Schematic of the reading network

Lastly, the third component of the reading network includes anterior areas of the inferior frontal gyrus and extends to the dorsal premotor cortex. This system relates to letter-speech sound associations in the earlier stages of alphabetic learning and to speech production (Sandak, Mencl, Frost, & Pugh, 2004). It also seems to be more involved in active discrimination tasks involving incongruent pairs of letters and speech sounds (van Atteveldt, Formisano, Goebel, & Blomert, 2007). The inferior frontal regions of this system are connected to the parieto-temporal system by the arcuate fasciculus (Vandermosten et al., 2012).

Development of the Posterior Neural Systems for Reading

The development of the posterior neural systems of the reading network plays a crucial role in the initial stages of reading acquisition. Some authors have a suggested a developmental model in which the parieto-temporal system starts specializing in earlier stages, when learning of the alphabetic code and audiovisual correspondences, and supports the specialization of the visual occipito-temporal system (McCandliss & Noble, 2003; Sandak et al., 2004). Accordingly, multisensory areas responsible for letter-speech integration are strongly engaged in the first years of instruction, and interact with the anterior systems that are involved in slow and effortful decoding of new words. Subsequently, as reading expertise increases, the specialization of the ventral system for fast visual print recognition becomes more relevant to fluent word decoding. With regard to the development of the VWFA, strong word selectivity was reported in 9 year-old children (Monzalvo, Fluss, Billard, Dehaene, & Dehaene-Lambertz, 2012). Visual word specialization seems to develop in a relatively short period of time after learning the alphabetic script. A study in 6-year-old children showed that word specific VWFA could

emerged after only a few months of grapheme-phoneme correspondence training (Brem et al., 2010). Additionally, similar studies in adults show increased ventral occipito-temporal activations for symbols of artificial scripts after just a few days of training (Hashimoto & Sakai, 2004; Mei et al., 2013; Perrone-Bertolotti et al., 2014; Xue, Chen, Jin, & Dong, 2006). Importantly, an inverted "U" trajectory has been proposed for the development of visual expertise (Maurer, Zevin, & McCandliss, 2008; Price & Devlin, 2011). Accordingly, activation of visual areas for reading strongly increases at the initial learning stages, but activation declines with reading expertise once print processing becomes more automatic and overlearned. In sum, the mutual interactions and specialization of different functional systems are essential in the development of the reading network.

Finally, there seems to be some degree of variability in the reading network across languages. The recruitment and shaping of the parieto-temporal and anterior systems seem to be more adaptive to language type, while the visual system for reading is more universal (van Atteveldt & Ansari, 2014). For example, involvement of frontal areas appears to be stronger in logographic scripts (Tan, Laird, Li, & Fox, 2005) and the activity of the temporal system relates more to variations within alphabetic scripts; i.e., orthographic depth (Bolger, Perfetti, & Schneider, 2005). In addition, within the same orthography, the influence of frontal systems on parieto-temporal activity seems to vary with word orthographic regularity (Bitan, Cheon, Lu, Burman, & Booth, 2009).

Electrophysiology of Reading

Electroencephalography (EEG) allows for examining the time course of the electrical activity of the brain with millisecond precision. Because of its high temporal resolution, EEG constitutes a powerful tool to investigate the dynamics of neural activity during fluent reading. The analysis of event-related potentials (ERPs) is used to study of brain responses to specific stimuli. ERPs are believed to reflect the summed post-synaptic activity of large neuronal populations that are spatially aligned (e.g. cortical pyramidal cells) and that are active synchronously, i.e. time-locked to the presentation of certain stimuli or events. The averaged ERP waveforms present a series of positive and negative voltage deflections as they unfold over time. The peaks and troughs in the ERP waveforms represent underlying 'components' that arguably reflect distinct neurocognitive processes. The peak amplitude (±μV) and latency (ms) are the most typical measures in ERP analysis.

In relation to the occipito-temporal system for visual specialization, electrophysiological studies yielded two relevant ERP components. The first is P1; an early positive component with latencies at around 100-150 ms after stimulus onset and a posterior occipital topography. P1 is associated with low-level visual analysis and it is influenced by word surface features such as length and typicality (Assadollahi & Pulvermüller, 2003; Hauk, Davis, Ford, Pulvermüller, & Marslen-Wilson, 2006). The second component is labeled N1 or N170 (referred hereafter as N1). N1 has a negative polarity, peak latencies around 200 ms and is typically observed at parieto-occipital or occipital sites. N1 responses are

related to perceptual expertise (Tanaka & Curran, 2001) and most interestingly, to orthographic processing (Bentin, Mouchetant-Rostaing, Giard, Echallier, & Pernier, 1999; Maurer, Brem, Bucher, & Brandeis, 2005). Moreover, the sources of N1 responses to letters and words have been localized in the VWFA (Rossion, Joyce, Cottrell, & Tarr, 2003; Tarkiainen, Helenius, Hansen, Cornelissen, & Salmelin, 1999). In addition to P1 and N1, a later positivity (labeled P2 in this thesis), with latencies around 300 ms and more temporal scalp distribution, has been associated with phonological as well as semantic processing in visual word recognition experiments (Landi & Perfetti, 2007; Nobre, Allison, & McCarthy, 1994).

This thesis has a special focus on the N1 component because of its relation to visual specialization for word recognition. Previously, N1 responses have shown sensitivity to familiarity and perceptual expertise in visual stimuli of ranging complexity (Brem et al., 2005; Scott, Tanaka, Sheinberg, & Curran, 2006). Most interestingly, studies reported enhanced N1 amplitudes to lexical stimuli in contrast to other stimuli matched in low-level features, such as symbol strings, pseudofont strings, shapes or dots (Bentin et al., 1999; Maurer et al., 2005; Tarkiainen et al., 1999). Because of this, N1 responses have been proposed as an index of visual specialization for words at different stages of reading development. In relation to this, a series of ERP studies examined the difference in N1 amplitudes to words vs. symbol strings in typically reading children (Maurer et al., 2011, 2008). These studies found that N1 word-symbol differences became larger and more left-lateralized from kindergarten to 2nd grade but this 'N1 tuning' effect leveled off between 2nd grade and 5th grade. This pattern was interpreted in accordance with an inverted "U" developmental trajectory of visual expertise. To sum up, N1 is a sensitive indicator of literacy (Pegado et al., 2014) and script learning (Brem et al., 2013; Maurer et al., 2005); together with other measures of VWFA activity, the N1 component is one of the most relevant correlates of literacy (Dehaene, Cohen, Morais, & Kolinsky, 2015)

Besides visual responses, studies have studied electrophysiological responses in the parieto-temporal system, which are associated with language-related auditory and audiovisual processing. One frequently examined component is the auditory mismatch negativity (MMN). The MMN is a response at around 100-200 ms elicited in passive oddball paradigms by an infrequent sound (deviant) that is presented within a repeated sequence of frequent (standard) stimulus (see review in Näätänen, Paavilainen, Rinne, & Alho, 2007). It represents an automatic detection of changes or deviation from traces in auditory short-term memory (Näätänen, 2001). With regard to reading, multiple studies have related MMN responses to speech processing and letter-speech integration in adults and children (Andres, Oram Cardy, & Joanisse, 2011; Bonte, Poelmans, & Blomert, 2007; Froyen, Van Atteveldt, Bonte, & Blomert, 2008). Furthermore, MMN may be followed by an additional late negativity (LN) response in a broader time window from 300 to 700 ms. The LN responses decrease from children to adults and has been suggested to represent additional processing resources before audiovisual

integration of letters and speech sounds becomes fully automatized (Cheour, Korpilahti, Martynova, & Lang, 2001; Žarić et al., 2014). MMN and LN responses are studied in relation to dyslexics' individual differences in reading fluency and intervention outcomes in the doctoral work of Gojko Žarić (Žarić et al., 2014, 2015).

1.3 Developmental Dyslexia

Developmental dyslexia is a specific reading and spelling disability with a genetic and neurobiological component and high prevalence rates around 5 % (Blomert, 2005; Snowling, 2013). Despite receiving adequate literacy instruction and unexpected in relation to intelligence and other cognitive abilities, individuals diagnosed with developmental dyslexia fail to achieve typical levels of reading skills. The most characteristic symptoms of dyslexia are dysfluent and inaccurate word recognition, poor spelling skills, and poor phonological decoding (Lyon, Shaywitz, & Shaywitz, 2003). The lack of reading fluency is one the most persistent symptoms and is hardly remediated by current interventions (Shaywitz & Shaywitz, 2008). Moreover, the slow and strenuous reading is assumed to lead to difficulties in reading comprehension (Samuels, 2002). The impairments in dyslexia have severe academic, economic and psychosocial consequences, thus requiring clinical intervention (Latta, Hendriksen-Neijssen, & Van Loenhout, 2007; Pape, Bjørngaard, Westin, Holmen, & Krokstad, 2011; UNESCO, 2005).

Most theories of dyslexia assume that reading impairments are ultimately caused by underlying neurocognitive anomalies. The majority of these theories conceptualize dyslexia in terms of failure of specific cognitive skills that are required for fluent word decoding. Additionally, however, some accounts of dyslexia have suggested deficits in a more general cognitive domain (i.e. not language-specific). Some examples are visual-spatial attention (Facoetti, Paganoni, Turatto, Marzola, & Mascetti, 2000), basic auditory processing (Hämäläinen, Salminen, & Leppänen, 2012) and the magnocellular component of the visual system (Stein & Walsh, 1997; for a review of sensory deficits in dyslexia see Goswami, 2015). Although some of these theories deserve considerable attention and receive partial empirical support, the most widely accepted accounts for dyslexia are those focused on language-specific deficits.

In particular, the phonological theory has been the dominant view in dyslexia research in the last decades. Accordingly, the ability to attend to and manipulate speech sounds, referred to as phonological awareness, is impaired in dyslexia, hindering the acquisition of reading skills (Shaywitz & Shaywitz, 2008; Vellutino, Fletcher, Snowling, & Scanlon, 2004). This theory is mainly supported by evidence indicating that dyslexics persistently perform worse in phonological awareness tasks across development (Bruck, 1992; Liberman & Shankweiler, 1991; Snowling, 2000) and show certain reading improvements after phonological training (Scanlon, Vellutino, Small, Fanuele, & Sweeney, 2005; Torgesen et al., 2001; Vellutino & Scanlon, 1996). However, competences in phonological awareness

do not seem to predict reading skills in subsequent stages of acquisition (Boets et al., 2010) or the occurrence of reading deficits in children at-risk of dyslexia (Blomert & Willems, 2010). In addition, phonological awareness also develops as a consequence rather than a precursor of reading acquisition (Bishop, 2006; Boets et al., 2010; Mann & Wimmer, 2002; Morais, Castro, Scliar-Cabral, Kolinsky, & Content, 1987). Furthermore, reading remains dysfluent in dyslexics even when phonological awareness and visual word decoding skills are adequate (Biancarosa & Snow, 2004; Blomert, 2011). In sum, the above reviewed empirical evidence seems to challenge the hypothesis of a phonological awareness deficit as a primary deficit in dyslexia.

Recently, a growing number of studies focuses on a letter-speech sound integration deficit as a more proximal cause of reading deficits in dyslexia (Froyen et al., 2011; Kronschnabel, Brem, Maurer, & Brandeis, 2014; Wallace, 2009; Žarić et al., 2014). Knowledge of letter-speech sound associations is essential in the initial stages of reading acquisition as they enable to link spelling to pronunciation and meaning of written words to enable automatic and effortless word decoding (Ehri, 2005; Sprenger-Charolles et al., 2006). Importantly, automation of these associations appears crucial for the acquisition of fluent reading, and requires much longer time than the initially required passive knowledge of them (Froyen & Bonte, 2009, Hahn, Foxe, & Molholm, 2014). As a consequence, if the letter-speech sound associations are not optimally automated children fail to obtain reading fluency. In addition, adequate letter-speech sound mappings may also support the development of phonological awareness during reading acquisition.

The account of a multisensory integration deficit in dyslexia, receives strong support from recent neuroimaging studies suggesting functional abnormalities in dyslexics in the parieto-temporal networks which are involved in multisensory processing (Blau et al., 2010; Blau, van Atteveldt, Ekkebus, Goebel, & Blomert, 2009; Froyen et al., 2009). Interestingly, dysregulation of these regions was reported even when dyslexics presented an adequate knowledge of these correspondences, which suggests an impairment that is mainly related to automation (Blau et al., 2010). In this line, one behavioral study showed that children with dyslexia attained levels of letter-speech sound knowledge comparable to those of their normal reading peers, but their level of letter-speech sound mapping fluency was significantly lower than that of normally reading children (Aravena et al., 2013). Importantly, additional evidence in favor of the multisensory deficit account comes from recent intervention studies demonstrating the clinical potential of training letter-speech sound correspondences in dyslexia (Aravena et al., 2013; Aravena & Tijms, 2009; Tijms, Hoeks, Paulussen-Hoogeboom, & Smolenaars, 2003). Those studies will be further discussed in the following sections of this introduction. In addition, it is also hypothesized that letter-speech sound integration developing at the earlier stages of reading instruction supports visual specialization for word recognition (Sandak et al., 2004). Interestingly, neural responses to print in visual systems were also found abnormal in dyslexics (Maurer et al., 2011).

The following sections offer a concise summary of neuroimaging findings in dyslexia, with special emphasis on electrophysiological studies. Next, we present a review of findings in connectivity within and beyond the reading network emphasizing the integrative nature of reading fluency.

Neural Signatures of Dyslexia

Convergent evidence from fMRI and positron emission tomography (PET) studies has suggested dysregulation in dyslexia across the main systems of the reading network. In particular, reduced activation in the posterior parieto-temporal and occipitotemporal systems has been consistently reported across studies in both adults and dyslexic children (Blau et al., 2010; Brunswick, McCrory, Price, Frith, & Frith, 1999; Paulesu et al., 2001; Shaywitz & Shaywitz, 2008; Simos, Breier, Fletcher, Bergman, & Papanicolaou, 2000). This was interpreted as reflecting deficits in multisensory integration and fast visual word recognition, respectively. Additionally, some studies also reported hyperactivation of the anterior system, which was interpreted as the result of a potential compensatory mechanism (Richlan, Kronbichler, & Wimmer, 2009; Sandak et al., 2004). Overall the pattern of hypoactivation in the posterior systems of the reading network can be considered as one of the most robust neural signatures of dyslexia.

Electrophysiological markers of dyslexia. Most interestingly, the fMRI findings that are reviewed above are supported by brain-potential studies yielding several ERP markers indicating neural timing deficits in dyslexics. The major ERP markers associated with the two posterior systems are described in the following section.

Visual N1 and impaired fast word recognition. A key feature in this thesis refers to the early occipito-temporal N1 responses as a neural marker for reading fluency deficits in dyslexia. As indicated previously, visual specialization for print is reflected in enhanced N1 amplitudes to orthographic compared to visually matched stimuli (Bentin et al., 1999; Maurer et al., 2005). In a series of studies, Maurer and colleagues examined N1 differential responses to words relative to strings of icon-like symbols, in dyslexics and typical readers at different stages of reading acquisition (Maurer & Mccandliss, 2003; Maurer et al., 2011). Typical readers showed a relatively stable tuning effect of left-lateralized word vs. symbol N1 amplitudes that increased from kindergarten to 2nd grade, but leveled off between 2nd grade and 5th grade (Maurer et al., 2011). This pattern was interpreted as indicative of an inverted "U" development of visual expertise, according to which initially increasing visual responses to words gradually decline with expertise. Dyslexics, on the other hand, showed reduced word-specific N1 amplitudes as compared to typical readers (Maurer et al., 2011). This finding was interpreted as the result of deficient visual expertise for words in dyslexics. However, in the same studies, the group difference was not significant in 5th grade and even an opposite trend was observed at that stage. Nevertheless, other studies using a similar paradigm have supported that the same deficits may remain in dyslexic pre-adolescents (Araújo, Bramão, Faísca, Petersson, & Reis, 2012) and adults (Helenius,

Tarkiainen, Cornelissen, Hansen, & Salmelin, 1999; Mahé, Bonnefond, Gavens, Dufour, & Doignon-Camus, 2012). Finally, correlations between N1 amplitudes and reading abilities were reported in typical readers (Korinth, Sommer, & Breznitz, 2012), and in a group including both dyslexic and typical readers (Maurer et al., 2006, 2007).

In view of this evidence, the second chapter of this thesis aims at further examining N1 word responses in dyslexics and typical readers in 3rd grade, which is arguably a critical stage for visual specialization in reading development. In that study we used letter-like symbols as contrast and we focused on the relation between N1 amplitudes and reading fluency in dyslexics. The results support the utility of N1 as a sensitive index for fast word recognition abilities in dyslexics.

MMN and reduced multisensory integration. As indicated above, ERP studies have used evoked MMN responses in a passive "oddball" paradigm to examine letter-speech sound integration across reading development. In support for the multisensory deficit account of dyslexia, a study using letters and speech sounds in a MMN paradigm indicated reduced crossmodal integration in dyslexic children compared to typical readers (Froyen et al., 2011). In addition, previous reports suggested that auditory MMN responses could discriminate between individuals with and without risk of dyslexia in children as young as 6 months of age (Bach, Richardson, Brandeis, Martin, & Brem, 2013; see review in Lyytinen et al., 2005). Altogether these studies indicate the potential of MMN responses as an early indicator of dyslexia. In two recent studies, Žarić and colleagues (2014, 2015) examined crossmodal integration in 9-year-old dyslexics and typical readers, employing an audiovisual oddball MMN paradigm presenting single letters and phonemes. The results of their first study showed deficiencies in letter-speech sound integration in dyslexics that scaled with individual differences in reading (Žarić et al., 2014). Those findings were extended in a second study showing an association between the latency of MMN responses and grains in reading fluency after training in dyslexic children (Žarić et al., 2015).

To conclude, ERP markers can be relevant indicators of the functioning of specific neural systems for reading such as those associated to crossmodal integration and visual specialization. Besides this, there is another important corpus of research that has focused on how the links between different brain systems may be affected in dyslexia. The main findings in structural and functional connectivity studies are discussed in the following section.

Connectivity disturbances in dyslexia. A number of diffusion tensor imaging (DTI) studies, examining white matter properties of neural tracts, have reported reduced structural connectivity in dyslexics relative to typical readers (for a review and meta-analysis Vandermosten, Boets, Wouters, & Ghesquière, 2012). Similarly, fMRI studies in adults reported reduced connectivity across regions of the reading network (e.g., Pugh, Mencl, & Jenner, 2000; Quaglino et al., 2008; Schurz et al., 2014; Shaywitz et al., 2003; Stanberry et al., 2006; van der Mark et al., 2011 but see Richards & Berninger, 2008). In this line, an earlier positron emission tomography (PET) study reported weaker connectivity in dyslexics

between the angular gyrus and other regions of the posterior system, including temporal and occipital areas, during a single word reading task (Horwitz, 1998). That result was supported by a later study that used a series of phonological tasks (Pugh, Mencl, Shaywitz, et al., 2000). On the other hand, EEG studies examining functional connectivity during task performance yielded a mixed pattern of results. Some studies reported reduced or more diffuse EEG coherence in poor relative to typical readers (Dhar, Been, Minderaa, & Althaus, 2010; Nagarajan & Mahncke, 1999) while other studies observed increased coherence in dyslexics compared to normal readers (Arns & Peters, 2007; Shiota, Koeda, & Takeshita, 2000) or a mixed pattern; that is, increased coherence for some EEG bands and reduced coherence for other bands (Marosi, Harmony, & Becker, 1995).

The research reviewed above focused on brain regions specified a priori based on their functional relation to reading. Additional connectivity studies used a different approach and included brain regions beyond the reading network. An fMRI study found abnormal connectivity in dyslexics in two distinct networks involved in executive and phonological processing during a verbal working memory task (Wolf et al., 2010). More recently, a study used a whole-brain data-driven approach to investigate a more complete connectivity profile of dyslexics and typical readers (Finn et al., 2014). Additionally, some fMRI studies have examined connectivity in resting-state data. Some of these studies linked the strength of resting-state connectivity between the visual word recognition areas and the dorsal attention network to age and reading skills (Vogel, Miezin, Petersen, & Schlaggar, 2012; Vogel, Petersen, & Schlaggar, 2014). Similarly, resting-state functional connectivity across the reading network was related to reading abilities in children and adults (Koyama et al., 2011, 2013; Schurz et al., 2014; Zhang et al., 2014). The latter studies attest for the utility of resting-state data to characterize the functional reading network (Hampson et al., 2006; Koyama et al., 2010).

Finally, recent studies on network organization may provide with new meaningful insights into the connectivity deficits in dyslexia. In this regard, analysis inspired in graph theory is a useful tool to model the large-scale organization of complex brain networks. A network of functional or structural connectivity can be represented as a graph, which is a set of nodes and links. Measures derived from graphs allow for characterizing network topologies in terms of the efficiency of information transfer and an optimal balance between 'segregation' and 'integration' (see reviews in Bullmore & Sporns, 2009; Bullmore & Sporns, 2012). The different network configurations also relate to aspects such as local interconnectedness and long-range connectivity. Using this approach, a study examining magnetoencephalographic (MEG) data in dyslexic children and controls showed task-dependent dysfunctional long- and short-range functional connectivity in dyslexics (Vourkas et al., 2011). Another graph analysis from the same group of MEG data obtained during rest revealed less organized network organization in dyslexic children (Dimitriadis et al., 2013). In addition, a recent MRI study examining topological organization in Chinese dyslexic children revealed a less integrated network organization

relative to typical readers, characterized by increased local processing and less long-range communication (Liu et al., 2015).

In sum, there is evidence to suggest disturbances in functional connectivity that may not be limited to reading areas and respond to a more global pattern of disorganization of brain networks. The fifth chapter of this thesis investigates the topology of functional networks in typical readers and dyslexic children. We used resting state EEG data and a recent graph analysis approach that minimizes bias in group comparisons. The results support previous evidence indicating less integrated network configuration in dyslexics. Prospective analysis on longitudinal changes in graph measures and sensitivity to training is suggested.

1.4 Remediation of Dyslexia

There is currently extensive literature on prevention and intervention of dyslexia indicating that it is possible to remediate some of the impairments in dyslexia through specialized treatments. Most promising results have come from studies evaluating phonologically based methods (Elliot, Davidson, & Lewin, 2007; Fletcher, Lyon, Fuchs, & Barnes, 2007; Vellutino, Scanlon, Small, & Fanuele, 2006). Accordingly, explicitly addressing phonemic awareness, phonics and semantics can reduce the risk of reading difficulties (Fuchs & Fuchs, 2006). Similarly, most effective interventions include explicit training in phonemic awareness, which is related to systematic reading instruction (Elliot et al., 2007). Additionally, teaching of metacognitive strategies to facilitate word identification seems to be another helpful treatment element (Lovett, Barron, & Benson, 2003). More generally speaking, intense, systematic and explicit interventions seem to be more successful (Shaywitz, Morris, & Shaywitz, 2008). Most specialized interventions have a duration of between 50 and 80 hours (Torgesen, 2005).

Despite the positive results previously described, the long-term effects of interventions are rarely evaluated (Tijms, Hoeks, Paulussen-Hoogeboom, & Smolenaars, 2003; Torgesen et al., 2001). In addition, in many studies it is hard to disentangle whether the effects are due to specific training characteristics or simply to enhanced reading experience (Kuhn & Stahl, 2003). Most importantly, a consistent result across studies is that reading rate is much less susceptible to remediation that accuracy (Lyon & Moats, 1997; Shaywitz, Morris, & Shaywitz, 2008; Torgesen, 2005). Indeed, current interventions hardly provide with substantial improvements in reading fluency, which remains low in dyslexics, as opposed to accuracy (Compton, Miller, Elleman, & Steacy, 2014; Gabrieli, 2009; Thaler, Ebner, Wimmer, & Landerl, 2004). Detecting instructional elements that can improve reading rate is a key issue in current remediation studies, yet there is still no evidence showing normalization of fluency in dyslexia after intervention (Aravena & Tijms, 2009; Torgesen, 2005). As concluded by Elliot and Grigorenko (2014), training alphabetic principles and decoding skills do not seem to sufficiently remediate dysfluent reading.

Most phonological interventions have a strong focus on accurate learning of phoneme-grapheme correspondences (Alexander & Slinger-Constant, 2004; Gabrieli, 2009; Wolff, 2011). However, as reviewed above in this introduction, this constitutes only the initial point towards the automation that letter-speech sound mappings requires to be efficiently used for fluent reading (Ehri, 2002). Thus, traditional interventions do not intentionally account for the time demands of multisensory integration, which seems to take place within a very brief time window in skilled readers (Froyen et al., 2009). Consequently, the remediation approach examined in this thesis addresses these automation demands by massive and intentional repetitive training of letter-speech sounds correspondences. The training in automaticity is combined with instruction oriented to establish a strong explicit knowledge of phonemic and orthographic regularities as well as decoding skills. These two treatment elements are proposed to enable dyslexics to take advantage of increasing reading experience facilitating the neural tuning processes required for fluent word identification (Aravena & Tijms, 2009). This intervention, inspired by the multisensory deficit account of dyslexia, is evaluated in the third chapter of this thesis in which we stress the effects on reading fluency. The results of the randomized controlled trial support the notion of an integration deficit showing that intensive training of mapping fluency leads to reading fluency gains; secondly, letter-speech sound knowledge is not associated with these gains; and thirdly, initial mapping fluency strongly limited the acquisition of reading speed in untrained dyslexics but not in trained dyslexics.

Finally, response to interventions varies significantly between individuals. For example, a review suggested that an estimate of about 2 % to 6 % of poor readers following special interventions in 1st or 2nd grade will remain having reading difficulties afterwards (Torgesen, 2000). For this reason, many studies have used 'response to intervention' (RTI) as an indicator of severity of the impairments (Fletcher & Vaughn, 2009; Snowling & Hulme, 2011). In view of this, identifying which individual factors can predict treatment outcomes are crucial for effectively designing and implementing early interventions. Besides demographic variables, such as socio-economic status (SES), several cognitive factors such as rapid naming and phonological awareness seem to be predictors of early intervention success (Al Otaiba & Fuchs, 2002; Nelson, Benner, & Gonzalez, 2003). However, a large proportion of variance in intervention response remains unexplained (Scheltinga, van der Leij, & Struiksma, 2010). Because of this, recent neuroimaging research has focused on identifying neurocognitive factors that may aid in improving predictability of treatment outcome.

Neurocognitive Training Studies

Previous research has suggested atypical patterns of brain activity associated to reading in dyslexics. As reviewed in the previous section, the most consistent neural signature of dyslexia seems to be the dysfunction of the posterior systems of the reading network; namely, the parieto-temporal and occipito-temporal systems which are involved in multisensory integration and visual specialization, respectively.

Additionally a potential compensatory role of frontal areas in dyslexia has been suggested. This evidence raises the question of to what extent the proposed neural markers of dyslexia are sensitive to improvements after treatment. Such sensitivity would strengthen the role of biomarkers on both clinical and educational research and practice. The following paragraphs review a corpus of remediation studies, mostly in dyslexic children, that include brain and behavioral measures. Collectively, the studies reviewed offer promising directions and indicate an added value of neuroimaging research on investigating individual differences and treatment outcome. We first describe those studies examining neural changes associated to reading remediation. Secondly, we discuss studies using neural responses as a predicting factor for intervention success in dyslexia.

Neural changes after remediation. Studies have investigated whether atypical responses in dyslexics change after remediation. The majority of these studies have focused on interventions that include phonological skills training of some sort. This is to be expected as phonologically based interventions seem to be among the most effective in improving word decoding difficulties (Snowling & Hulme, 2011). There are differences across studies in aspects such as imaging technique, brain regions examined, type of training and experimental task (Heim et al., 2014). Importantly, however, the evidence consistently suggests brain changes coupled with behavioral performance improvements, contributing to our current functional interpretations of the neural systems for reading.

A number of studies reported 'normalization' of functional activity after intervention; that is, neural responses that were initially deviant in dyslexics or poor readers (in some studies) became comparable to those of typical readers. This result was reported in parieto-temporal areas (Aylward et al., 2003; Eden, Jones, Cappell, & Gareau, 2004; Meyler, Keller, Cherkassky, Gabrieli, & Just, 2008; Richards, 2002; Shaywitz et al., 2004; Simos et al., 2007; Simos, Fletcher, & Bergman, 2002; Temple et al., 2003) as well as in the occipito-temporal system (Aylward et al., 2003; Heim et al., 2014). Additionally, some studies found similar results in frontal regions (Aylward et al., 2003; Heim et al., 2014; Shaywitz et al., 2004).

On the other hand, a few studies reported 'compensatory' responses in dyslexics after intervention. These studies suggested atypical responses observed in dyslexics after remediation but not before, in the right parietal cortex (G. Eden et al., 2004) and left parieto-temporal region (Temple et al., 2003). This pattern of findings was interpreted to reflect adaptive strategies aimed at compensating neural deficits. The specific compensatory mechanisms remain unclear and may depend on the type of intervention (G. Eden et al., 2004), although their attentional nature has been suggested (Temple et al., 2003). In relation to this, two ERP studies reported remediation effects on the visual P2 during a lexical decision task (Jucla, Nenert, Chaix, & Demonet, 2009) and on the late positivity related to performance on a prosodic congruency discrimination task (Santos, Joly-Pottuz, Moreno, Habib, & Besson, 2007). Interestingly, one MEG study studying regional activation profiles reported normalization of neural

activity in children showing larger improvements after training, while compensatory activations were found in those who did not improve reading (Simos et al., 2007). This suggests that emerging responses after intervention may not always reflect the acquisition of the most optimal strategies for reading. Finally, it highlights the relevance of examining neural responses changes in relation to individual differences in response to intervention.

Neural predictors of treatment success. Neural markers could potentially be used as additional predicting factors of intervention outcomes. To date, a few studies have directly related brain activity to treatment responses. Two fMRI studies reported stronger resemblance in neural responses to control readers in responders relative to poor responders to treatment (Davis et al., 2011; Odegard, Ring, Smith, Biggan, & Black, 2008). This was supported by a study indicating a pattern of functional connectivity between inferior frontal areas in typical readers and responders, that was absent in poor responders (Farris et al., 2011). Similarly, some brain potential studies reported ERPs that discriminated between responders and poor responders in reading impaired children. One of these studies examined three different tasks and showed that ERP responses in a letter sound matching task were correlated to reading gains after a short intervention in children in 1st grade (Lemons et al., 2010). Other studies used a word rhyming task in children in 2nd grade (P. J. Molfese, Fletcher, & Denton, 2013) and a phonological decision task related to response to intervention in children in 3rd grade (Hasko, Groth, Bruder, Bartling, & Schulte-Körne, 2014). In addition, two MEG studies related parieto-temporal activations to outcomes of educational interventions in adolescent poor readers (Rezaie et al., 2011a, 2011b). Finally, other studies have accounted for the predictive value of neurophysiological responses on the acquisition of reading abilities at school in typical readers, dyslexics and children at risk of dyslexia (Hoeft et al., 2011; Lyytinen et al., 2005; Maurer et al., 2009).

To sum up, there is some evidence available for neural changes associated to behavioral improvements after intervention (see reviews in Barquero, Davis, & Cutting, 2014 and Ylinen & Kujala, 2015). However, the neural mechanisms driving fluency development and the interactive role of letter-speech sound mapping in visual specialization are not yet clear. In the fourth chapter of this thesis we extend this research in dyslexics using longitudinal ERP data (following the same visual word recognition paradigm as chapter 2) and a training program focused on letter-speech sound integration (which is evaluated in chapter 3). This study demonstrates that a well-stablished ERP marker of visual word specialization, the N1 component, can discriminate between improvers and poor improvers prior to training. In addition, the results show that larger changes in left-lateralized N1 responses after training correlated with gains in reading fluency.

1.5 Outline of the Present Thesis

Our research aims at identifying neural markers of reading fluency and treatment success factors in dyslexics and typically reading children. To attain these aims, the current thesis combines neurophysiological and a broad range of behavioral measures in a longitudinal design. A substantial part of this thesis is concerned with the specialization of visual areas, as this has been shown to be a crucial indicator of reading acquisition. This is particularly relevant to the developmental stage under consideration and the diagnosis of dyslexia. This investigation is extended by the application of a recent analytic framework to examine global deficits in the functional organization of brain networks. The present work will contribute to previous research in this domain by providing a window on the neural dynamics of fluent reading development and remediation factors in dyslexic children.

In **chapter 2** we examine brain potentials in dyslexics and typically reading children during a visual word recognition task. This study also focuses on relating the word-specific visual N1 responses, indicating visual specialization for words, to reading fluency scores in dyslexics.

In **chapter 3** we provide a behavioral evaluation of training fluency of letter-speech sound associations in dyslexics. This is done by means of a randomized controlled trial (RCT) design that allow us to compare pre-posttest reading scores in dyslexics following the training with an untrained group of dyslexics and a control group of typical readers. We pay special attention to reading fluency gains and how they relate to initial levels of letter-speech sound mapping skills.

Given the beneficial effects of the present training and the relation of N1 neural responses with reading fluency, **chapter 4** examines changes in N1 after training in dyslexics. The study in this chapter has a special focus on the relation between gains in reading fluency and 'normalization' of N1 responses to print. Additionally, we also examined whether initial N1 responses could discriminate between children who would benefit more from the letter-speech sound training and those who would show poor reading improvements.

In **chapter 5** we use resting state EEG to examine the organization of functional connectivity networks in dyslexia. In this study, we examine whole-brain network topologies in dyslexics and typical readers by means of a recently developed method based on graph theoretical analysis. We use a minimum spanning tree (MST) sub-graphs derived from connectivity matrices to characterize large-scale network properties related to integration of information and efficiency of communication within the network.

Finally, **chapter 6** presents a summary of the results that emerged from these studies and will provide a neurocognitive interpretation of the main results. The implications of neurophysiological research in the remediation of dyslexia are also discussed in this chapter.

Chapter 2

Brain-Potential Analysis of Visual Word Recognition in Dyslexics and Typically Reading Children

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Abstract

The specialization of visual brain areas for fast processing of printed words plays an important role in the acquisition of reading skills. Dysregulation of these areas may be among the deficits underlying developmental dyslexia. The present study examines the specificity of word activation in dyslexic children in 3rd grade by comparing early components of brain potentials elicited by visually presented words vs. strings of meaningless letter-like symbols. Results showed a more pronounced N1 component for words compared to symbols for both groups. The dyslexic group revealed larger left-lateralized, word-specific N1 responses than the typically reading group. Furthermore, positive correlations between N1 amplitudes and reading fluency were found in the dyslexic group. Our results support the notion of N1 as a sensitive index of visual word processing involved in reading fluency.

2.1 Introduction

Reading involves decoding visual information to access a series of speech sounds, and word meanings. Fluent readers develop visual expertise that allows fast identification, recognition and categorization of letters, and this specialization is proposed to recruit specific cortical areas evolved for visual object recognition (Dehaene & Cohen, 2007). This ability is compromised in individuals diagnosed with developmental dyslexia. Dyslexia is a specific reading disability with a neurobiological origin, persistent symptoms and high prevalence rates ranging from 5 to 10 percent (Blomert, 2005; Shaywitz & Shaywitz, 2005). It is characterized by dysfluent and inaccurate word recognition, spelling and phonological decoding (Lyon & Shaywitz, 2003). The lack of fluency seems to be the most persistent feature and typical levels of automaticity in reading are hardly achieved after treatment (Benjamin & Gaab, 2012; Shaywitz & Shaywitz, 2008; Tijms et al., 2003).

Neuroimaging studies explored the neural correlates of both phonological and visual recognition processes during reading. Two posterior neural systems, primarily in the left hemisphere, have been described as particularly important in the development of reading skills (McCandliss, Cohen, & Dehaene, 2003). One of these systems is located in the left dorsal parieto-temporal region and involves areas of the superior temporal gyrus, supramarginal gyrus and angular gyrus. This system is related to phonological processing and cross-modal integration of letter and speech sounds (Blomert, 2011; van Atteveldt et al., 2004). The second system, which is the focus of the present study, is located in the ventral left occipito-temporal region, and involves areas in the middle and inferior temporal and occipital gyrus. Within this system, the area located at the left lateral occipito-temporal sulcus has been called the 'Visual Word Form Area' (VWFA) because of its suggested specialization for printed word recognition (Dehaene & Cohen, 2011; McCandliss et al., 2003).

Longitudinal studies suggest that the left dorsal parieto-temporal system and the left occipito-temporal system interact and play an important role in the development of reading acquisition. Accordingly, some authors proposed a model in which the temporo-parietal system develops earlier and establishes letter-speech sounds mappings that later supports the rapid word recognition specialization subserved by the occipito-temporal system (Blomert, 2011; McCandliss & Noble, 2003; Sandak et al., 2004). Most importantly, dysregulation in both the posterior parieto-temporal and occipito-temporal systems for reading have been found in dyslexic adults (Blau et al., 2010; Brunswick et al., 1999; Helenius et al., 1999; Paulesu et al., 2001; Shaywitz & Shaywitz, 2008; Simos et al., 2000).

Electrophysiological studies allow for taking a closer look at the time course of neural responses to print and can provide substantial information regarding the functional aspects of the occipito-temporal system during reading. Studies examining event-related brain potentials (ERPs) yielded two components related to early visual processing of orthographic stimuli. The first is a positive component

labeled P1, it peaks between 100 and 150 ms after stimulus onset and it has posterior-occipital topography. P1 has been associated with low-level analysis of word features, including word length and typicality (Assadollahi & Pulvermüller, 2003; Hauk et al., 2006). A second component, labeled N1 or N170, has a negative polarity and peak latencies around 200 ms, and is usually observed at parieto-occipital or occipital sites. Most interestingly, N1 has been related to visual expertise and orthographic processing (Bentin et al., 1999; Maurer et al., 2005), and its sources have been localized in the VWFA (Rossion et al., 2003; Tarkiainen et al., 1999). In addition to P1 and N1, a later positivity (labeled P2 in this study), with latencies around 300 ms and more temporal topographies, has been associated with phonological as well as semantic aspects of stimuli in visual word experiments (Landi & Perfetti, 2007; Nobre et al., 1994).

The N1 component is the main focus of the present study because of its relation to visual processing and VWFA activity. Expertise in the visual processing of different categories of objects is associated with an enhancement of N1 amplitude (Tanaka & Curran, 2001). Interestingly, besides general visual expertise, N1 seems to be particularly sensitive to lexical processing. Larger N1 amplitudes are found for words compared to strings of symbols, shapes or dots (Bentin et al., 1999; Maurer et al., 2005; Tarkiainen et al., 1999). Moreover, N1 responses appear to be sensitive to word similarity, being larger to letters-like stimuli like pseudofonts compared to stimuli matched on low-level features (Eulitz et al., 2000; Schendan, Ganis, & Kutas, 1998; Tarkiainen et al., 1999). Further, consonant strings and pseudowords usually evoke N1 responses similar to those elicited by words (Bentin et al., 1999). In addition, the N1 specialization for word processing seems to be automatic, and is observed when using tasks that do not require reading (Bentin et al., 1999; Brem et al., 2005; Eulitz et al., 2000). To some extent, N1 responses to words may relate to a more general N1 sensitivity to familiarity. However, evidence supporting the left lateralization of N1 word responses suggests that this may be a special of perceptual expertise. A number of studies have reported left lateralized enhancement of N1 amplitudes to orthographical compared to contrast visual stimuli (Bentin et al., 1999; Maurer et al., 2005, 2008; Rossion et al., 2003; Xue & Poldrack, 2007). Collectively, these findings suggest that N1 can be used to examine fast and automatic neural responses to print. In view of this evidence, N1 amplitude differences between words vs. symbol strings have been used to provide an index for 'visual tuning' for print that is proposed to develop with visual learning during the first years of reading acquisition (Maurer et al., 2008). This is referred to as the 'visual tuning' hypothesis.

In a series of ERP studies, Maurer and colleagues compared N1 differences between words vs. strings of icon-like symbols at different stages of reading acquisition in both normal readers and dyslexics (Maurer & Mccandliss, 2003; Maurer et al., 2011). The data of normal readers suggested a significant left-lateralized N1 tuning effect that remains relatively stable during the first years of reading acquisition (Maurer, Brem, Bucher, & Brandeis, 2005). The N1 word-symbol differences in typically

reading children were larger for 2nd grade children relative to kindergartners, but leveled off between 2nd grade and 5th grade (Maurer et al., 2011). This pattern of findings was taken to suggest an inverted "U" model of development of visual expertise, in which perceptual learning becomes highly important during the first two or three years of learning to read and then gradually declines as expertise develops. In the same series of studies, the dyslexic children in 2nd grade showed a reduced word vs. symbol difference in N1 amplitude as compared to normal readers. The authors interpreted the reduced word-symbol difference in dyslexics as a lack of visual specialization for print, reflecting a deficit in expertise for rapid word recognition. The N1 amplitude difference between 2nd grade typical readers and dyslexic readers did not reach significance when the groups were compared at 5th grade (Hasko, Bruder, Bartling, & Schulte-Körne, 2012; Maurer et al., 2011). Related ERP studies suggested, however, that this deficit continues to persist in pre-adolescents (Araújo et al., 2012) and adulthood (Helenius et al., 1999; Mahé et al., 2012). Similarly, an fMRI study found differences also in 4th and 5th grade (van der Mark et al., 2009).

The present study further examines the N1 component in dyslexic readers by using an implicit word-reading task and presenting letter-like strings of symbols as contrast. The false font used resembles alphabetic letters but consists of completely novel symbols. Thus we expect this type of symbols to prevent top-down influences from letter representations. In addition, the use of an implicit reading task allows for the assessment of early visual processing, not biased by reading level (Brunswick et al., 1999). This experimental design should demonstrate that N1 amplitude qualifies as a sensitive index of visual specialization for print. Furthermore, the relation between N1 amplitude and reading in typical and dyslexic 3rd grade readers will be assessed with a special emphasis on fluency. Previously, Maurer et al., (2006; 2007) observed a relation between N1 amplitude to word-symbols and reading speed but only when collapsing the typically reading and dyslexic groups. In the present study we will examine the relation between N1 and reading fluency in both groups, separately.

2.2 Materials and Methods

Participants

Third-grade dyslexic children (N = 19; 8.97 ± 0.39 years old) were recruited from a nation-wide center for dyslexia in the Netherlands. All of them had a percentile score of 10 or lower on a standard reading test and they participated in the ERP experiment before starting their treatment program at the center. A group of 20 third-grade, typical readers (8.78 ± 0.35 years old) was recruited from several primary schools attended by children with the same sociodemographical background as the dyslexic group (see Table 2.1 for group characteristics). They had no history of reading difficulties and had a percentile score of 25 or higher on standard reading tests (see below). All participants were native Dutch speakers, received two and a half years of formal reading instruction in primary education. Children with below

average IQ (IQ < 85 on a non-verbal IQ-test), uncorrected sight problems, hearing loss, diagnosis of ADHD or other neurological or cognitive impairments were excluded. The study was approved by the ethics committee of the university and all parents or caretakers signed informed consent before the children participated.

Behavioral Measurements

A series of tests were used to assess the reading skills of the participants. The children took the tests at their school.

Word reading skills were measured using a Dutch version of the *One-minute test* (*Een-Minuut-Test*, EMT; Brus & Voeten, 1973). It is a time-limited test consisting of a list of 116 unrelated words of increasing difficulty and the number of correctly read words within 1 minute serves as reading fluency score. Text reading fluency was assessed also using a test consisting of a coherent text of increasing difficulty. The children were asked to read the story out loud within one minute (*Schoolvaardigheidstoets Technisch Lezen*; De Vos, 2007). In addition, the 3DM battery of tests (test reliability information available in *Dyslexia Differential Diagnosis*; 3DM, Blomert & Vaessen, 2009) was individually administered. The scores of the following 3DM subtests were used. *Word Reading task*: contains visually presented high-frequency words, low-frequency words and pseudowords. Accuracy (% correct) and fluency (correct words in 1 minute) were measured. *Rapid automatized naming (RAN):* blocks of letters or numbers are presented and items have to be read as fast and accurate as possible. Fluency is the time in seconds needed to name a screen of 15 items. *Letter-speech sound (LSS) association tasks*: consist of identification and discrimination tasks. In the identification task an aurally presented speech sound has to be matched to one out of four visually presented letters. In the discrimination task the child has to judge whether the speech sound and letter on the screen are congruent or incongruent. *Computerized Spelling:* words are aurally presented and visually displayed on screen with missing letters. The participants have to select the missing letter out of four alternatives. For the last two subtests, accuracy (% correct) as well as response time (sec/item) is measured.

Finally, the *RAVEN Coloured Progressive Matrices* was used to obtain an estimate of fluid IQ (RAVEN CPM; Raven, Court, & Raven, 1998) and the Child Behavior Checklist (CBCL) was completed by the parents to exclude any additional behavioral problems (Achenbach, 2003).

The group differences in reading accuracy and speed measures are displayed in Table 2.1. The table shows a deficit in dyslexics that is mainly manifested by large differences in the reading fluency measures, while both groups attained reasonably high levels of accuracy.

Table 2.1. Descriptive statistics showing reading accuracy and fluency scores

	Typical Readers	Dyslexics		
	M (SD)	*M (SD)*	*p*-value	η^2
N	20	19		
Sex ratio (m:f)	8:12	8:11		
Handedness (L:R)*	2:15	3:16		
Age	8.78 (0.35)	8.97 (0.39)	.122	0.34
3DM Word reading - *accuracy* [a]				
HF	99.12 (1.12)	93.75 (4.33)	.000	0.44
LF	97.25 (3.23)	86.46 (13.52)	.001	0.24
Pseudo	87.37 (9.65)	69.14 (17.77)	.000	0.30
Total [T][b]	49.50 (9.06)	31.05(10.23)	.000	0.49
3DM Word reading - *fluency* [T]				
HF	52.95 (7.58)	31.68 (6.03)	.000	0.72
LF	54.65 (9.02)	31.53 (5.92)	.000	0.70
Pseudo	53.00 (9.44)	29.84 (6.70)	.000	0.68
Total	53.95 (9.34)	30.68 (4.84)	.000	0.72
One-Minute Test -*fluency* [C][c]	6.05 (1.76)	2.00 (0.88)	.000	0.69
Text Reading - *fluency*[T]**	54.70 (8.04)	32.94 (5.94)	.000	0.71
3DM Spelling - *accuracy*[T]	50.60 (9.14)	34.37 (5.00)	.000	0.56
3DM Spelling - *fluency*[T]	54.55 (8.70)	36.68 (6.28)	.000	0.60
Letter-speech sound associations [T]				
L-SS identificacion - *accuracy*	46.95 (7.70)	39.00 (9.08)	.005	0.19
L-SS discrimination - *accuracy***	50.20 (9.25)	40.72 (8.04)	.002	0.24
L-SS identificacion - *fluency*	52.80 (7.08)	41.53 (8.02)	.000	0.37
L-SS discrimination - *fluency***	51.10 (8.01)	43.28 (8.61)	.006	0.19
3DM Naming speed scores[T]				
Letters	50.05(7.13)	37.95(7.67)	.000	0.41
numbers	50.65(10.92)	38.95(8.60)	.001	0.27
Total	49.85(7.91)	36.84(8.60)	.000	0.40

[a]Raw scores. [b] T scores (M = 50, SD = 10). [c] C scores (M = 5, SD= 2)
*Data missing for 3 participants; Typical n = 17. ** Data missing for one participant; Dyslexics n = 18.

ERP Measurement

Procedure and equipment. The ERP measurements were taken within a period of around 2 months. The EEG recording took place in a video-controlled and soundproof room with temperature regulated by an air-conditioning system. There was no exposure to sunlight and the lightning of the room allowed a uniform and glare-free illumination. Participants and lab assistants were together at all times in the room while the experimenter controlling the recording, subject performance and stimuli presentation was in an adjacent room. Participants were seated at approximately 80 cm distance from the computer screen and the lab assistant sat behind at a distance that safely avoided any possible distraction or interference on the visual field of the participant. At both arms of the participant's chair response buttons were placed. The experiment lasted around 16 minutes including pauses, and it was part of a longer experimental session (around 2 hours long). There were short pauses between blocks and longer breaks (around 5 minutes long) between experiments. The length of these pauses and breaks varied according to the needs of the participants and all of them received a present at the end of the experimental session. The stimuli were presented using an ASUS VW22U (resolution 1680x1050) monitor with a Dell Optiplex 760 dual-core 3.0GHz computer and an ATI HD 6570, 2Gb graphic card. The software used to present the stimuli was Presentation (Version 14.4, www.neurobs.com).

The ERP data were collected using a 64 channels Biosemi ActiveTwo system (Biosemi, Amsterdam, Netherlands). EEG was recorded DC (low-pass: 5th order sync digital filter) with a 1024 Hz sample rate. The Biosemi system uses two additional electrodes (Common Mode Sense [CMS] and Driven Right Leg [DRL]) as recording reference and ground (see www.biosemi.com/faq/cms&drl.htm for details). The 64 electrodes were distributed across the scalp according to the 10-20 International system and applied using an elastic electrode cap (Electro-cap International Inc.). Electrode sites across the scalp are presented in Figure 2.1 and the electrodes used in the analyses are indicated by highlighting. In addition, six external Flat-Type Active electrodes were used, four of which recorded vertical and horizontal electro-oculogram (EOG) and two were placed at mastoids for off-line reference.

Stimuli. Strings of words and symbols were used in the experiment (see Appendix A for the list of the stimuli used). 80 bi-syllabic Dutch words were selected using estimates of age of acquisition (AOA). Our AOA criterion was 6 years or earlier. Estimates of AOA were based on two published ratings (1) vocabulary estimates of 6-year-olds (Schaerlaekens et al., 1999), (2) AOA of Dutch words (Ghyselinck et al., 2000), and a subsequent student/parent familiarity rating of the selected words. The current selection criterion was motivated by a study indicating that AOA is a more sensitive index of lexical familiarity than either word frequency or neighbourhood density when examining developmental change in visual word recognition (Garlock et al., 2001). Short vs. long strings contained 4 or 5 letters and long strings contained 6 and 7 letters. 80 symbol strings were created by converting the previous

words into a special font: "3elementSymbols-1600" (P.L. Cornelissen, personal communication October 2011) with similar number of line elements and comparable spatial frequency and contrast characteristics to actual letters (Pammer, Lavis, Hansen, & Cornelissen, 2004). To avoid symbols resembling the fixation cross, the letters 'z' and 'y' were replaced by 's' and 'u' in the symbol strings. Short vs. long strings contained 4 or 5 characters and long strings contained 6 and 7 characters.

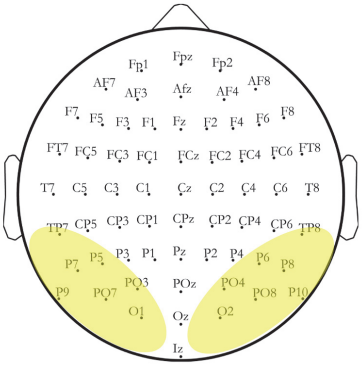


Figure 2.2. Electrode sites across the scalp used in the current study. Electrodes used in the analyses are indicated by highlighting.

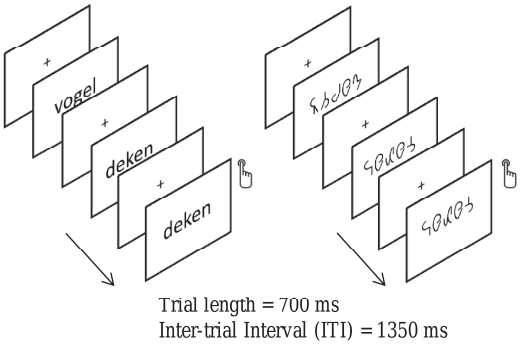


Figure 2.1. An illustration of the word and symbol strings used in the present study. Children were required to attend to the strings and to depress a button whenever a string was identical to its immediate predecessor. Strings of words and letter-like symbols were presented in a blocked design. A fixation cross was presented in between strings.

Experimental design and task. All stimuli were presented at the center of the screen with a visual angle subtending on average 1.5° x 6.4° (height x width), using the lower case font "Arial" in white on a black background, at a font size of 40 and bold. They were presented during 700 ms followed by a 1350 ms inter-stimulus interval (ISI) during which a white centered fixation cross was displayed. Blocks comprised 44 trials, four of which were target trials (i.e., immediate repetitions). The experiment had a

2x2 design with the experimental conditions String Length (short vs. long) and String type (word vs. symbol) evenly distributed in 8 trial blocks. 4 Word and 4 symbol blocks alternated pseudo-randomly across participants. The presentation of the targets was pseudo-randomized to avoid consecutive presentations of targets. The participants were instructed to press a button when they detected a target (i.e., when a stimulus was immediately followed by itself). An example of the stimuli used and a schematic of the design are shown in Figure 2.2.

ERP preprocessing. All EEG data were preprocessed and analyzed with EEGLAB v.11.0.0.0b (Delorme & Makeig, 2004), an open source toolbox for Matlab (Mathworks, Inc.). When imported to EEGlab, the data were referenced to average mastoids, digitally filtered using a basic FIR filter (high pass 1 Hz and low pass 70 Hz), resampled to 256 Hz and epoched (from -500 to 1550 ms after stimulus onset). The baseline of each epoch was then corrected to remove residual activity differences prior to stimuli (this is done by subtracting the mean prestimulus activity from the waveform for each channel and epoch). Artifact removal was done in two steps. The first step consisted of visual inspection of the epochs to remove those epochs containing non-stereotyped artifacts such us head or muscle movements. Secondly, an Independent Component Analysis (ICA) was run using the 'runica' algorithm available in EEGlab (Makeig et al., 1997). The extended option was used to perform a version of the infomax ICA algorithm (Lee, Girolami, & Sejnowski, 1999) that results in a better detection of sources with sub-Gaussian distribution, such as line current artifacts and slow activity. The resulting 64 ICA components were pruned by visual inspection of their scalp map, time course and mean activity, in order to remove components related to artifacts like line noise, eye blinks and ocular movements. The data was then reconstructed on an average (SD) of 34.75 (4.73) ICA components in the control group, and 32.32 (5.60) components in the dyslexic group. Spline interpolation was applied to channels with excessive artifacts. P9 and P10 were interpolated for only one participant. After artifact removal by ICA a new baseline correction was done. Afterwards, data were low pass filtered to 30 Hz (48 dB/octave) and re-referenced to the average of the 64 scalp electrodes. Trials with responses (i.e., target trials and false alarms) were not included in the statistical analysis. The mean (SD) number of trials included in the analysis (after removal of artifacts and response epochs) in the typical readers group, for short words, long words, short symbols and long symbols were 78.95 (1.79), 78.95 (1.27), 73.90 (3.40) and 73.2 (4.11), respectively. The mean (SD) number of trials included in the analysis in the dyslexic group for short words, long words, short symbols and long symbols were 78.63 (1.12), 77.79 (2.22), 75.74 (2.76) and 72.00 (6.09), respectively. Finally, individual subject averages were calculated for each experimental condition.

Statistical Analysis

A repeated measures mixed-model ANOVA statistical analysis was performed comparing typical vs. dyslexic readers (between subjects factor *Dyslexia*). The within subjects factors defined in the analysis

were the following. *String Type* (2 levels: words or strings of letter-like symbols); *String Length* (2 levels: short or long strings). *Hemisphere* (2 levels: right and left hemisphere); *Electrode* (7 levels. Electrodes pairs at occipital, occipito-temporal and parietal locations were included; O1-O2, PO7-PO8, PO3-PO4, TP7-TP8, P9-P10, P7-P8, P5-P6). Peaks were detected by searching for the maximum amplitude value within the time ranges of 50-180 ms for P1, 175-300 ms for N1, and 250-400 ms for P2. The peak values of amplitudes (μV) and latencies (ms) were used in analysis. Greenhouse-Geisser correction of degrees of freedom was used to calculate *p* values when the assumption of sphericity was violated.

In order to assess the relation between the N1 effect and reading fluency the left hemisphere sites (TP7, P9, P7, P5, PO7, PO3, and O1) were selected and averaged based on their proximity to the VWFA location. A composite score of word reading fluency was computed by averaging the One-Minute Test score and the 3DM word reading scores for high frequency and low frequency words. These three scores were combined because they are all based on single-word reading within one minute time and are, arguably, related to visual word recognition processes. Other fluency measures used in the behavioral tests were not included in the composite score since they may be sensitive to different processes (i.e. grapheme-phoneme conversion) and some use different stimuli (i.e. single letters or pseudowords). A linear regression analysis was then performed, for both groups, separately, between the N1 word-symbol difference in amplitude and the composite word fluency score.

2.3 Results

Experimental Task Performance

Accuracy. The performance accuracy data were not normally distributed. Thus, Wilcoxon Signed-ranks test was performed to examine the differences between string type and string length, and independent samples Mann-Whitney-U test was performed to examine differences between groups.

The percentage of correct responses (button presses to targets) was significantly larger for words relative to symbol strings, $Z = 5.02$, $p < .001$. The mean (SD) percentages of correct answers to words and symbol strings were 83.65 (15.35) and 58.33 (18.99), respectively. The mean rank in favor of words was 19.53 while the mean rank in favor of symbol strings was 9.75. The percentages did not significantly differ between short and long strings, $p = .632$. With regard to the group differences, the percentage of correct responses was significantly larger in typical readers relative to dyslexics, for short words ($U = 114$, $p = .033$), and for long words ($U = 116$, $p = .038$). The percentages for short and long words were 89.37 (17.33) and 90 (9.60), for typical readers; and for dyslexics they were 78.29 (20.77) and 76.31 (21.20), respectively. Finally, the percentage of correct responses was larger in typical readers relative to dyslexics for long symbol strings, $U = 110$, $p = .024$, but not for short symbol strings, $p = .095$. The percentages for long symbol strings in typical readers and dyslexics were 66.87 (15.85) and 53.95 (17.70), respectively.

The percentage of false alarms (button presses to non-target stimuli) was larger for symbol strings than for words, $Z = 5.32$, $p < .001$. The mean (SD) percentage of false alarms to words was 1.10 (1.56) and to symbol strings 9.07 (4.74). The mean rank in favor of symbols was 19.92 while the mean rank in favor of words was 4.00. The percentage did not differ between short and long words, $p = .418$, but it was larger for long relative to short symbol strings, $Z = 2.71$, $p = .007$. The mean (SD) percentages for short and long symbol strings were 7.37 (4.69) and 10.77 (7.35), respectively. The mean rank in favor of long symbol strings was 17.26 while the mean rank in favor of short symbols was 16.19. Dyslexics and typical readers did not significantly differ in the percentages of false alarms, $ps > .095$.

Reaction times. Reaction times (RTs) of correct responses to target stimuli were subjected to repeated measures ANOVA with the within-subject factors String Length and String Type, and the between-subject factor Dyslexia. The analysis yielded a significant main effect of String Type, F (1, 37) = 33.93, $p < .001$, $\eta^2 = 0.48$, indicating shorter RTs to symbol strings [553.49 (216.68) ms] than RTs to word targets [751.69 (192.32) ms]. Furthermore, there was a significant effect of Dyslexia, F (1, 37) = 4.85, $p < .034$, $\eta^2 = 0.12$, indicating faster RTs in dyslexics [611.30 (241.80) ms], relative to typical readers [691.83 (206.25) ms]. All other effects did not reach significance, $ps > .163$ The performance pattern suggests a group difference in speed-accuracy tradeoff; dyslectics responded faster than typical readers but made more errors.

ERP Results

P1 component. The P1, peaking on average at around 127 ms, is presented in Figure 2.3.

P1 amplitudes. The ANOVA performed on P1 amplitudes included the within-subject factors String Type, String Length, Electrode and Hemisphere and the between-subject factor Dyslexia. The analysis yielded a significant main effect of String Type, F (1, 37) = 46.27, $p < .001$, $\eta^2 = 0.56$, indicating that P1 amplitudes were larger for words than for symbol strings. The mean (SD) amplitude for words was 6.89 (2.04) μV and for symbol strings 5.32 (1.92) μV. The main effect of String Type was qualified by an interaction with String Length F (1, 37) = 4.32, $p = .045$, $\eta^2 = 0.10$, indicating a larger Type effect for long relative to short strings. Moreover, String Type also interacted with Electrode, F (3, 116) = 17.74, $p < .001$, $\eta^2 = 0.32$, and Hemisphere, F (1, 37) = 5.13, $p = .030$, $\eta^2 = 0.12$. This interaction indicated that the String Type effect was more pronounced at the most posterior sites PO7-PO8, P7-P8 and O1-O2, and at the left relative to the right hemisphere sites. In addition, there was a significant interaction between String Length and Electrode, F (3, 96) = 3.68, $p = .019$, $\eta^2 = 0.09$, indicating that at PO3-PO4 and O1-O2 sites amplitudes were slightly larger for long relative to short strings.

Most importantly, there was a significant three-way interaction including Dyslexia, String Type and String Length, F (1, 37) = 4.30, $p = .045$, $\eta^2 = 0.10$, suggesting larger amplitudes for typical readers relative to dyslexics for short symbol strings but not for long symbol strings nor for words. This

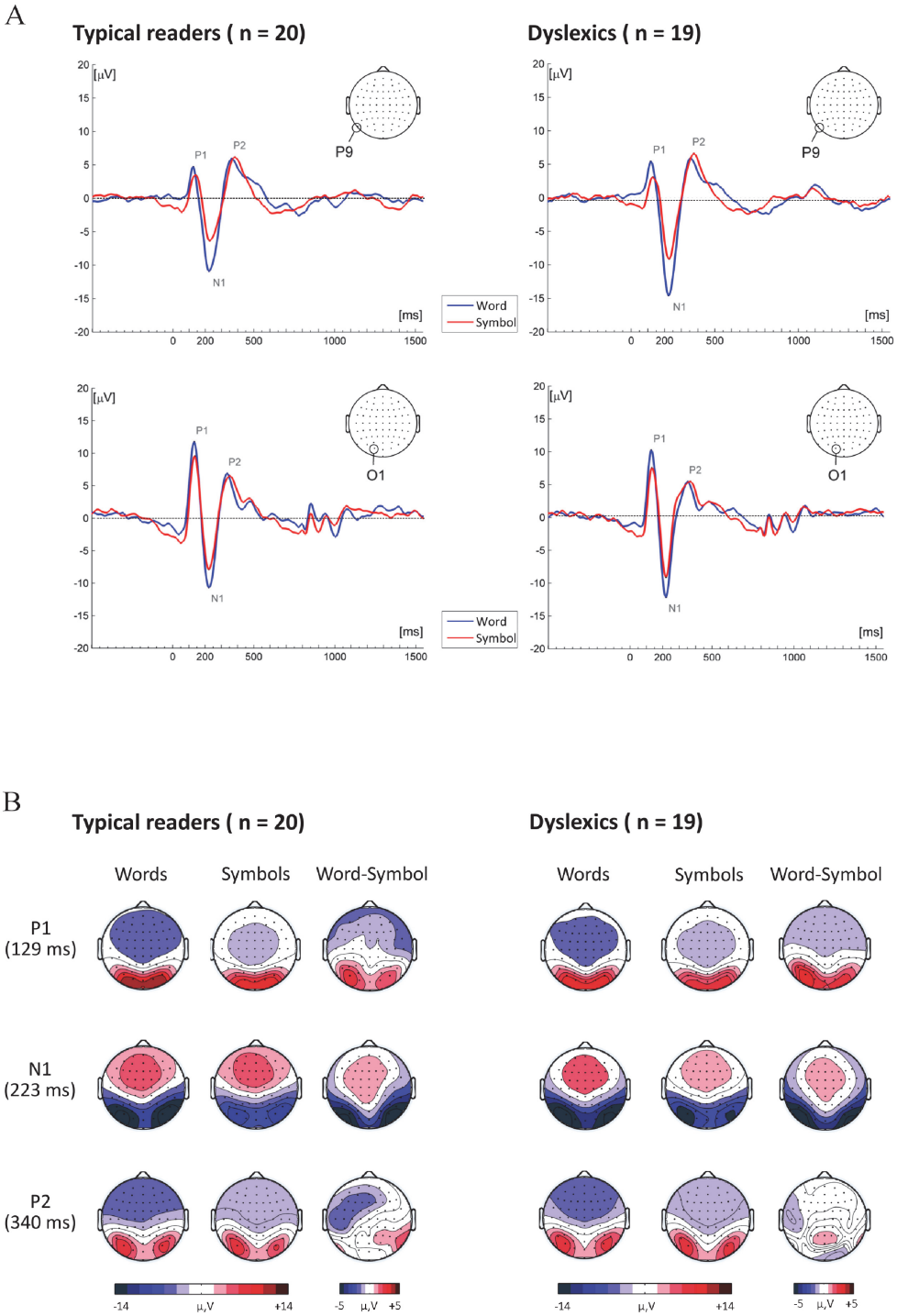


Figure 2.3. (A) Event-related brain potentials to word and symbol strings at P9 and O1. (B) Topographical maps showing the time course of neural activity following stimulus presentation.

interaction is plotted in Figure 2.4. Finally, there was a higher-order interaction including Dyslexia, String Length, Hemisphere and Electrode, F (4, 134) = 3.93, p = .006, η^2 = 0.10. This interaction indicated that P1 amplitudes at the PO3-PO4 and O1-O2 sites were larger for typical readers relative to dyslexics, and this effect was more pronounced at left relative to right hemisphere sites and for short relative long strings (see follow-up analysis below). All other effects did not reach significance, ps > .159.

Follow-up analysis for symbol strings revealed a significant interaction between String Length and Dyslexia, F (1, 37) = 4.58, p = .039, η^2 =0.11, showing larger amplitudes for typical readers relative to dyslexics to short symbol strings but not to long symbol strings (see Figure 2.4). This interaction was not significant for words, p = .481. Separate ANOVAs were performed for each hemisphere. The analysis for left hemisphere sites revealed a significant interaction between Dyslexia, String Length and Electrodes, F (3, 123) = 2.67, p = .045, η^2 = 0.07. This interaction indicated that amplitudes were larger at PO3 and O1 sites for typical readers relative to dyslexics, and this difference was more pronounced for short relative to long strings. The interaction was not significant for the right hemisphere sites, p = .515.

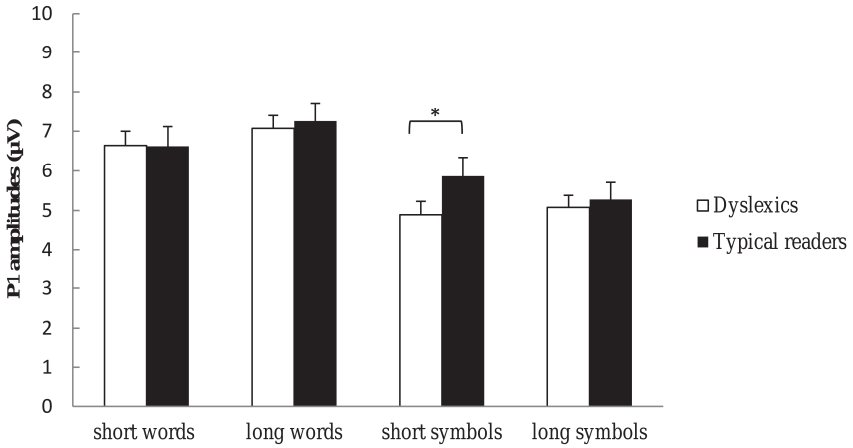


Figure 2.4. P1 amplitudes to each of the string types and string lengths used in the present study. Open bars refer to the P1 amplitudes of dyslexic readers and filled bars to the P1 amplitudes of typical readers. P1 amplitudes are averaged across TP7, TP8, P9, P10, P7, P8, P5, P6, PO7, PO8, PO3, PO4, O1 and O2 electrode sites.

In short, the analysis of P1 amplitudes indicated that P1 amplitude is larger for words compared to symbol strings. This enhancement was more pronounced for long relative to short strings and at the

most posterior sites over the left hemisphere. Finally, P1 amplitude was larger to short symbol strings in typical readers compared to dyslexics.

P1 latencies. The ANOVA performed on P1 latencies yielded a significant main effect of String Type, F (1, 37) = 16.63, p < .001, η^2 = 0.31, indicating shorter latencies for word stimuli than for symbol strings. The mean (SD) latencies were 123.73 (9.00) ms 130.19 (10.84) ms for words and symbol strings, respectively. The effect of String Type was qualified by an interaction with Electrode, F (4, 142) = 3.66, p = .008, η^2 = 0.09, indicating that the effect was primarily at the TP7-TP8 sites, and a higher-order interaction including Electrode, String Length and Hemisphere, F (3, 112) = 4.67, p = .004, η^2 = 0.11. The latter interaction showed that the effect of String Type at the right TP8 site was more pronounced for short relative to long strings, while at the left TP7 site the String Type effect was more pronounced for long relative to short strings. All other effects were not significant, ps > .178, although the main effect of Dyslexia approached significance, F (1, 37) = 3.51, p = .069, η^2 = 0.09, suggesting a trend for shorter latencies in dyslexics relative to typical readers. The mean (SD) latencies for typical readers and dyslexics were 129.42 (7.32) and 124.37 (9.43), respectively.

N1 component. A pronounced negativity, peaking at around 223 ms, is visible in the topographical maps presented in Figure 2.3.

N1 amplitudes. N1 amplitudes were submitted to ANOVA with the within-subjects factors String Type, String Length, Electrode and Hemisphere and the between-subjects factor Dyslexia. The analysis yielded a significant main effect of String Type, F (1, 37) = 131.26, p < .001, η^2 = 0.78, indicating larger amplitudes for words (12.15 (3.78) μV), relative to symbol strings (9.00 (3.48) μV). This effect was qualified by an interaction with Electrode, F (3, 97) = 28.03, p < .001, η^2 = 0.43, and a three-way interaction with String Length and Electrode, F (3, 107) = 4.07, p = .010, η^2 = 0.10, indicating that the String Type effect was more pronounced at P9-P10, P7-P8, PO7-PO8 and O1-O2 electrode sites, and larger for long strings.

The ANOVA also yielded a significant main effect of String Length F (1, 37) = 4.55, p = .040, η^2 = 0.11, indicating that N1 amplitudes were slightly larger for long relative to short strings, 10.75 (3.68) μV and 10.39 (3.46) μV, respectively. This effect was qualified by interactions with Electrode and Hemisphere, F (2, 81) = 4.79, p = .009, η^2 = 0.11, and F (1, 37) = 13.86, p = .001, η^2 = 0.27 respectively. These interactions indicated an effect of String Length that was more pronounced at the P7-P8, P5-P6, PO7-PO8 and PO3-PO4 electrode sites, and at the right relative to the left hemisphere sites.

Most importantly, there was a significant three-way interaction including String Type, Hemisphere and Dyslexia, F (1, 37) = 6.99, p = .012, η^2 = 0.16. This interaction is plotted in Figure 2.5. The String Type effect was more pronounced in typical readers relative to dyslexics at the right hemisphere sites, while the String Type effect was less pronounced in typical readers relative to dyslexics at the left

hemisphere sites (see follow-up ANOVAs below). Additionally, there was a three-way interaction between Dyslexia and Hemisphere that approached significance F (1, 37) = 3.47, p = .070, η^2 = 0.09, suggesting a trend for larger amplitudes in dyslexics relative to typical readers, at the left hemisphere sites but not at the right hemisphere sites. All other effects were not significant, ps >.094.

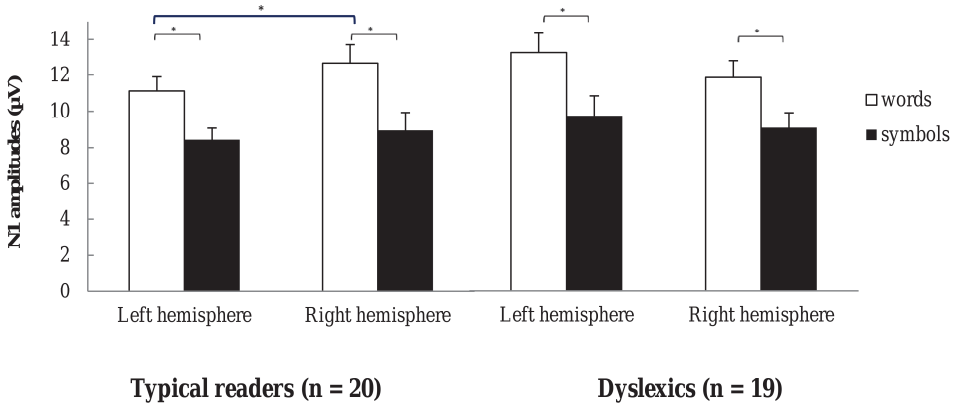


Figure 2.5. N1 amplitudes for words and symbols recorded over the left and right hemisphere sites. Open bars refer to N1 amplitudes for word strings and filled bars to the N1 amplitudes for symbol strings. The left hemisphere N1 amplitudes are averaged across the sites TP7, P9, P7, P5, PO7, PO3 and O1, and the right hemisphere amplitudes across homologue pairs. Plots represent N1 amplitudes in typical readers (left) and in dyslexics (right).

Follow-up ANOVAs were performed in both groups and string types, separately. The analysis for the typical readers data revealed that the String Type effect was reduced at the left hemisphere relative to the right hemisphere sites, F (1,19) = 5.54, p = .029, η^2 = 0.23. The analysis for words revealed a main effect of Hemisphere, F (1, 19) = 4.49, p = .048, η^2 = 0.19, suggesting that the amplitude for words was reduced at the left hemisphere relative to the right hemisphere sites. The analysis for symbol strings did not show a significant main effect of Hemisphere, p = .512. In addition, the interaction including Hemisphere and String Length F (1, 19) = 9.86, p = .005, η^2 = 0.34, indicated that at the right hemisphere sites, long symbols elicited larger amplitudes relative to short symbols. In the dyslexics data none of the interactions with Hemisphere approached significance, ps > .158, indicating that neither symbol nor word N1 amplitudes differed across hemispheres.

To sum up, the analysis of N1 amplitudes revealed larger responses to words compared to symbol strings. This effect was more pronounced for long stimuli and at posterior sites. N1 amplitudes were also enhanced for long relative to short strings at the posterior right-hemisphere sites. Importantly, the analysis revealed that for typical readers, N1 word amplitudes were reduced at the left compared to the right hemisphere sites, but this effect was absent in dyslexics.

N1 latencies. The ANOVA on N1 latencies revealed an interaction between String Type and Hemisphere, F (1,37) = 5.47, p = .025, η^2 = 0.13, indicating that latencies were longer for symbols than word strings but only at the right hemisphere electrode sites. N1 latencies at the right hemisphere for words and symbols were 222.81 (14.09) and 225.20 (14.28), respectively. The main effect of Dyslexia, just fell short of significance, F (1, 37) = 4.06, p = .051, η^2 = 0.09, but was included in a three-way interaction with Hemisphere and Electrode, F (3, 128) = 3.02, p = .026, η^2 = 0.07. This interaction indicated that the effect of Dyslexia was more pronounced at the right relative to the left hemisphere at

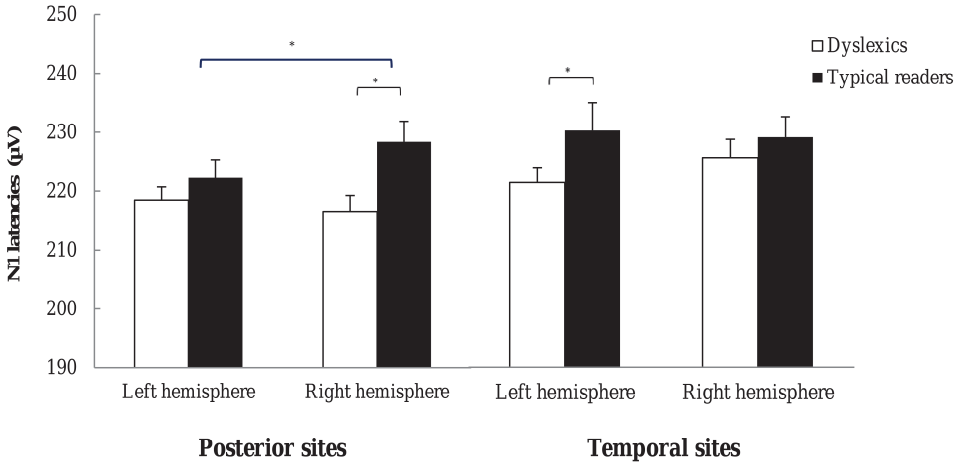


Figure 2.6. N1 latencies observed for each hemisphere. Open bars refer to the N1 latencies of dyslexic readers and filled bars to the N1 latencies of typical readers. For each plot latencies are averaged across the most posterior P7-P8, P5-P6, PO7-PO8, and O1-O2 pairs (left) and across the most temporal P9-P10 and TP7-TP8 electrode pairs (right).

the sites P7-P8, P5-P6, PO7-PO8, PO3-PO4, and O1-O2; while it was more pronounced at left relative to right hemisphere at sites TP7-TP8 and P9-10. The interaction is plotted in Figure 2.6. Finally, the interaction including String Type, Hemisphere and Electrode just fell short of significance, F (2, 92) = 2.63, p = .065, η^2 = 0.06. The String Type effect tended to be larger at the right TP8 and P10 electrodes, relative to their left hemisphere homologue pairs. All other effects were not significant, ps > .117.

P2 component. The P2 peaked at around 341 ms and is presented in Figure 2.3.

P2 amplitudes. The ANOVA performed on P2 amplitudes revealed a small but significant effect of String Type, F (1, 37) = 4.95, p = .032, η^2 = 0.12, indicating slightly larger positivities for words relative to symbol strings; 7.52 (2.73) µV and 7.03 (2.32) µV, respectively. This effect was qualified by interactions with Electrode and Hemisphere, F (3,114) = 5.61, p = .001, η^2 = 0.13, and F (1, 37) = 5.04 p = .031, η^2 = 0.12, respectively. In addition, there was a three-way interaction of String Type, Electrode

and Hemisphere, F (4, 146) = 3.97, p = .005, η^2 = 0.10, showing that the word-related enhancement was more pronounced at P9-P10, P7-P8, P5-P6 and PO3-PO4 sites, and larger at the right relative to the left hemisphere sites (see additional ANOVAs below). The main effect of Hemisphere was also significant, F (1, 37) = 5.34, p = .026, η^2 = 0.13, indicating that amplitudes were larger at the left relative to the right hemisphere sites. P2 amplitudes for left and right hemisphere sites were 7.73 (2.89) and 6.82 (2.54), respectively. Moreover, there was a significant effect of String Length in interaction with Electrode, F (1, 90) = 6.40, p = .001, η^2 = 0.15, indicating larger amplitudes for long relative to short strings at PO3-PO4 and O1-O2 sites.

Most importantly, there was a three-way interaction including Dyslexia, String Type and String Length, F (1, 37) = 6.48, p = .015, η^2 = 0.15. This interaction showed that the String Type effect was larger in typical readers relative to dyslexics for long strings but the groups did not differ in the String Type effect for short strings. This interaction is plotted in Figure 2.7 (A). Finally, a three-way interaction between String Type, String Length and Electrode approached significance F (3, 100) = 2.47, p = .072, η^2 = 0.06, indicating a trend for a larger String Type effect associated with short relative to long strings. All other effects were not significant, ps > .133.

Additional ANOVAs were performed for each String Length and String Type. The analysis for long strings revealed a significant interaction between String Type and Dyslexia, F (1, 37) = 5.87, p = .020, η^2 = 0.14, suggesting that the String Type effect was larger in typical readers relative to dyslexics. The analysis for short strings did not show significant interactions including String Type and Dyslexia, p = .608. Finally, the interaction between String Length and Dyslexia just fell short of significance for symbol strings, F (1, 37) = 3.97, p = .054, η^2 = 0.10, but did not approach significance for words, p = .173. P2 amplitudes for long symbol strings tended to be smaller for typical readers relative to dyslexics (see Figure 2.7 (A)).

The current analysis of P2 amplitudes revealed a small but significant enhancement to words relative to symbol strings. This effect appeared to be larger at right posterior sites compared to left sites. Moreover larger amplitudes for long relative to short strings were observed at occipital sites. Importantly, typical readers showed larger P2 responses for long words relative to long symbols relative to dyslectics but this effect was absent for short strings.

P2 Latencies. For P2 latencies, there was a significant effect of String Type, F (1, 37) = 25.48, p < .001, η^2 =0.41, indicating that words elicited faster P2 responses than symbol strings, 337.28 (16.51) ms and 345.40 (16.11) ms, respectively. This effect was qualified by an interaction with Electrode, F (4,151) = 4.03, p = .004, η^2 = 0.10, suggesting that the effect was less pronounced at PO3-PO4 and O1-O2 sites. In addition, there was a main effect of Hemisphere, F (1, 37) = 5.78, p = .021, η^2 = 0.13, indicating that latencies were longer at the left relative to the right hemisphere sites. Latencies for left and right hemisphere sites were 344.09 (17.96) and 338.58 (16.37) ms, respectively. Furthermore, there

was a main effect of String Length, F (1, 37) = 6.58, p = .014, η^2 = 0.15, suggesting that P2 peaked later for short compared to long strings; latencies were 343.09 (15.54) ms and 339.59 (16.69) ms, respectively.

Importantly, the ANOVA yielded a significant three-way interaction between Dyslexia, String Length and Hemisphere, F (1, 37) = 4.97, p = .032, η^2 = 0.12. This interaction is plotted in Figure 2.7 (B). This interaction indicated shorter latencies at the right relative to the left hemisphere for long strings in dyslexics, but not for typical readers. Finally, the interaction between String Type, Electrode and Dyslexia approached significance, F (4, 151) = 2.24, p = .066, η^2 = 0.06, showing a trend for a more pronounced String Type effect in typical readers relative to dyslexics, at PO3-PO4 and O1-O2 sites. All other effects were not significant, ps > .163.

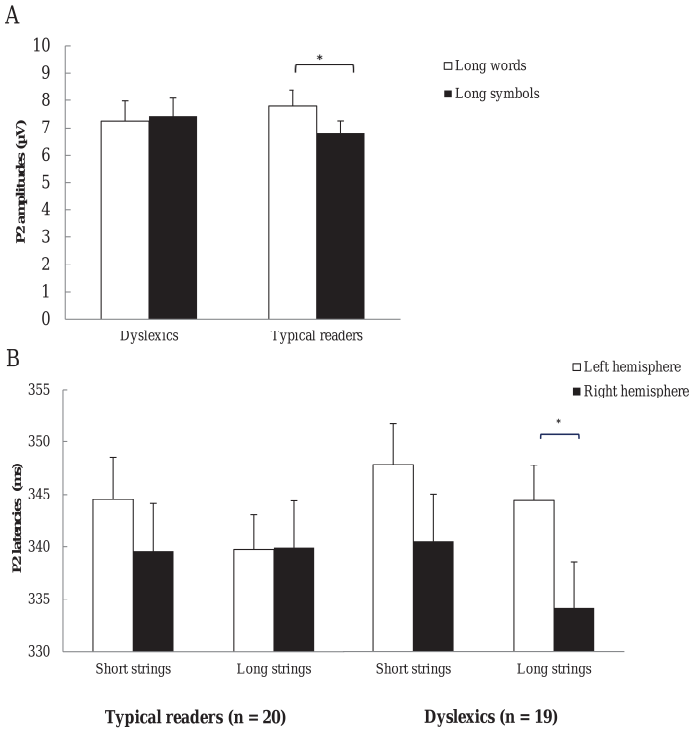


Figure 2.7. P2 (A) P2 amplitudes for each group. Open bars refer to the P2 amplitudes to words and filled bars to the P2 amplitudes to symbol strings. Plots represent P2 amplitudes to long strings. P2 amplitudes are averaged across TP7, TP8, P9, P10, P7, P8, P5, P6, PO7, PO8, PO3, PO4, O1 and O2 electrode sites. (B) P2 latencies to each string length. Open bars refer to the P2 latencies at left hemisphere sites and filled bars to P2 latencies at right hemisphere sites. Plots represent P2 latencies of typical readers (left) and dyslexics (right).

Additional ANOVAs were performed for each String Length. The analysis for long strings showed a significant interaction between Dyslexia and Hemisphere, F (1, 37) = 4.70, p = .035, η^2 = 0.11. The effect of Hemisphere was significant in dyslexics, F (1, 18) = 9.34, p = .007, η^2 = 0.34, but not in typical readers, p = .961. More specifically, latencies were shorter at the right relative to the left hemisphere sites for dyslexics but not for typical readers. The analysis for short strings did not reveal significant interactions with Dyslexia and Hemisphere, ps > .640.

Relation to Reading Fluency

The word vs. symbol difference in N1 amplitude was computed and averaged across the left hemisphere electrode sites (TP7, P9, P7, P5, PO7, PO3, and O1). These difference scores were then submitted to regression analysis to assess the relation with reading fluency in dyslexic readers. An estimate of reading fluency was obtained by using the number of correctly read words per minute (composite score of three word reading tasks, see Statistical Analysis). The relation between N1 amplitude and reading fluency was significant, R = 0.78, R^2 = 0.60, β = 1.97, t = 5.07, p < .001, and is plotted in Figure 2.8. It can be seen that faster dyslexic readers showed a more pronounced difference in N1 amplitude between words vs. symbols. A similar analysis was performed on the data obtained from the normal readers but this analysis did not show a significant relation between the N1 amplitude difference and reading fluency (see Figure 2.8).

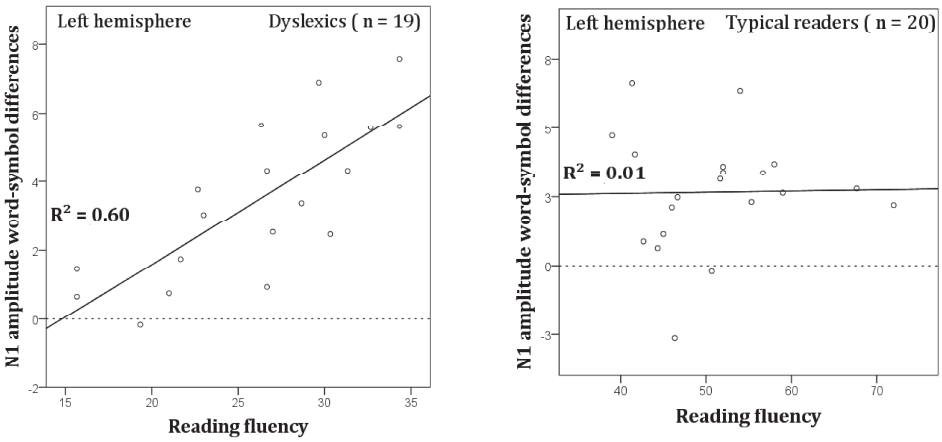


Figure 2.8. Correlation between N1 word-symbol amplitudes averaged across the left hemisphere sites TP7, P9, P7, P5, PO7, PO3 and O1, and the composite reading fluency scores for dyslexic (left) and typical readers (right).

2.4 Discussion

The present study obtained significant evidence for word specialization in early ERP components, as revealed by P1 and N1 amplitudes, at posterior temporo-occipital and parietal sites. N1 amplitudes

were larger for words relative to symbol strings in both groups. Most interestingly, N1 amplitudes to words were smaller at the left compared to the right hemisphere sites in typical readers but not in dyslexics. Furthermore, the difference in N1 amplitude between words and symbols observed over the left hemisphere was related to reading fluency in the dyslexic group. Collectively, this pattern of results supports the notion that N1 amplitude is sensitive to visual word specialization (Bentin et al., 1999; Maurer et al., 2005) and discriminates between typical readers and dyslexics (Dujardin et al., 2011; Maurer et al., 2011).

The major focus of the current study was the sensitivity of the N1 component to word reading in normal and dyslexic readers. The results showed that N1 amplitude was sensitive to string length; i.e., longer strings elicited larger N1 amplitudes irrespective of the type of string. This may suggest that long strings imposed greater processing demands than short strings. As anticipated, there was also a pronounced effect of string type on N1 amplitude. That is, N1 amplitude was larger for words compared to symbol strings. This effect was found in both typical and dyslexic readers and can be interpreted in terms of N1 sensitivity to visual expertise and familiarity. The N1 enhancement for words vs. false fonts in children with dyslexia at the beginning of grade three was also reported in a previous study (Hasko, Groth, Bruder, Bartling, & Schulte-Körne, 2013) suggesting that there is some degree of print sensitivity at this level of reading experience also in dyslexic readers. In this study, both dyslexic and typical readers, already have an advanced level of letter knowledge (3rd grade). Indeed, the current behavioral results indicate that accuracy of the dyslexic children is reasonably high on most of the reading tasks. Their deficit is manifested primarily in reading fluency. A fluency deficit seems to be a common finding in dyslexia studies involving languages with relatively shallow orthographies such as German or Dutch (Frith, Wimmer, & Landerl, 1998; Landerl, Wimmer, & Frith, 1997; Paulesu et al., 2001). Thus, in view of the level of expertise, some degree of low-level visual specialization for print in both groups can be expected. In typical readers, this is further supported by longitudinal data indicating that the majority of children show a distinct N1 for words relative to symbols already in 2nd grade (Maurer et al., 2006).

Importantly, in typical readers N1 amplitude for words was reduced at the left hemisphere compared to the right hemisphere. This hemispheric difference was not present in the dyslexic group. In this regard, there is an apparent discrepancy between the current results and previous findings showing a reduced difference between the N1 to words vs. symbols for reading impaired relative to normal readers (Helenius et al., 1999; Kronschnabel, Schmid, Maurer, & Brandeis, 2013; Maurer et al., 2007). This discrepancy can be interpreted in various ways.

One interpretation refers to VWFA specialization. The lower N1 word amplitudes at the left hemisphere sites in typical readers relative to dyslexics might reflect facilitated lexical access. Lower N1 amplitudes in relation to higher frequency words that are easier to retrieve have been reported

previously (Assadollahi & Pulvermüller, 2003; Hauk & Pulvermüller, 2004; Kronbichler, Bergmann, Hutzler, Staffen, & Mair, 2007). Thus, typical readers might have benefited from a whole-word level of specialization for the current word strings (all familiar words). This beneficial effect might be less pronounced in dyslexics, as suggested by the behavioral word reading scores showing that dyslexics underperformed on the word reading tests. On the experimental task, dyslexics also were less accurate than typical readers when words were presented, suggesting a deficit in whole-word level specialization. The interpretation based on the VWFA word-level specialization is supported by fMRI studies reporting a lack of word familiarity effect in VWFA activation in dyslexia (van der Mark et al., 2009), and an increased engagement of visual occipital areas relative to non-impaired readers (Wimmer et al., 2010). A reduced left-lateralized activation of occipito-temporal areas, as current results suggest in typical readers, might correspond to more automatized reading (Maurer et al., 2006) or to a level of higher expertise at which the facilitation from phonological and semantic areas may become more efficient (Price & Devlin, 2011). Furthermore, longitudinal studies in typical readers suggest that N1 amplitudes to print-specific stimuli are larger and more bilateral in 2nd grade compared to adults (Maurer et al., 2006). A similar decrease in N1 amplitude has been reported from 2nd to 5th grade in typical readers while an opposite trend was observed in dyslexics (Maurer et al., 2011).

An alternative interpretation assumes that attentional strategies might have contributed to the group differences in N1 amplitudes. Deficits in visual-spatial attention processing in dyslexia have been reported in previous behavioral studies (Facoetti et al., 2000; Valdois, Bosse, & Tainturier, 2004). Accordingly, reduced sensitivity has been shown in dyslexic children required to detect small changes in false-font symbol strings (Pammer et al., 2004). The lower rate of correct responses to symbol strings in dyslexics observed in the current experiment might then be a manifestation of deficient or deviant allocation of visual attention resources to the strings presented during the task. Furthermore, the higher percentage of false alarms and lower rate of correct responses to symbol strings compared to words suggest increased task demands associated with symbol strings. Attention modulation of early ERPs has been previously reported in the literature (see review in Luck, Woodman, & Vogel, 2000). Stronger N1 responses have been observed in relation to stimuli presented at attended relative to unattended locations (see reviews in Luck et al., 2000; Vogel & Luck, 2000), and the interaction of attentional systems and the VWFA have been previously reported (Vogel et al., 2012). In the current study, relative to normal readers, dyslexics might have allocated more attention to word strings. This interpretation is consistent with the deficits manifested by the performance on word reading tests (see Table 2.1) and with the performance on the experimental task showing a lower rate of correct responses for words and shorter RTs in dyslexic compared to typical readers. The allocation of more attention to word strings is likely to result in a more pronounced activation of VWFA, thus enhancing N1 activation for words in dyslexics relative to typical readers. In this context, dyslexic children might have relied more strongly than typical readers on orthographic rather than phonological or semantic information. This

could contribute to enhanced N1 amplitudes, as it has been previously reported that attention allocation to orthography evoked larger negativity compared to a semantic or phonological focus of attention (Ruz & Nobre, 2008). This interpretation is supported by a study reporting left fusiform activation that is inversely related to word-likeness of visually presented stimuli in a one-back task (Wang, Yang, Shu, & Zevin, 2011). These findings have been interpreted to suggest increased pressure on the visual system relating to higher short-memory demands imposed by stimuli lacking semantic or phonological information.

In the current study, we obtained a relation between word reading fluency scores (number of correct words read in a minute) and N1 amplitude enhancement for words at left hemisphere sites in dyslexic readers. While other studies collapsed groups of typical and dyslexic readers (Maurer et al., 2006, 2007), the current study showed this relation for dyslexic children but not for typical readers. N1 word amplitudes have been previously related to faster reading in unimpaired readers (Korinth et al., 2012). Collectively, the current findings suggest a stronger reliance on visual processing in dyslexics, which might be comparable to typical readers during earlier stages of reading acquisition. This is in accordance to longitudinal studies suggesting that N1 word-specific responses progressively decline after the first years of reading acquisition (Maurer et al., 2006). In this regard, the faster dyslexic readers might have benefitted from a stronger allocation of attentional resources to visual orthographic cues, which would also be consistent with attentional modulation of N1 amplitude, as discussed previously.

Finally, although not the target components of the present study, the P1 and P2 appeared to discriminate between groups. The P1 amplitudes to short strings at left occipital sites, and to short symbol strings across all sites, were larger for typical readers than for dyslexics. This pattern of findings might suggest that proficient readers co-activated letter representations to detect repetitions in short symbol strings, resulting in larger P1 amplitudes. P2 amplitudes for long strings did not discriminate between words and symbols in dyslexics but they did so in typical readers. Moreover, P2 latencies for long strings were shorter over the right relative to the left hemisphere in dyslexics but did not differ across hemisphere in typical readers. This difference might suggest facilitated access and, possibly, a more efficient allocation of attentional resources between typical and dyslexic readers. This interpretation is supported by studies showing that ERP positivities, peaking around 300 ms, are associated with improved performance on tasks using visual stimuli (Jucla et al., 2009; Wickens, Kramer, Vanesse, & Emanuel, 1983)

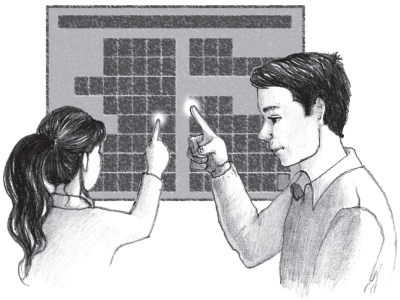
Conclusion

The present results provide evidence for differences in N1 word specialization between dyslexic and typical readers. Both groups showed N1 enhancement for words vs. symbol strings, but in typical readers the N1 amplitude for words was reduced over the left relative to the right hemisphere sites. This effect was absent in dyslexic readers. The current study differed from previous research with

regard to the symbol strings used to assess the efficiency of word processing. The pattern of results suggests that the symbol strings used in this study might provide a sensitive tool for assessing N1 word specialization in dyslexic readers. The relation observed between the N1 word-specific amplitudes and reading speed measurements in the dyslexic children provides further support for this sensitivity. The current findings, suggesting a deficit at the level of visual word specialization in dyslexics, should be followed up by a longitudinal analysis to assess whether the apparent deficit in visual word specialization in dyslexic children decreases when they attain higher levels of reading fluency (e.g., following a remediation program).

Chapter 3

A Randomized Controlled Trial on The Beneficial Effects of Training Letter-speech Sound Integration on Reading Fluency in Children with Dyslexia



Fraga González, G., Žarić G, Tijms J, Bonte M, Blomert L, van der Molen MW (2015). A Randomized Controlled Trial on The Beneficial Effects of Training Letter-speech Sound Integration on Reading Fluency in Children with Dyslexia. PloS one, 10(12): e0143914. doi:10.1371/journal.pone.0143914.

Abstract

A recent account of dyslexia assumes that a failure to develop automated letter-speech sound integration might be responsible for the observed lack of reading fluency. This study uses a pretest-training-posttest design to evaluate the effects of a training program based on letter-speech sound associations with a special focus on gains in reading fluency. A sample of 44 children with dyslexia and 23 typical readers, aged 8 to 9, was recruited. Children with dyslexia were randomly allocated to either the training program group (n=23) or a waiting-list control group (n=21). The training intensively focused on letter-speech sound mapping and consisted of 34 individual sessions of 45 minutes over a five months period. The children with dyslexia showed substantial reading gains for the main word reading and spelling measures after training, improving at a faster rate than typical readers and waiting-list controls. The results are interpreted within the conceptual framework assuming a multisensory integration deficit as the most proximal cause of dysfluent reading in dyslexia. This is a clinical trial registered under the number ISRCTN12783279 in the ISRCTN register (isrctn.com).

3.1 Introduction

Dyslexia is a specific reading and spelling disability with a neurobiological basis and prevalence estimates between 3% and 10 % depending on the study and precise assessment criteria (Blomert, 2005; Snowling, 2013). The most characterizing symptom is a persistent failure to develop fluent reading skills (Gabrieli, 2009; Shaywitz & Shaywitz, 2008). These impairments can have severe academic, economic and psychosocial consequences, thus requiring clinical intervention (UNESCO, 2005).

During the last decades, research focused on the phonological theory of dyslexia. Accordingly, the ability to attend to and manipulate speech sounds, referred to as phonological awareness, is impaired in dyslexic readers, hindering the acquisition of reading skills (Shaywitz & Shaywitz, 2008; Vellutino et al., 2004). Nonetheless, concerns can be raised regarding the causal role of phonological awareness in dyslexia (Bishop, 2006; Blomert & Willems, 2010). Firstly, as concluded in a review of the pertinent literature by Castles & Coltheart (2004), there is still no convincing evidence that phonological awareness precedes and directly influences reading acquisition. The results of a study in which a group of preliterate children was provided with either phonemic awareness training, letter awareness training or a control task, followed by teaching the alphabetic principle and decoding skills are in line with this conclusion (Castles, Coltheart, Wilson, Valpied, & Wedgwood, 2009). The results of this study revealed that, although phonemic awareness training was successful in itself, it had no effect on the subsequent acquisition of reading skills. Along similar lines, Blomert & Willems (2010), showed that only a small part of preliterate children at risk for dyslexia present phonemic awareness problems in kindergarten, and that 80% of the at-risk children who later develop a reading deficit do not reveal a phonemic awareness problem in kindergarten. Secondly, phonological awareness has been shown to develop as a consequence rather than as a precursor of reading acquisition (Bishop, 2006; Boets et al., 2010; Dehaene et al., 2010; Mann & Wimmer, 2002; Morais et al., 1987; but see Molfese, 2000). Thirdly, a phonological awareness deficit fails to explain why, especially for (semi-) transparent languages, dysfluent reading is the most persistent symptom of dyslexia, and why, even when phonological awareness and visual word decoding skills are adequate, dyslexic reading remains dysfluent (Biancarosa & Snow, 2004; Blomert, 2011).

A rapidly growing body of research thus focuses on a letter-speech sound binding deficit as the most proximal cause for dyslexia (Froyen et al., 2011; Kronschnabel et al., 2014; Maurer, Blau, Yoncheva, & McCandliss, 2010; Wallace, 2009; Žarić et al., 2014). The development of grapheme-phoneme associations is considered essential for the acquisition of fluent reading skills (Ehri, 2005; Frith, 1985). Accordingly, knowledge of these correspondences is used to link spelling of written words to their pronunciation and meaning. This enables sight word learning, that is, automatic and accurate word reading from memory (Ehri, 2005). If the grapheme-phoneme mapping is not correctly automatized, acquiring normal levels of fluency in word reading may require much more time and

practice (Ehri & Saltmarsh, 1995). Moreover, these associations may support the development of phonological awareness for isolated speech sounds during reading acquisition. Additionally, previous studies suggested that temporal processing (unimodal and cross-modal) may contribute to reading deficits in dyslexia, emphasizing speed of integration as a critical factor (Breznitz & Berman, 2003; Meyler & Breznitz, 2005).

Neuroimaging studies suggested that the network for multimodal processing in left temporo-parietal brain regions is involved in letter-sound integration (Blau et al., 2010; Blomert, 2011; Hashimoto & Sakai, 2004; Raij, Uutela, & Hari, 2000; van Atteveldt et al., 2004). It has been suggested that this network develops first during reading acquisition and then supports the subsequent specialization of occipito-temporal areas for visual word recognition (Blomert, 2011; McCandliss & Noble, 2003; Sandak et al., 2004). Dysregulation in the temporo-parietal and occipito-temporal networks for reading have been found in dyslexics (Blau et al., 2010; Brunswick et al., 1999; Fraga González et al., 2014; Helenius et al., 1999; Paulesu et al., 2001; Shaywitz & Shaywitz, 2008; Simos et al., 2000). Interestingly, deviant processing of letters and speech sounds in the multisensory temporo-parietal brain areas has been reported in dyslexic children even if they attained adequate knowledge about letter-speech sound correspondences (Blau et al., 2010; Froyen et al., 2009). Additionally, activation in these brain areas correlates to the speed of performance in letter-speech sound matching tasks (Blau et al., 2010). In yet another study, reduced activation in integration areas was observed to be directly associated with a deficit in the auditory processing of speech sounds, which in turn predicted performance on phonological tasks (Blau et al., 2009). Similarly, brain studies examining preliterate children at risk of dyslexia suggested that neural deficits in auditory processing in temporal and parietal areas could be used as early predictors of reading impairments (Lyytinen et al., 2005; Molfese, 2000; Raschle, Stering, Meissner, & Gaab, 2013).

Collectively, the findings reviewed above support the notion that reduced letter-sound integration qualifies as the proximal cause of the reading failure in dyslexics. Comparable results have been reported in a cognitive study by Aravena et al. (2013), who developed a task for letter-speech sound learning in an artificial script. The results of this study showed that children with dyslexia attained levels of letter-speech sound knowledge comparable to those of their normal reading peers, but their level of letter-speech sound mapping fluency was significantly lower than that of normal reading children. These results indicate that letter-speech sound knowledge is not sufficient to develop automated letter-speech sound integration, and suggest that children with dyslexia have a specific deficit in this speeded integration (Aravena et al., 2013).

Current interventions for dyslexia show that reasonable levels of accuracy in reading may be attainable (Hatcher et al., 2006; Lovett et al., 2003; National Reading Panel, 2000; Tijms, 2007). However, they still do not provide an effective remediation for the lack of reading fluency (Alexander

& Slinger-Constant, 2004; Chard, Vaughn, & Tyler, 2002; Compton et al., 2014; G. F. Eden & Moats, 2002; Gabrieli, 2009; Levy, 2001; Thaler et al., 2004). A typical example is the study of Torgesen and colleagues, in which dyslexic children received 67.5 hours of treatment on phonemic awareness and phonemic decoding skills (Torgesen et al., 2001). Results revealed large effects on reading accuracy, children's average scores on accuracy were within the average range after treatment. In contrast, dyslexics' standard scores in reading fluency were virtually unchanged, 96% to 100% of the children were still below the average range on after treatment (Torgesen et al., 2001). Importantly, the training specific effects on addressing the 'fluency barrier' in dyslexia are still unclear (see review in 49). As concluded by Elliott & Grigorenko (2014), training of alphabetic principle and decoding skills, despite long-lasting assumptions to the contrary, does not appear to lead to improved reading fluency (p. 171).

Inspired by the multisensory integration deficit account (Blomert, 2011), assuming a failure to develop automatic letter-speech sound integration in dyslexia, the present study will examine a cognitive training focusing on the development of automated letter-speech sound integration. The current training provides for systematic practice on regular and irregular letter-speech sound mappings at increasing levels of complexity. Importantly, the attainment of these correspondences is facilitated by intensive exposure to ensure the automation of letter-speech sound mapping and, thus, reading fluency. Furthermore, we used a randomized-controlled trial (RCT) design, including waiting-list dyslexic readers besides age-matched typical readers, and a wide range of outcome measures, for both accuracy and speed, including word reading, spelling and letter-speech sound mapping. This should allow for a detailed assessment of training benefits.

The present evaluation will consist of the following steps. First, we will perform a baseline analysis on test scores to obtain a complete assessment of reading deficits in the dyslexic groups vis-a-vis the typical readers. Subsequently, we will compare reading gains in trained vs. untrained dyslexics in terms of test scores, while accounting for potential group differences in initial performance. Secondly, we will identify latent factors to assess the relation between outcome measures. The latent factors emerging from the principal component analysis (PCA) will be used in the subsequent analyses to facilitate the interpretation of potential effects of training on reading fluency. Thirdly, we will assess baseline differences and training effects between the dyslexic groups in terms of factor scores. This analysis will be followed by a mixed-model analysis to assess between-groups differences relative to the typical readers, in the rate of change on reading fluency during the intervention period. Finally, a correlational analysis will be performed to examine the relation between initial letter-speech sound mapping skills and the development of reading fluency.

In brief, the overall objective of the current study is to broaden our insights in how to remedy reading fluency problems in children with dyslexia. We aim to contribute to current research on remediation programs on dyslexia by providing a detailed window on the relation between training

letter-speech sound mappings and reading fluency, using a large number of outcome measures, a strictly controlled and systematized training procedure, and a RCT design.

3.2 Methods

The study was an open randomized controlled trial comparing an intervention addressing letter-speech sound integration to a waiting list control group (allocation ratio 1:1). The approval for the research was obtained from the local ethical committee of the Developmental Psychology department of the University of Amsterdam. All parents or caretakers signed informed consent before the children participated in this study.

Participants

The inclusion period for the trial was from October 2011 to December 2011. The flow of participants in the study is presented in Figure 3.1. Third-grade children with the diagnosis of dyslexia (N= 44; 8.86 ± 0.43 years old, 24 boys and 20 girls) were recruited from a nation-wide center for dyslexia in the Netherlands. To be eligible the children had to have a percentile score of 10 or lower on standard reading measures, and to be referred to the center because of persistent and specific reading problems. They were randomly allocated to either the training program group (N= 23; 8.94 ± 0.44 years old, 11 boys and 12 girls) or to a waiting-list control group (N = 21; 8.77 ± 0.41 years old, 13 boys and 8 girls). Participants allocated to the waiting-list control condition received the intervention program after the waiting period had elapsed. Participants were randomized using a computerized random number generator by a staff member not involved in training or testing. Simple randomization was used with no restrictions (e.g., blocking or stratification). A group consisting of 23 third-grade, typical readers (8.67 ± 0.34 years old, 9 boys and 14 girls) was recruited from several primary schools attended by children with the same sociodemographical background as the dyslexic group (see Table 3.1 for group characteristics). To be eligible, they had to have no history of reading difficulties, and a percentile score of 25 or higher on standard reading tests (see below). One child of the waiting-list control group dropped out, resulting in a sample of 20 children for the posttest measures. The posttest scores for the 3DM word-reading task were discarded for one child of the training group who obtained extremely low accuracy scores (below 3 x Inter Quartile Range). Additional missing values in some of the outcome measures were due to computer failure (see footnotes in the corresponding tables).

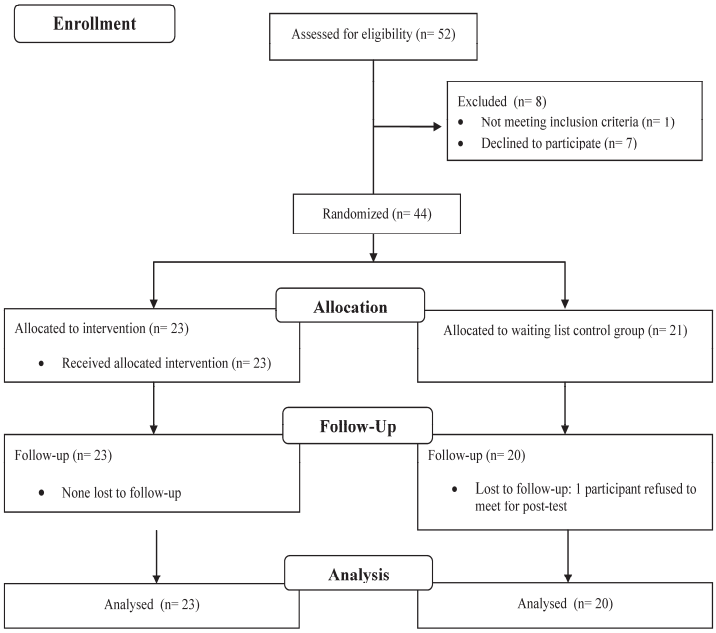


Figure 3.1. Participant flow diagram.

Table 3.1. Descriptive statistics showing demographics and IQ

	Typical Readers	Dyslexics Control	Dyslexics Training	group differences	
	M (SD)	*M (SD)*	*M (SD)*	*F*	*p-value*
N	23	21	23		
Sex ratio (m:f)	9:14	13:8	11:12		
Age	8.68 (0.34)	8.82 (0.33)	8.94 (0.44)	2.76	.071
RAVEN - IQ test [C][a]	7.19 (1.48)	6.80 (1.50)	7.48 (1.35)	1.24	.297

[a] C scores (M = 5, SD = 2).

All participants were native Dutch speakers, received two and a half years of formal reading instruction in primary education. The RAVEN Coloured Progressive Matrices (RAVEN CPM) was used as a control non-verbal measurement of IQ to obtain an estimate of fluid intelligence (Raven & Court, 1998). Additionally, the Child Behavior Checklist (CBCL) was completed by the parents to exclude any additional behavioral problems (Achenbach & McConaughy, 2003). Children with below average IQ (IQ < 85 on a non-verbal IQ-test), uncorrected sight problems, hearing loss, diagnosis of ADHD or other neurological or cognitive impairments were excluded. Both the clinical center and the schools participating were located in the Amsterdam area.

Sample size calculation (Power & Precision V4 software; (Borenstein, Rothstein, & Cohen, 2001)) indicated that a sample size of n ≥ 20 per intervention condition would be required for a power of at least 0.80 to detect an intervention effect of medium to large effect size for gains in reading fluency, for

an ANCOVA with 1 factor (intervention condition) and 1 covariate (pretest level, R^2 = .37, based on previous intervention studies), and $\alpha = 0.05$.

Outcome Measures

A series of tests was used to assess the reading skills of the participants. In accordance with our main objective, we considered reading fluency scores as our primary outcome measure, and the other scores as secondary outcome measures. The 3DM battery of tests (test reliability and normative sample information available in Differential Diagnosis; 3DM Blomert & Vaessen, 2009) contains word reading, phonological awareness, naming speed and letter-speech sound association tasks. This battery is administered individually using a computer and a specialized response-box records reaction time with millisecond accuracy. The scores of the following 3DM subtests have been used in the present study.

Word reading task. This task includes three different subtasks containing high-frequency words, low-frequency words and pseudowords. The mean frequencies of the high-frequency words are between 790 and 45810 and for the low-frequency words they range between 6 and 342 (CELEX-database; (Baayen, Piepenbrock, & Gulikers, 1995). There are 75 words for each level (5 screens with 15 items each). The difficulty of each level increases systematically from monosyllabic words without consonant clusters to 3 or 4 syllabic words with consonant clusters at the fifth level. The participants are asked to read accurately as many words as possible. When they finish reading one screen the experimenter presses a button to continue until the time limit of 30 seconds per subtask is reached. The number of words read correctly within 30 seconds determines the reading fluency score per subtask (r = .91-.93 for the subtasks, and r = .95 for total task, test-retest). The proportion of correctly read words within the time limit accounts for the reading accuracy scores (r = .73, test-retest).

Letter-speech sound (LSS) association tasks. Two tasks were used to measure accuracy and automation of letter-speech sound (LSS) mapping; LSS identification and LSS discrimination. LSS identification requires a child to match a speech sound to one of four presented letter (combinations) by pressing the corresponding button (e.g. /b/ and 'b' 'd' 't' 'p'). LSS discrimination asks a child to judge whether a speech sound and letter are congruent or incongruent (e.g. /ui/ and 'oe'). Accuracy (% correct) as well as response time (sec/item) is measured (LSS identification: r = .72 for accuracy and r = .90 for response time; LSS discrimination: r = .82 for accuracy and r = .96 for response time, internal consistency).

Computerized spelling. A word is presented aurally (over headphones) as well as visually (at the computer screen). In the visually presented word, a letter (combination) is missing and the child is instructed to choose the missing part out of four visually presented options by pressing the corresponding button (e.g. auditory stimulus /boom/ (tree), visual stimulus 'b__m', options 'oo' 'o' 'a' 'aa'). Words are spelled either phonetically (18 items) or contain Dutch spelling rules (36 words). Word

frequencies are varied systematically. Accuracy (% correct) as well as response time (sec/item) is measured (r = .80 for accuracy and r = .94 for response time, internal consistency).

Rapid naming task. The rapid automatized naming (RAN) task consisted of three subtasks: letters, digits and objects. Each subtask contains 5 items repeated six times, distributed in two screens of 15 items. Participants are instructed to name the items as fast and accurate as possible. The score per subtask was determined by taking the mean response time of the two screens (r = .80 for letters, r = .83 for digits, and r = .71 for objects, split-half reliability).

Phonological awareness (PA). An estimate of phonological awareness is obtained by using a phoneme deletion task presenting 23 pseudowords with a CVC or CCVCC structure. The participant must omit a consonant that is either at the beginning or at the end of a word or within a consonant cluster as fast as possible. The score is determined by the percentage of correct responses. (r = .85, internal consistency).

In addition to the 3DM battery the following tests were used:

Word reading fluency. The Dutch version of the *One-minute test* (Een-Minuut-Test; (Van den Bos, Spelberg, Scheepsma, & De Vries, 1999), was used to provide an additional estimate of word reading skills. It is a time-limited test consisting of a list of 116 unrelated words of increasing difficulty. The number of correctly read words within 1 minute serves as reading fluency score (r = .90, test-retest).

Text reading fluency. The text-reading fluency test consists of a coherent text of increasing difficulty. The child is asked to read the text out loud within one minute (Schoolvaardigheidstoets Technisch Lezen; de Vos, 2007). Again, the number of correctly read words within 1 minute serves as reading fluency score (r = .88, test-retest).

Procedure

The study used a pretest-training-posttest design. Pretest (period: December 2011 to Januari2012) and posttest (period June 2012 to July 2012) were administered at either the clinical center for the dyslexic children or at school for the normal readers during a session of approximately one hour. Children are tested individually in a silent room.

The training-program group received an average of 33.65 ± 0.83 sessions while the other two groups received no training. The average number of weeks between pre- and posttest measurements was 22.92 ± 3.51 across the three groups; 20.17 ± 1.56 for typical readers, 25.70 ± 3.33 for the training-program group and 23.26 ± 3.08 for the waiting-list control group. The number of weeks between tests differed between the three groups, $F(2,63) = 22.07$, $p = <.001$, $\eta^2 = 0.41$. Post-hoc comparisons revealed the differences between the two dyslexic groups in the number of weeks was statistically significant, $p = .015$. Thus, comparisons between groups will take into account the difference in the number of weeks elapsing between pre- and posttest.

Training

Dyslexic children followed an intensive tutor and computer-assisted training program. The program was provided by well-instructed junior psychologists, on a one-to-one basis during 45-min sessions. The training frequency was two sessions per week.

The training is constructed in accordance with general skill acquisition paradigms (Davydov, 1995; Schneider, 2003), which basically implies that each (letter-speech sound) element is taught explicitly at first and consequently repeated intensively in order to obtain a transition from accurate, controlled to associative, automatic processing. Accordingly, a previous study showed that massive exposure to letter-speech sound correspondences is substantially more effective in automatizing letter-speech sound integration when it is preceded by explicit teaching of these correspondences than when it is presented on its own (Aravena et al., 2013). Sessions consist therefore in an instruction part and a practice part. In the instruction part the letter-speech sound correspondences are explicitly taught aiming at accurate mastery of the learned associations. During the practice part, the computer training provides a high exposure to the specific letter speech sound associations that were taught during the instruction part, to stimulate the automatic integration of letters and speech sounds.

The training started with the tutor explaining consistent letter-speech sound correspondences. First, the standard letter-speech sound correspondences are being trained and, subsequently, the irregular letter-speech sound mappings. To do so, a reconfigured touchscreen was used that consists of buttons for each Dutch speech sound (see Appendix B for an illustration of the touchscreen buttons). Each button shows the standard letter or letter-cluster of the corresponding speech sound. In addition, the touchscreen includes several icons to indicate the type of phoneme (e.g., 'long vowel'), syllable icons (e.g., 'stressed syllable') and rule icons to perform operation (e.g., delete a selected grapheme; see kernel algorithm below). During instruction, the tutor asks the child to pronounce the corresponding speech sound, which is presented not only in isolation but also within the context of a (visual) word. Subsequently, the child is asked to identify the item both orally and by pressing the corresponding buttons in the touch screen. When the child presses a button the computer produces the corresponding speech sound (by a natural voice). This is done to ensure that attention is directed to the matching of letters and speech sounds. Throughout the session, the tutor corrects the child if the response would be wrong. Similarly, the computer screen provides performance feedback following erroneous button presses. The letter-speech sound couplings are taught step-by-step, e.g., first the short vowels, then long vowels, and later on diphthongs.

Dutch orthography is considered to be of intermediate complexity (e.g., (Grigorenko, 2001)), which implies that the one-to-one mapping between letters and speech sounds can be broken. To learn these inconsistent correspondences, phonological-orthographic mapping operations are introduced during

the second part of the program. These operations follow a uniform inferential algorithm that constitutes the kernel of the present training, i.e.:

$$\text{IF } p \ / \ \# \in Pi \text{ then } O\,(p) \rightarrow g \in G.$$

When the terminal phonic element p of a syllable belongs to the ith category of phonetic elements Pi then the result of an operator O on p will be mapped onto a graphic element g that need not be the standard mapping.

The basic principles of the Dutch written language can be structured within a learning system incorporating five types of operations as a consequence of five types of terminal phonic elements; long vowels, short vowels, unvoiced consonants, sonic vowels and unstressed morphemes. For example, in Dutch, voiced consonants (/d/ and /b/) lose the voice property at the terminal position, which is not reflected in their orthographic representation. Consequently, the algorithm prescribes: if the last speech sound in a syllable is an unvoiced consonant then extends the word (operation) and if this results in a voiced consonant the voiced consonant graph should be written (e.g., paard [IPA: part] - paarden [pardən] (English: horse - horses), otherwise the standard consonant (e.g., kat [kɑt] - katten [kɑtən] (cat - cats)). All these rules and elements are incorporated in the touchscreen (see Appendix B). Thus, the essential terms in the algorithm have an explicit and exhaustive description in the program with regards to the set of speech sounds, the categories of speech sounds, the corresponding orthographic elements, and the mapping operations. Consequently, the focus of attention remains continuously on the integration of letters and speech sounds.

Along with the learning of both consistent and inconsistent letter-speech sound mappings, the computer training provides a high exposure to letter-speech sound mappings at increasing levels of complexity. A typical example of an exercise during practice refers to the projection of individual words, speech sound by speech sound, on the computer screen under (progressive) time demands (see Figure 3.2). The child is asked to pronounce the word sound by sound (and in the end the whole word), guided by the time-constraints of the graphemic presentation rate. During presentation, the whole word is projected faintly on the screen to allow anticipation (cf., (Legge, Mansfield, & Chung, 2001)). During a practice session, specific letter-speech sound mappings or clusters of mappings (e.g., all long vowels) are presented, matching those addressed in the preceding instruction part (but in a different body of words from those used during instruction). Practice is adjusted to the individual rate of acquisition by adapting time-constraints to the level of the child's performance. When at least 80% of the items are correctly executed the participant moves to the next step of the training.

The current training is an adaptation of an existing intervention program. The adaptation consists of an exclusive focus on letter-speech sound mapping integration. An extensive description, including a more detailed illustration of the tutor-participant interaction during sessions, can be found in Tijms et al. (2007).

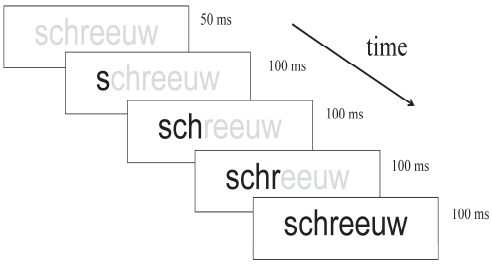


Figure 3.2. Example of a practice item. The presentation of the word schreeuw [sxreːu] (English: shout) under time-demanding conditions. The visual presentation is sound by sound: s[s] _ ch[x] _ r[r] _ eeuw[eːu]. (IPA symbols in brackets). The participant must pronounce the corresponding (visually presented) sounds and in the end the whole word.

Statistical Analysis

For the AN(C)OVAs (see below), standardized scores were used instead of raw scores, in order to assess the child's position within the distribution of a normative sample. For the latent factor analysis, factor scores were obtained from raw scores. In addition, due to reduced variance, no reliable norm scores were available for the accuracy measures of the three subtasks of the 3DM word reading; thus raw scores were used for these measures. The evaluation of potential training effects comprised the following sequence of steps.

First, one-way ANOVAs were performed to examine baseline differences. The outcome of this analysis should provide a first impression of group differences before evaluating training effects. Planned comparisons were then performed between typical readers and the dyslexic groups, and between the two dyslexic groups at pretest. Then, in order to test potential training effects, ANCOVAs were performed comparing the two groups of dyslexics, using posttest scores as dependent variables and the corresponding pretest scores as covariate (one-tailed p values are reported). This approach was selected because of its higher statistical power in randomized studies relative to other methods of analysis (Van Breukelen, 2006). In order to account for potential effects of between group differences in pre- to posttest interval, an additional control analysis was performed including the number of weeks between tests as a covariate. The pattern of results did not differ between the two analyses, thus we will report only the results of the ANCOVA with pretest scores as covariate.

Subsequently, Principal Component Analysis (PCA), with varimax rotation, was performed to reduce the number of outcome variables by taking into account the relations between measures. This

should facilitate the interpretation of the potential training effects (Thompson, 2004). The analysis was performed including pretest data from the entire sample consisting of the main 3DM fluency and accuracy scores associated with word reading (high frequency, low frequency and pseudowords), spelling and LSS identification and discrimination. Only the 3DM scores were used as they are part of the assessment battery that is most used in diagnosis of dyslexia in the Netherlands and constitute the primary measures in the current study. Factors were extracted using the eigenvalue-one procedure. We obtained factor scores (with mean zero) weighted by regression coefficients obtained by multiplying the inverse of the variables correlation matrix by the matrix of factor loadings. The same procedure was applied to post-test data to obtain factor scores used in the subsequent analyses. Baseline differences between groups and potential training effects were examined by submitting the factor scores to, respectively, one-way ANOVA and ANCOVA.

Additionally, we used a mixed model to evaluate rate of change on the extracted factor scores between pre and posttest between the three groups. This allows for examining the relationship between covariate and dependent variables across groups (Snijders & Bosker, 1999). In addition, it is suited for longitudinal data analysis and can handle missing values (see participants section for details about attrition and missing values). The present analysis used a random intercept model including three groups and accounting for significant baseline differences between typical readers and dyslexics. The fixed part of the model included the factor group, time (pre-posttest) and their interaction. The factor scores were used as dependent variable. The analysis focused on the fixed effects estimates for the interaction of each group with the factor time. The group of typical readers was used as a reference, as they are expected to exhibit the lowest improvement rate. The estimates for dyslexics training and dyslexics control were then compared to those of the typical readers group.

Finally, we examined the relationship between letter-speech sound mapping skills and reading improvement. For this purpose, partial correlations were performed between the pretest letter-speech sound fluency factor score and the posttest word reading fluency scores (controlled for pretest differences).

3.3 Results

AN(C)OVAs

Baseline. The results of the ANOVAs performed on the pretest standard scores in reading accuracy and speed measures are displayed in Table 3.2. Levene's test was significant for the accuracy measures of the 3DM word reading tasks (high frequency words, F (2, 64) = 11.42, p = .000, low frequency words, F (2, 64) = 11.67, p = .000, pseudowords, F (2, 64) = 4.71, p = .012 and overall score, F (2, 64) = 3.57, p = .034), as well as for the accuracy scores associated with letter-speech sound

identification; F (2, 64) = 3.74, p = .029. So in the first contrast (dyslexics vs. typical readers) the degrees of freedom for these measures were adjusted from 64 to 43.01, 49.21, 62.96, 56.41 and 60.90, respectively. In the second contrast (dyslexics training vs. waiting-list group) the adjusted degrees of freedom were 38.01, 41.73, 41.03, 40.15 and 41.37. The table shows a deficit in dyslexics that is mainly manifested by large differences in the reading fluency measures. Overall, the three groups attained reasonably high levels of accuracy, with the exception of the spelling task where dyslexics performed on average below the 10th percentile. For the majority of the tests, the two dyslexic groups showed significantly lower levels than those of the typical readers. With regard to the letter-speech sound measures, the results are somewhat more diffuse. The scores of the two dyslexic groups were significantly below those of the typical readers for most tasks with the exception of the fluency score associated with letter-speech sound discrimination (p = .347) and the accuracy scores associated with letter-speech sound identification (p = .100). In addition, the results showed differences between the two dyslexic groups in letter-speech sound fluency scores, but not in the accuracy scores.

Training. The two dyslexic groups were compared with regard to their posttest scores, including pretest scores as covariate. The results are displayed in Table 3.3. Importantly, the table shows that the training-group dyslexic outperformed waiting-group dyslexics after the letter-speech sound training program. The most substantial differences were present in reading fluency, as expressed by the large effect size of the gains in total reading fluency. This gain in reading fluency holds for high frequency, low frequency and pseudowords. Obviously, training effects were less pronounced for reading accuracy. This absence of substantial effects was to be expected in view of the relatively high accuracy scores prior to training. The training-group dyslexics outperformed waiting-list controls in total reading accuracy score but significance was absent for the three word-type subtests. Finally, with regard to the letter-speech sound mapping tasks, the training-group dyslexics showed significant gains in spelling accuracy, spelling fluency, and fluency associated with letter-speech sound identification relative to the control-group dyslexics.

Table 3.2. Descriptive statistics showing reading accuracy and fluency scores at pretest

	T		DC		DT		Contrasts					
	N = 23		*N* = 21		*N* = 23		DT & DC : T			DC:DT		
	M	*(SD)*	*M*	*(SD)*	*M*	*(SD)*	*t*	*p*-value	*Cohen's d*	*t*	*p*-value	*Cohen's d*
3DM Word reading - *accuracy* [a]												
High Frequency[d]	99.15	(1.10)	94.34	(4.51)	92.62	(6.98)	6.24	.000	1.34	0.98	.498	0.29
Low Frequency[d]	97.40	(3.15)	86.41	(12.86)	84.59	(15.31)	5.35	.000	1.17	0.43	.806	0.13
Pseudowords[d]	87.99	(9.13)	69.88	(17.14)	73.03	(16.13)	5.24	.000	1.23	-0.62	.718	-0.19
Total [T][b,d]	50.13	(8.66)	31.62	(9.92)	33.96	(13.58)	6.84	.000	1.66	-0.66	.718	-0.20
3DM Word reading - *fluency* [T]												
High Frequency	52.83	(7.11)	32.00	(5.88)	31.04	(5.35)	13.42	.000	3.34	0.51	.752	0.17
Low Frequency	54.09	(8.54)	31.43	(5.64)	32.09	(6.30)	12.44	.000	3.04	-0.31	.857	-0.11
Pseudowords	52.48	(9.13)	29.81	(6.36)	31.13	(5.63)	11.84	.000	2.85	-0.61	.718	-0.22
Total	53.52	(8.82)	30.76	(4.62)	30.52	(5.41)	13.48	.000	3.19	0.12	.934	0.05
One-Minute Test -*fluency* [SS][c]	11.35	(2.67)	3.76	(2.00)	3.65	(1.87)	13.40	.000	3.34	0.16	.934	0.06
Text Reading - *fluency*[T][1]	54.04	(7.82)	33.11	(5.82)	33.83	(6.06)	11.86	.000	2.97	-0.35	.851	-0.12
3DM Spelling - *accuracy*[T]	50.43	(8.54)	35.57	(6.08)	36.87	(8.31)	7.11	.000	1.79	-0.55	.741	-0.18
3DM Spelling - *fluency*[T]	54.30	(8.25)	36.05	(6.36)	40.78	(8.46)	7.93	.000	1.96	-2.01	.092	-0.63
LSS identification - *accuracy*[T][d]	47.52	(7.50)	40.71	(10.35)	45.13	(12.87)	1.96	.100	0.45	-1.26	.347	-0.38
LSS discrimination - *accuracy*[T][2]	50.74	(9.05)	41.55	(8.34)	46.52	(9.47)	2.88	.011	0.72	-1.81	.131	-0.56
LSS identification - *fluency* [T]	52.57	(6.66)	41.48	(7.71)	46.17	(7.35)	4.69	.000	1.19	-2.15	.070	-0.62
LSS discrimination - *fluency*[T][2]	50.43	(7.70)	44.45	(9.12)	50.96	(8.48)	1.25	.347	0.29	-2.53	.029	-0.74
3DM phoneme deletion - *accuracy*[T][3]	53.09	(7.57)	40.38	(7.26)	37.90	(0.12)	6.71	.000	1.76	1.01	.498	0.31
3DM Naming speed scores[T][3]												
Letters	49.65	(7.59)	37.48	(7.85)	37.22	(7.75)	6.19	.000	1.58	-0.11	.934	0.03
numbers	50.43	(11.32)	38.81	(8.35)	36.61	(8.77)	5.15	.000	1.28	0.76	.653	0.26
objects	50.70	(7.07)	41.43	(11.77)	41.56	(9.42)	3.75	.000	1.03	0.05	.962	-0.01
Total	49.96	(8.08)	36.05	(8.78)	35.56	(9.04)	6.36	.000	1.66	0.18	.934	0.05

T = typical readers; DT = dyslexics-training; DC = dyslexics control; LSS = Letter-speech sound. [a] Raw scores. [b] T scores (M = 50, SD = 10). [c] SS scores (M = 10, SD= 3). [d] Statistics for equal variances not assumed ($p < .05$ in Levene's test). [1] Data missing for 2 participants: $N_{DC} = 19$. [2] Data missing for 1 participant: $N_{DC} = 20$. [3]Data missing for 2 participants $N_{DT} = 21$. False Discovery Rate (FDR) correction for multiple comparisons was applied to the *p* values.

Table 3.3. ANCOVA comparing dyslexics training and control group in posttest scores with pretest as covariate

	Dyslexics control N = 21		Dyslexics training N = 23		ANCOVA (pretest as covariate)		
	M	*(SD)*	*M*	*(SD)*	*F*	*p-value* (one-sided)	η^2
3DM Word reading - *accuracy* [a,1,2]							
High Frequency	94.68	(4.02)	97.55	(2.91)	9.21	.006	0.19
Low Frequency	91.27	(8.69)	93.42	(7.90)	1.21	.161	0.03
Pseudowords	71.76	(18.35)	81.82	(14.23)	3.27	.062	0.08
Total [T][b,]	32.85	(10.23)	41.32	(12.81)	4.49	.040	0.10
3DM Word reading - *fluency* [T][1,2]							
High Frequency	32.85	(5.66)	37.36	(6.56)	14.28	.001	0.27
Low Frequency	30.25	(5.02)	36.55	(6.13)	25.39	.001	0.40
Pseudowords	28.25	(5.36)	33.91	(6.63)	8.46	.008	0.18
Total	29.60	(4.15)	35.36	(6.40)	30.30	.001	0.44
One-Minute Test -*fluency* [SS][c,1]	3.20	(1.94)	4.09	(2.41)	3.91	.080	0.09
Text Reading - *fluency*[T][2]	33.10	(5.51)	35.04	(6.68)	1.92	.116	0.05
3DM Spelling - *accuracy*[T][1]	37.25	(6.16)	44.91	(10.08)	10.48	.004	0.21
3DM Spelling - *fluency*[T][1]	35.20	(8.45)	44.39	(10.23)	5.15	.035	0.11
LSS identificacion - *accuracy*[T][d,3]	44.00	(10.26)	46.22	(7.84)	0.09	.384	0.00
LSS discrimination - *accuracy*[T][2]	43.58	(8.14)	47.78	(9.50)	1.20	.161	0.03
LSS identificacion - *fluency* [T][3]	40.74	(11.28)	48.83	(9.50)	3.86	.052	0.09
LSS discrimination - *fluency*[2]	48.21	(10.15)	54.22	(9.82)	0.61	.236	0.02

LSS = Letter-speech sound. [a]Raw scores. [b] T scores (M = 50, SD = 10). [c] SS scores (M = 10, SD= 3). [1]Data missing for 1 participant: N_{DC} = 20. [2] Data missing for 1 participant: N_{DT} = 22. [3] Data missing for 3 participants: N_{DC} = 18. [4] Data missing for 2 participants: N_{DC} = 19. False Discovery Rate (FDR) correction for multiple comparisons was applied to the *p* values.

Latent Factors Analysis

The PCA with varimax rotation was conducted on speed and accuracy measures associated with word reading (high frequency, low frequency and pseudowords), spelling, and letter-speech sound identification and discrimination. Three factors were extracted using the eigenvalue-one procedure. The factors (Eigenvalues = 7.34, 2.18 and 1.28) accounted for, respectively, 38.33%, 21.26% and 17.58% of the variance. The factor loadings are shown in Table 3.4. The scores that loaded highly on Factor 1 were related to word reading speed and accuracy measures, thus this factor was labelled 'word reading'. The scores that loaded highly on Factor 2 were related to spelling fluency and fluency associated with letter-speech sound association (identification and discrimination). Thus, this factor was labeled 'mapping fluency'. Finally, scores related the accuracy of identification and discrimination and spelling accuracy loaded highly on the Factor 3, which was then labeled 'mapping accuracy'.

Group performance in terms of the latent factors loadings is presented in Table 3.5. The results are clear-cut. That is, the results for all three factors are similar for the two dyslexic groups; both groups differ significantly from the typical readers. The training effects are presented in Table 3.6. It can be

seen that the training-group dyslexics improved significantly with regard to the word reading factor relative to the waiting-list group who showed little if any improvement. The dyslexic groups did not differ with regard to the two mapping factors.

Table 3.4. Varimax rotated factor loadings

Measure	Factor 1 Word reading	Factor 2 mapping fluency	Factor 3 mapping accuracy
Word reading - accuracy - Total	**.96**	.01	.15
Word reading - accuracy - Low Frequency	**.92**	.05	.06
Word reading - accuracy - Pseudowords	**.78**	.07	.27
Word reading - accuracy - High Frequency	**.76**	-.19	.04
Word reading - fluency- Low Frequency	**.73**	-.44	.43
Word reading - fluency- Total	**.71**	-.47	.45
Word reading - fluency - Pseudowords	**.69**	-.41	.45
Word reading - fluency - High Frequency	**.65**	-.52	.44
LSS identificacion - fluency	-.12	**.87**	-.09
Spelling - fluency	-.33	**.86**	-.01
LSS discrimination - fluency	.18	**.74**	.09
LSS identificacion - accuracy	.02	-.01	**.79**
LSS discrimination - accuracy	.22	.09	**.75**
Spelling - accuracy	.51	-.19	**.61**

LSS = Letter-speech sound. Factor loadings >. 60 are in boldface. All pretest raw scores from 3DM test. Factor 1 accounted for 38.33 % of the variance, Factor 2 accounted for 21.26% of the variance and Factor 3 accounted for 17.58 % of the variance, after rotation of Sums of Squared Loadings. Note that LSS fluency scores refer to reaction times while word reading fluency scores refer to number of words per minute.

Table 3.5. Descriptive statistics showing baseline differences in factor scores

	T		DC[1]		DT		Contrasts					
	N = 23		N = 21		N = 23		DT & DC : T			DC:DT		
	M	*(SD)*	*M*	*(SD)*	*M*	*(SD)*	*t*	*p*-value	*Cohen's d*	*t*	*p*-value	*Cohen's d*
Word reading [a]	.77	(0.39)	-.26	(0.85)	-.54	(1.09)	-6.88	.000	1.57	0.94	.354	0.29
Mapping fluency [a]	-.73	(0.61)	.61	(0.95)	.20	(0.93)	-5.92	.000	-1.4	1.42	.162	0.44
Mapping accuracy	.52	(0.69)	-.44	(0.85)	-.14	(1.17)	-3.34	.001	0.91	-1.06	.293	-0.33

T = typical readers; DT = dyslexics-training; DC = dyslexics control.
[a] Statistics for unequal variances ($p < .05$ in Levene's test) [1] Data missing for 1 participant: $N_{DC} = 20$.

Table 3.6. ANCOVA comparing dyslexics training and control group in posttest factor scores with pretest as covariate

	DC		DT		ANCOVA (pretest as covariate)		
	N = 21[a]		N = 23[b]				
	M	*(SD)*	*M*	*(SD)*	*F*	*p-value* (one-sided)	η^2
Word reading [b]	-.58	(1.26)	-.16	(0.94)	3.42	.037	0.09
Mapping fluency	-.72	(1.19)	-.18	(0.78)	1.27	.133	0.03
Mapping accuracy	-.48	(0.97)	-.07	(1.09)	0.57	.228	0.02

T = typical readers; DT = dyslexics-training; DC = dyslexics control. [a] Valid cases for DC= 17.[b] Valid cases for DT = 22.

Mixed Model Analysis

A mixed model with a random intercept and fixed factors Time and Group was performed. The t-test results in fixed effects estimates for the interaction between Group and Time are presented in Table 3.7. The results show that the slope of the word-reading factor associated with the training-group dyslexics was significantly different from that associated with the typical readers, whereas the slopes did not differ between untrained dyslexics and typical readers. The slopes of the average of all the scores that loaded highly on the word-reading factor are plotted in Figure 3.3. It can be seen that the rate of improvement is more pronounced for the training-group of dyslexics relative to the waiting-list group of dyslexics and typical readers. The waiting-list group of dyslexics did not differ from the typical readers in this regard.

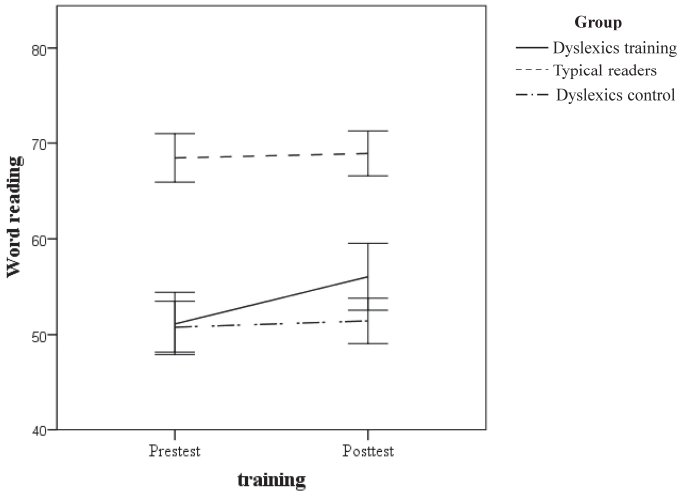


Figure 3.3. Group slopes for word reading. The figure displays the changes from pre- to posttest in the average of all test scores (accuracy and fluency) that loaded highly in the word-reading factor.

Table 3.7.Estimates of fixed effects for a random intercept model including time and group as fixed factors

	Fixed effects estimates Group - time interactions			
	DT : T		DC : T	
	t	*p-value*	*t*	*p-value*
Word reading	2.55	.013	0.45	.654
Mapping fluency	-1.18	.239	-0.08	.939
Mapping accuracy	0.70	.487	0.58	.566

T = typical readers; DT = dyslexics-training; DC = dyslexics control.

Correlational Analysis

An important aspect to consider when interpreting the training effects is that of the individual differences in reading gains. It is of interest to consider whether individual differences in letter-speech sound mapping are associated with variation in reading-fluency gains between pre- and posttest. Partial correlations were performed between the baseline factor scores associated with mapping fluency and posttest word reading fluency scores (controlled for pretest differences in word reading fluency). The results are displayed in Table 3.8.

Table 3.8. Partial correlations with Letter-speech sound fluency factor score and posttest scores in reading fluency (pretest controlled)

	Partial correlations with the factor LSS fluency					
	Typical readers N = 23		Dyslexics control N = 21[c]		Dyslexics training N = 23[d]	
	r	*p*	*r*	*p*	*r*	*p*
3DM Word reading - *fluency* [T][a]						
High Frequency	0.16	.468	-0.49	.037	0.39	.079
Low Frequency	0.07	.756	-0.42	.080	-0.01	.971
Pseudowords	-0.19	.403	-0.11	.650	-0.15	.504
Total	0.11	.632	-0.60	.008	0.03	.876
One-Minute Test -*fluency* [SS][b]	0.41	.060	-0.59	.010	0.18	.431

[a] T scores (M = 50, SD = 10). [b] SS scores (M = 10, SD= 3) [c]Valid cases for DC = 20 (attrition of one subject). [d] Valid cases for DT = 22

Significant negative correlations between (baseline) mapping fluency and gains in reading fluency were found for waiting-list dyslexics for the main word reading scores, with the exception of low frequency word and pseudo-word reading scores. In training-group dyslexics these correlations were not significant. These results indicate that poorer initial mapping fluency is associated with lower gains in reading fluency in the untrained group. Significant correlations were absent for the typical readers group. Notably, for both untrained dyslexics, trained dyslexics and typical readers, letter-speech sound mapping accuracy was not correlated with any of the reading fluency gains (all *r*'s between -0.31 and 0.18, *ps* > .210), except for a significant correlation between mapping accuracy and low frequency word scores ($r = -0.53$, $p = .023$; the poorer the initial accuracy, the higher the reading gain) in the untrained group. This result may indicate a less efficient identification of unfamiliar words for which effortful item-by-item decoding is required. But such an interpretation would be inconsistent with the apparent lack of a significant correlation between mapping accuracy and pseudowords, as the latter would arguably require similar decoding strategies as very low frequency words.

3.4 Discussion

The present RCT study examines the beneficial effects of training letter-speech sound integration on reading fluency in 3rd grade dyslexic readers. Groups were compared on a wide range of reading and

letter-speech sound mapping measures. The latent factors derived from these measures were analyzed to evaluate training effects as well as differences in the rate of improvement between dyslexics and typical readers. Finally, the relationship between letter-speech sound mapping skills and reading improvement was examined in a correlational analysis. The results are interpreted within the framework of a letter-speech sound integration deficit in dyslexia.

Baseline Characteristics

Regarding the group comparisons at pretest, the dyslexic groups showed a more severe impairment in word reading speed measures than in accuracy. This is consistent with previous research showing that in (semi-)transparent orthographies dyslexics may attain relatively high levels of reading accuracy after the first years of instructions while fluency is severely impaired (de Jong & van der Leij, 2003; Landerl et al., 1997; Yap & Leij, 1993). In relation to letter-speech sound associations, the baseline group differences were less prominent than those of word reading. The pretest group comparisons between dyslexics and typical readers revealed slightly larger effects on fluency than on accuracy scores, with the exception of the 3DM discrimination task, which was not sensitive to group differences in mapping fluency. A less pronounced deficit in mapping accuracy could be expected since children in 3rd grade already present a reasonably advanced knowledge of letter-sound correspondences, even within poor readers. In addition, a previous study suggested that the letter-speech sound mapping accuracy deficit in dyslexics was absent after grade 2, while there was a halting of performance speed compared to typical readers in grade 3 (Vaessen & Blomert, 2010). According to the multisensory integration account, poor readers may know which letter correspond to which speech sound but still be unable to use these associations for fluent reading (Blomert, 2011).

Training Effects on Test Scores

With regard to the remediation effects, the training-group dyslexics outperformed the waiting-group dyslexics after the letter-speech sound training program. The gains in word reading after training were more pronounced for fluency scores than for accuracy scores. Additionally, spelling scores and letter-speech sound identification fluency scores also showed improvement after training. The relatively small effects on word reading accuracy were anticipated given the high accuracy scores at pretest. The effects of interventions for dyslexia on reading accuracy have been demonstrated in previous studies (Alexander & Slinger-Constant, 2004; Galuschka, Ise, Krick, & Schulte-Körne, 2014; Tijms, 2011). However, as argued in the introduction there is still a lack of robust evidence for effective treatments in terms of reading fluency. Interestingly, in the present study the largest effect sizes for gains after treatment were found in word reading fluency measures.

Most traditional intervention methods are based on phoneme awareness practice and phonemic decoding (Alexander & Slinger-Constant, 2004; Gabrieli, 2009; Wolff, 2011) which strongly focuses on the accurate learning of letter-speech sound correspondence rather than their automatic integration. In

contrast, the present training aims to obtain automation of grapheme-phoneme mapping besides instruction and practice of accurate correspondences. The current results show that dyslexics are able to become more fluent readers by a systematic training in the automatisation of letters-speech sound correspondences. A potential confound might relate to group differences in the time between measurements. However, the inclusion of the time between measurements as a covariate did not change the pattern of results and the use of standardized scores controls for effects of time of reading instruction. Moreover, deficits in dyslexia have been shown to persist without special training (Snowling, Muter, & Carroll, 2007), thus it seems unlikely that a few additional weeks of school attendance would have a significant impact on the observed differences between the dyslexic groups.

Training Effects Manifested in Factor Scores

The results of the PCA analysis yielded three latent factors derived from the multiple outcome measures at pretest; word reading, letter-speech sound mapping fluency and letter-speech sound mapping accuracy (see Table 3.4). The word reading measures of accuracy and speed accounted for the largest proportion of the variance, followed by letter-speech sound mapping fluency and accuracy, respectively. The reading speed measures also loaded on the other two factors. This may reflect that the contribution of letter-speech sound mapping skills to reading fluency is still relatively important in children in grade 3. This is supported by a previous study reporting moderate correlations between letter-speech sound identification and discrimination tasks and word reading tasks in transparent orthographies (Vaessen et al., 2010). In addition, whereas letter-speech sound association scores of fluency and accuracy loaded highly on distinct factors, this was not the case for the word reading factor, which included both speed and accuracy scores.

The current finding of separate factors for fluency and accuracy of letter-speech sound associations has been reported in previous studies (Vaessen & Blomert, 2010) [1]. This pattern is in line with the notion that adequate knowledge of grapheme-phoneme correspondences does not necessarily lead to effective integration and fluent word reading (Blomert, 2011). With regard to the observed group differences, comparisons at pre-test revealed a clear difference between the two dyslexic groups vs. the typical readers for the three latent factor loadings. This was expected in view of the initial ANOVAs, suggesting that although the deficit in dyslexics was more prominent for word reading, their performance in letter-speech sound mapping tasks was also below the level of typical readers.

Most importantly, the analysis of training effects showed significant gains for the word reading factor in the training-group relative to the waiting-list group. The current training is exclusively focused on automatizing letter-speech sound mapping processes. These processes are essential for reading

[1] A potential confound may relate to the different response formats for fluency and accuracy (i.e., reaction time and proportion correct, respectively). But this confound would apply also to reading speed (indexed by the number of words) and accuracy (indexed by the percentage of words read correctly), both loading high on factor 1, which shared the highest loads.

acquisition (Ehri, 2005). After training to develop more robust and automatic letter-speech sound associations, dyslexics may have been able to use these correspondences in a more efficient way for learning automatic word reading (Ehri & Saltmarsh, 1995). The gains in word reading after the current training further support the notion of a multisensory integration deficit underlying dyslexia (Blau et al., 2010; Blomert, 2011; Froyen et al., 2011). Finally, the groups did not differ in gains in the two letter-speech sound mapping factors. Although there were differences present at test-level on letter-speech association tasks, the analysis failed to reveal statistical differences at the factor level. It could be possible that this lack is partially due to indifference of the behavioral letter-speech sound mapping measures (Vaessen & Blomert, 2010) or insufficient statistical power in the present sample. In addition, the mapping fluency factor included the scores from letter-speech sound mapping discrimination task that, in our baseline comparison, failed to show a dyslexic deficit while the other tasks tapping mapping fluency, including spelling fluency and letter-speech sound identification, did show a moderate improvement after training in our analysis of test scores. Another plausible explanation would be that the current training improved reading fluency by other processes that are influenced by but not reflected in the letter-speech sound mapping tasks, such as visual word specialization. This is supported by the suggestion that the earlier development of grapheme-phoneme integration areas may support the later specialization of visual areas for fast recognition of words, which develops with increasing expertise in word reading (McCandliss et al., 2003; Pugh et al., 2013).

Rate of Change

The rate of improvement for the word reading factor was faster in the training dyslexic group than in typical readers. Importantly, the rate of improvement for word reading did not differ between the control-group dyslexics vs. typical readers. Previous studies on normal reading development have indicated that while reading accuracy approaches ceiling levels after the first few years of instruction, reading fluency increase remains moderate over the years (Vaessen & Blomert, 2010; Wimmer & Hummer, 1990). In view of this, low improvement in the word reading factor, which relates to both accuracy and speed measures, may be expected in typical readers in third grade, after attaining high fluency levels. The lack of differences between waiting-list dyslexics and typical readers suggests that severely deficient readers do not tend to catch up with those with higher reading skills. This is in line with previous longitudinal studies that have suggested stability in reading abilities. These studies found high correlations between reading scores across elementary grades (Aunola, Nurmi, Niemi, Lerkannen, & Rasku-Puttonen, 2002; Juel, 1988; Parrila, Kirby, & McQuarrie, 2004; Wagner et al., 1997). The present results suggest that dyslexics do not overcome their deficit without special training. Moreover, the faster rate of change in training-group underscores the need for early and specialized intervention in dyslexia.

Relation of Reading Fluency with Mapping Initial Skills

The partial correlations suggested that reading fluency gains were related to baseline differences in letter-speech sound mapping fluency, in the waiting-list group but not in the training-group. This relation was absent in the typical readers group as well. Using the current longitudinal design, we show that in untrained dyslexics, reading fluency development is constrained by letter-speech sound association processes. This finding provides support for Blomert's (2011), suggestion that deficits in automatizing multisensory mapping may underlie reading dysfluency in dyslexia. Furthermore, this result supports the notion that training in automatizing letter-speech sound correspondences reduces integration deficits in reading fluency development. A possible interpretation of the current findings is that dyslexics at third grade might rely strongly on phonological decoding, similarly to typical readers during the initial stages of reading, unless specific training is provided (Maurer et al., 2011).

Limitations of the current study

There are two main limitations regarding the interpretation of current results. The first one relates to design the present study as only one type of intervention was tested. Consequently, the current design does not allow disentangling effects due to the specifics of the current training from those due to training in general training, such as increased reading exposure. Although this seems to be a common limitation in many intervention studies, reading dysfluency in dyslexia seems to persist even after specialized phonologically based interventions that can remediate accuracy problems (Shaywitz et al., 2008). Thus, the current improvements observed after a relatively short training are unlikely to be attributed to just increased reading exposure. A second limitation, related to the previous one, is concerned with the interpretation of our results based on the multisensory integration hypothesis. Obviously, our results offer only partial rather than decisive support for this hypothesis, as we did not find improvement in the dyslexics training group for the letter-speech sound mapping fluency factor. In addition, the deficits manifested in dyslexics in mapping fluency measures seemed to be less pronounced than in word reading. Previously, a study using these measures in a large sample primary school children showed a decrease in response latencies until grade 5 in typical readers whereas in poor readers performance halted prematurely in grade 3 (Blomert & Vaessen, 2009). That study also found that accurate identification and discrimination of letter-speech sound pairs typically develops within the first year of instruction. Neuroimaging studies, however, showed a more prolonged period for the attainment of automatic integration at the neural level (Booth et al., 2001; Froyen et al., 2009). This observation may suggest that behavioral measures are not optimally sensitive to reveal the time demands of fully automatized multisensory integration. In this regard, apparent indifference of some of our behavioral measures may have influenced the specific patterning of the present results.

Conclusions

The current RCT study demonstrates that a relative short but intensive training in letter-speech sound mapping fluency can significantly improve word reading in dyslexia. Importantly, the effects were not limited to reading accuracy skills; they also extended to reading fluency. The rate of improvement in the training-group was faster than both in typical readers and in dyslexics without special training. This is a promising result as reading fluency has repeatedly been shown to be unsusceptible to intervention in dyslexia (Compton et al., 2014; Elliott & Grigorenko, 2014; Gabrieli, 2009). Furthermore, reading fluency gains were strongly correlated to initial letter-speech sound mapping fluency in untrained dyslexics, suggesting that their reading fluency development is restricted by their mapping fluency. In contrast, reading fluency gains in the training group were unrelated to their initial mapping fluency. By systematically training fluency in grapheme-phoneme correspondences dyslexics thus seem to overcome their initial mapping deficiency barrier and able to improve their reading fluency. This conclusion concurs with neurophysiological research showing that the ability to fluently integrate cross modal letter-speech sound information is critical for the development of a neural circuit for fast visual word recognition (Blomert, 2011; Gullick & Booth, 2014; Hahn, Foxe, & Molholm, 2014; Sandak et al., 2004), as well as with reading development models in which the attainment of fluent letter-speech sound mappings are considered a critical step in the acquisition of fluent reading (Ehri, 2005; Gombert, 2003). More specifically, reading research suggests that while children explicitly acquire initial knowledge of letter-speech sound mappings, the consequent implicit, statistical learning of grapheme-phoneme associations by repeated exposure drives the development towards the automatic integration of these mappings and their instrumental use in fluent reading (Aravena & Tijms, 2009; Gombert, 2003; Pavlidou & Williams, 2014). Our results in accordance with this view, and thus suggest that intensive training towards automation of letter-speech sound integration is an important remedial activity in addressing reading fluency in dyslexia. At the same time, one might argue that these results provide an explanation for why interventions focusing essentially on phoneme awareness and decoding skills fail to improve reading fluency (e.g., Elliott & Grigorenko, 2014), as they bolster letter-speech sound mapping accuracy but do not intensively address the automation of letter-speech sound integration processes.

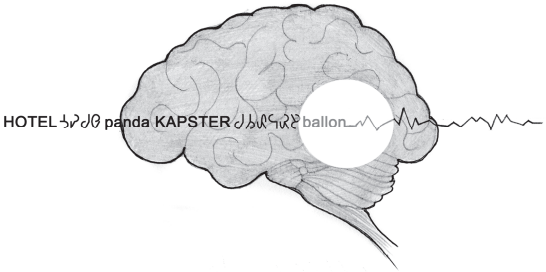
Recent neurophysiological and neuroanatomical studies have shown a deficit in the crossmodal integration of letters and speech sounds in a temporo-parietal network in dyslexia (Blomert, 2011; Hahn et al., 2014; Kronschnabel et al., 2014; Wallace, 2009; Žarić et al., 2014). Notably, this deviant processing of letters and speech sounds in these multisensory areas has been reported in dyslexic children even if they attained adequate knowledge of letter-speech sound correspondences (Blau et al., 2010; Froyen et al., 2009). Based on these brain findings, a theoretical account of dyslexia has been postulated that states that a failure to develop automatic letter-speech sound integration will first and for all result in an impairment in the acquisition of fluent reading skills (Blomert, 2011). Using a behavioral intervention paradigm, we provided support for this account by showing that (a) accuracy in knowledge of letter-speech sound correspondences was not associated with reading fluency gains, (b)

letter-speech sound mapping fluency was strongly correlated with fluency gains in untrained dyslexics, but not in trained dyslexics, and (c) an intensive training addressing the automation of letter-speech sound mappings produced reading fluency improvements.

Attaining reading fluency is a long process and previous studies have shown that even non-impaired readers may take years to become fluent readers (Vaessen & Blomert, 2010). The present results, together with those reported in Aravena et al. (2013), illustrate the clinical potential of the letter-speech sound mapping framework for remediation programs in dyslexia.

Chapter 4

Visual ERP Changes in Dyslexia Associated with a Letter-Speech Sound Reading Training



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Abstract

Dysregulation of visual brain areas specialized for fast processing of print contributes to the reading fluency deficit in dyslexia. The current study examined the relation between training gains in reading fluency and event-related potentials (ERPs) recorded over occipito-temporal brain areas. A sample of 18 children with dyslexia, aged 8 to 9 years, participated in a training, focusing on letter-speech sound mapping, that has been demonstrated to improve reading fluency in previous research. ERPs were recorded during an implicit visual word reading task before and after training. The results revealed a moderately positive relation between gains in reading fluency and the effect of training on the amplitude of an early negative ERP component, N1, at the left hemisphere. More specifically, the N1 responses to words differentiated between responders vs. non-responders. That is, the pre-training N1 amplitudes were larger in children for whom the training had a beneficial effect compared to children who were training resistant. The current results demonstrate the potential use of N1 as a predictor of training responsiveness. A neurocognitive interpretation of the results is provided and clinical implications are discussed.

4.1 Introduction

Dyslexia is a specific reading disability characterized by dysfluent and inaccurate word recognition, spelling and phonological decoding (Lyon et al., 2003). Reading dysfluency is one of the most persistent symptoms of developmental dyslexia (Shaywitz & Shaywitz, 2008). Fluent readers are able to develop visual expertise for fast and automatic identification of words, whereas dyslexic readers persistently fail to acquire fluent reading. Neuroimaging studies have identified two posterior neural systems, primarily in the left hemisphere, that are particularly important for the development of reading skills (Schlaggar & McCandliss, 2007). The first system is located in the left dorsal temporo-parietal region and relates to phonological processing and cross-modal integration of letters and speech sounds (Blomert, 2011; van Atteveldt et al., 2004). The second system is located in the ventral left occipito-temporal region and involves areas in the middle and inferior temporal and occipital gyrus. Within this system the area located at the left lateral occipito-temporal sulcus has been called the "visual word form area" (VWFA) because of its suggested specialization for printed word recognition (Dehaene & Cohen, 2011; McCandliss et al., 2003). Longitudinal studies suggested a model in which the left dorsal temporo-parietal system develops at the first stages of reading acquisition when letter-speech sound (LSS) mappings are established, and later supports the specialization of the visual system for word recognition (McCandliss & Noble, 2003; Sandak et al., 2004). Importantly, dysregulation in both the temporo-parietal and occipito-temporal system have been found in dyslexics (Blau et al., 2010; Brunswick, McCrory, Price, Frith, & Frith, 1999; Helenius, Tarkiainen, Cornelissen, Hansen, & Salmelin, 1999; Paulesu et al., 2001; Shaywitz & Shaywitz, 2008; Simos, Breier, Fletcher, Bergman, & Papanicolaou, 2000; Žarić et al., 2014).

Electrophysiological studies have used brain event-related potentials (ERPs) to examine the temporal dynamics of the activity of the occipito-temporal system during reading. Two components have been related to early visual processing of print in both children and adult readers. The first is a positive component labeled P1; it peaks between 100 and 150 ms after stimulus onset and has a posterior-occipital topography. P1 has been associated with low-level analysis of word features, including word length and typicality (Assadollahi & Pulvermüller, 2003; Moscoso del Prado Martín, Hauk, & Pulvermüller, 2006). A second component, labeled N1 or N170, has a negative polarity and peaks at around 200 ms after stimulus onset. N1 is typically observed at the junction of parieto-occipital or occipito-temporal sites. Most interestingly, N1 has been related to visual expertise and orthographic processing (Bentin et al., 1999; Maurer et al., 2005) and its sources have been localized in the VWFA (Rossion et al., 2003; Tarkiainen et al., 1999). In addition to P1 and N1, a later positivity, labeled P2, with latencies around 300 ms and more temporal topographies, has been associated with phonological as well as semantic aspects of stimuli in visual word experiments (Landi & Perfetti, 2007; Nobre et al., 1994).

The present study will focus on the N1 component because of its relation to visual processing and the alleged association with VWFA activity. Expertise in the visual processing of different categories of objects is associated with an enhancement of N1 amplitude (Tanaka & Curran, 2001). Importantly, besides general visual expertise, N1 seems to be particularly sensitive to lexical processing. In literate individuals, larger N1 amplitudes are found for words compared to strings of symbols, shapes or dots (Bentin et al., 1999; Maurer et al., 2005; Tarkiainen et al., 1999). Moreover, N1 responses appear to be sensitive to word similarity, being larger to letters-like stimuli (e.g., pseudofonts) compared to stimuli matched on low-level features (Eulitz et al., 2000; Schendan et al., 1998; Tarkiainen et al., 1999). Consonant strings and pseudowords usually evoke N1 responses similar to those elicited by words (Bentin et al., 1999). A number of studies have reported left lateralized enhancement of N1 amplitudes to orthographical compared to contrast visual stimuli (Bentin et al., 1999; Maurer et al., 2005, 2008; Rossion et al., 2003; Xue & Poldrack, 2007). In view of this evidence, N1 amplitude differences between words vs. symbol strings have been hypothesized to provide an index for 'visual tuning' for print that is proposed to develop with visual learning during the first years of reading acquisition (Maurer et al., 2008).

In a series of ERP studies, Maurer and colleagues compared N1 differences between words vs. strings of icon-like symbols at different stages of reading acquisition in both normal readers and dyslexics (Maurer & Mccandliss, 2003; Maurer et al., 2011). The data of normal readers suggested a significant left-lateralized N1 tuning effect that remains relatively stable during the first years of reading acquisition (Maurer, Brem, Bucher, & Brandeis, 2005). The N1 word-symbol differences in typically reading children were larger for 2nd grade children relative to kindergartners, but leveled off between 2nd grade and 5th grade (Maurer et al., 2011). This pattern of findings was taken to suggest an inverted "U" model of development of visual expertise, in which perceptual learning is critically important during the first two or three years of learning to read and then gradually declines as expertise develops. In the same series of studies, the dyslexic children in 2nd grade showed a reduced word vs. symbol difference in N1 amplitude as compared to normal readers. The authors interpreted the reduced word-symbol difference in dyslexics as a lack of visual specialization for print, reflecting a deficit in expertise for rapid word recognition. Related ERP studies suggested, however, that the N1 difference between dyslexic and typical readers continues to persist in pre-adolescents (Araújo et al., 2012) and adulthood (Helenius et al., 1999; Mahé et al., 2012). Moreover, Fraga Gonzalez et al. (2014) reported a smaller N1 to words at the left vs. right hemisphere sites in typical readers that was absent in dyslexics. This pattern was taken to suggest that visual decoding of words requires less effort in typical compared to dyslexic readers.

The primary goal of the present study was to examine the effects of fluency training on N1 amplitudes to words in dyslexics. Previous treatment studies suggested that dyslexic readers can reach

reasonable levels of accuracy (Hatcher et al., 2006; Lovett et al., 2003; National Reading Panel, 2000; Tijms, 2007) but are still lagging behind in reading fluency (Alexander & Slinger-Constant, 2004; Chard et al., 2002; Compton et al., 2014; Gabrieli, 2009; Thaler et al., 2004). The current training is an adaptation of the intervention program reported by Tijms (2007). The intervention is inspired by a rapidly growing body of research suggesting a letter-speech sound binding deficit as the most proximal cause for dyslexia (Blau et al., 2010; Froyen et al., 2011; Kronschnabel et al., 2014; Wallace, 2009; Žarić et al., 2014). The present training provides for systematic practice on regular and irregular letter-speech sound mappings at increasing levels of complexity, and its focus is on attaining automated letter-speech sound integration. Importantly, the training focuses not only on learning of letter-speech sound correspondences, but it also emphasizes intensive exposure in order to gain fluency in automation of these associations. The beneficial effects of this training on reading fluency have been evaluated in detail in a previous study (Fraga González, Tijms, Bonte, Blomert, & van der Molen, *submitted*; Tijms, 2007). We predicted the intervention to normalize N1 lateralization in our dyslexic sample; that is, N1 should be reduced over the left compared to the right hemisphere (Fraga González et al., 2014).

Another goal of the present study was to evaluate individual differences in response to treatment. It is estimated that around 2% to 6% of all children with reading difficulties might remain poor readers after intervention during the first and second grades (Torgesen, 2000). Only a few studies have related brain activity in dyslexics to intervention outcomes. Two fMRI studies reported that the resemblance to typical readers in neural activation following training was more pronounced in responders compared to poor responders (Davis et al., 2011; Odegard et al., 2008). Similarly, two MEG studies reported larger temporo-parietal activations to better outcome in adolescent poor readers (Rezaie et al., 2011a, 2011b). With regard to brain potentials, Molfese and co-workers, using a visual word rhyming task, reported larger normalization of N1 and P1 amplitudes in 2nd grade responders but not in poor responders (Molfese et al., 2013). Another study examined ERPs in three different tasks and found that responses (particularly in the 400-600 ms time window) to letter sound matching predicted reading gains after a short intervention in first-grade children (Lemons et al., 2010). Finally, Hasko and colleagues observed that fronto-temporal ERPs in a phonological decision task were associated with intervention gains in third grade dyslexics (Hasko et al., 2014). Collectively, this pattern of results led us to predict that the N1 response to our intervention would be related to reading gains in our sample of dyslexics.

The present study has three aims. First, we expect dyslexics to show changes in N1 responses to words towards the lateralized pattern previously observed in typical readers. Thus we anticipate that the current intervention will lead to normalization of neural responses in dyslexics. Second, we investigate the relation between changes in N1 and gains in reading fluency after training. That analysis tests the validity of N1 as a marker of reading fluency. Furthermore, we classify based on their responsiveness to training and examine N1 changes in those children who showed larger reading fluency improvements.

Finally, we examine initial differences in N1 between responders and poor responders to evaluate the potential of N1 as predictor of treatment responsiveness.

4.2 Methods

Participants

Third-grade dyslexic children (N = 18; 9.05 ± 0.46 years old) were recruited from a nation-wide center for dyslexia in the Netherlands [2]. The initial sample size for this group was 22 children. Two children did not take part in the posttest ERP recordings and data from two children was discarded due to technical problems during recording. Some behavioral measures are missing due to computer failure (see footnotes in Table 4.1). All participants had a percentile score of 10 or lower on a standard reading test. A group of 20 third-grade, typical readers (8.78 ± 0.35 years old) was recruited from several primary schools attended by children with the same socio-demographical background as the dyslexic group (see Table 4.1 for group characteristics). They had no history of reading difficulties and had a percentile score of 25 or higher on standard reading tests (see below). The group of typical readers did not take part in the letter-speech sound training. All children were native Dutch speakers, received two and a half years of formal reading instruction in primary education. Children with below average IQ (IQ < 85 on a non-verbal IQ-test), uncorrected sight problems, hearing loss, diagnosis of ADHD or other neurological or cognitive impairments were excluded. The study was approved by the ethics committee of the university and all parents or caretakers signed informed consent.

Procedure

The present study used a pretest-training-posttest design. The dyslexic children received an extensive differential diagnostic baseline assessment before and after the training. They received an average of 33.83 ± 0.51 training sessions (see Training). The average number of weeks between pre- and posttest for the behavioral assessments was 23.11 ± 3.39 weeks and for the ERP measurements it was 22.00 ± 2.85 weeks. The number of weeks elapsing between pre- and posttest did not significantly differ between behavioral and ERP measurements, $p = .109$. The measurements of typical readers used for baseline comparisons took place within a period of around 3 months from the pretest measurements in the dyslexic readers.

Behavioral Measurements

A series of tests was used to assess the reading skills of the participants. The children took the tests at their school. Test scores at the pretest are presented in Table 4.1.

[2] The participants of the current study were included as part of a larger sample in our behavioral study assessing training effects on reading (Fraga González et al., submitted.). Further, the group of typical readers, used as a baseline in the present study, participated in our previous ERP study (Fraga González et al., 2014).

The 3DM battery of tests (test reliability information available in Differential Diagnosis; 3DM, Blomert & Vaessen, 2009) contains word reading, phonological awareness, naming speed and letter-speech sound association tasks. This battery is administered individually using a computer and a specialized response-box records reaction time with millisecond accuracy. The scores of the following 3DM subtests have been used in the present study.

Word-reading task. This task includes three different subtasks containing high-frequency words, low-frequency words and pseudowords. The mean frequencies of the high-frequency words are between 790 and 45810 and for the low-frequency words they range between 6 and 342 (CELEX-database; Baayen, Piepenbrock, & Gulikers, 1995). There are 75 words for each level (5 screens with 15 items each). The difficulty of each level increases systematically from monosyllabic words without consonant clusters to 3 or 4 syllabic words with consonant clusters at the fifth level. The participants are asked to read accurately as many words as possible. When they finish reading one screen the experimenter presses a button to continue until the time limit of 30 seconds per subtask is reached. The number of words read correctly within 30 seconds determines the reading fluency score per subtask (r = .91-.93 for the subtasks, and r = .95 for total task, test-retest). The proportion of words correctly read within the time limit accounts for the reading accuracy scores (r = .73, test-retest).

Letter-speech sound (LSS) association tasks. Two tasks were used to measure accuracy and automation of letter-speech sound (LSS) mapping; LSS identification and LSS discrimination. LSS identification requires a child to match a speech sound to one of four presented letter (combinations) by pressing the corresponding button (e.g. /b/ and 'b' 'd' 't' 'p'). LSS discrimination asks a child to judge whether a speech sound and letter are congruent or incongruent (e.g. /ui/ and 'oe'). Accuracy (% correct) as well as response time (sec/item) is measured (LSS identification: r = .72 for accuracy and r = .90 for response time; LSS discrimination: r = .82 for accuracy and r = .96 for response time, internal consistency).

Computerized spelling. A word is presented aurally (over headphones) as well as visually (at the computer screen). In the visually presented word, a letter (combination) is missing and the child is instructed to choose the missing part out of four visually presented options by pressing the corresponding button (e.g. auditory stimulus /boom/ (tree), visual stimulus 'b__m', options 'oo' 'o' 'a' 'aa'). Words are spelled either phonetically (18 items) or contain Dutch spelling rules (36 words). Word frequencies are varied systematically. Accuracy (% correct) as well as response time (sec/item) is measured (r = .80 for accuracy and r = .94 for response time, internal consistency).

Table 4.1. Descriptive statistics of reading accuracy and fluency scores

	Typical Readers	Dyslexics		
	M (SD)	*M (SD)*	*p*-value	η^2
N	20	18		
Sex ratio (m:f)	8:12	8:10		
Handedness (L:R)*	2:15	3:15		
Age	8.78 (0.35)	9.05 (0.46)	.052	0.10
3DM Word reading - *accuracy* [a]				
High Frequency	99.12 (1.12)	92.02 (7.20)	.000	0.34
Low Frequency	97.25 (3.23)	82.96 (16.54)	.001	0.28
Pseudowords	87.37 (9.65)	70.72 (16.37)	.000	0.29
Total [T][b]	49.50 (9.06)	32.33 (12.76)	.000	0.39
3DM Word reading - *fluency* [T]				
High Frequency	52.95 (7.58)	30.50 (5.43)	.000	0.75
Low Frequency	54.65 (9.02)	31.11 (6.46)	.000	0.70
Pseudowords	53.00 (9.44)	30.78 (5.55)	.000	0.68
Total	53.95 (9.34)	29.83 (5.53)	.000	0.72
One-Minute Test -*fluency* [SS][c]	11.55 (2.82)	3.44 (1.82)	.000	0.75
Text Reading - *fluency*[T]**	54.70 (8.04)	33.11 (5.66)	.000	0.71
Letter-speech sound associations [T]				
LSS identificacion - *accuracy*	46.95 (7.70)	43.83 (13.27)	.376	0.02
LSS discrimination - *accuracy*	50.20 (9.25)	45.72 (8.59)	.132	0.06
LSS identificacion - *fluency*	52.80 (7.08)	46.00 (7.06)	.005	0.20
LSS discrimination - *fluency*	51.10 (8.01)	51.83 (8.92)	.791	0.00
3DM Spelling - *accuracy*	50.60 (9.14)	36.11 (8.34)	.000	0.42
3DM Spelling - *fluency*	54.55 (8.70)	40.61 (8.30)	.000	0.41
Phoneme deletion -accuracy[T]**	52.70 (7.63)	39.06 (9.39)	.000	0.40
3DM Naming speed scores[T]**				
Letters	50.05 (7.13)	37.53 (7.71)	.000	0.43
numbers	50.65 (10.92)	36.53 (8.58)	.000	0.35
Total	49.85 (7.91)	35.18 (9.31)	.000	0.43

LSS = Letter-speech sound.
[a]Raw scores. [b] T scores (M = 50, SD = 10). [c] SS scores (M = 10, SD= 3).
*Data missing for 3 participants; Typical n = 17. ** Data missing for one participant; Dyslexics n = 17.

Rapid Naming Task. The rapid naming (RAN) task consisted of three subtasks: letters, digits and objects. Each subtask contains 5 items repeated six times, distributed in two screens of 15 items. Participants are instructed to name the items as fast and accurate as possible. The score per subtask was determined by taking the mean response time of the two screens (r = .80 for letters, r = .83 for digits, and r = .71 for objects, split-half reliability).

Phonological awareness (PA). An estimate of phonological awareness is obtained by using a phoneme deletion task presenting 23 pseudowords with a CVC or CCVCC structure. The participant must omit a consonant that is either at the beginning or at the end of a word or within a consonant cluster as fast as possible. The score is determined by the percentage of correct responses. (r = .85, internal consistency).

In addition to the 3DM battery the following tests were used:

Word-reading fluency. The Dutch version of the *One-minute test* (Een-Minuut-Test; Van den Bos, Spelberg, Scheepsma, & De Vries, 1999) was used to provide an additional estimate of word reading skills. It is a time-limited test consisting of a list of 116 unrelated words of increasing difficulty. The number of correctly read words within 1 minute serves as reading fluency score (r = .90, test-retest).

Text-reading fluency. The text-reading fluency test consists of a coherent text of increasing difficulty. The child is asked to read the text out loud within one minute (Schoolvaardigheidstoets Technisch Lezen; de Vos, 2007). Again, the number of correctly read words within 1 minute serves as reading fluency score (r = .88, test-retest).

Training

Dyslexic children were provided with an intensive tutor and computer-assisted training program. First the standard letter-speech sound correspondences are trained and, subsequently, the irregular letter-speech sound mappings. The training is constructed in accordance with general skill acquisition paradigms (Davydov, 1995; Schneider, 2003), which basically implies that each (letter-speech sound) element is taught explicitly at first and consequently repeated intensively in order to obtain a transition from accurate, controlled to associative, automatic processing. In a previous study, we showed that massive exposure to letter-speech sound correspondences is substantially more effective in automatizing letter-speech sound integration when it is preceded by explicit teaching of these correspondences than when it is presented on its own (Aravena, Snellings, Tijms, & van der Molen, 2013). Sessions consist therefore in an instruction part and a practice part. In the instruction part letter-speech sound correspondences are explicitly trained, aiming at a step-by-step accurate mastery of the learned associations. During the practice part, the computer training provides a high exposure to the specific letter speech sound associations that were taught during the instruction part, to stimulate the automatic integration of letters and speech sounds.

The training started with teaching consistent letter-speech sound correspondences. To do so, a reconfigured touchscreen was used that consists of buttons for each Dutch speech sound. Each button shows the standard letter or letter-cluster of the corresponding speech sound. When the child presses a button the computer produces the corresponding speech sound (by a natural voice). This is done to ensure that attention is directed to the matching of letters and speech sounds. The letter-speech sound couplings are taught step-by-step, e.g., first the short vowels, then long vowels, and later on diphthongs. During this instruction part, the letter-speech sound correspondence is presented not only in isolation but also within the context of a (visual) word.

Dutch orthography is considered to be of intermediate complexity (e.g., Grigorenko, 2001), which implies that the one-to-one mapping between letters and speech sounds can be broken. To learn these inconsistent correspondences, phonological-orthographic mapping operations are introduced during the second part of the program. These operations follow a uniform algorithm, i.e.:

$$\text{IF } p \ / \ \# \in Pi \text{ then } O\,(p) \rightarrow g \in G.$$

When the terminal phonic element p of a syllable belongs to the ith category of phonetic elements Pi then the result of an operator O on p will be mapped onto a graphic element g that need not be the standard mapping.

The basic principles of the Dutch written language can be structured within a learning system incorporating five types of operations as a consequence of five types of terminal phonic elements; long vowels, short vowels, unvoiced consonants, sonic vowels and unstressed morphemes. For example, in Dutch, voiced consonants (/d/ and /b/) lose the voice property at the terminal position, which is not reflected in their orthographic representation. Consequently, the algorithm prescribes: if the last speech sound in a syllable is an unvoiced consonant then extends the word (operation) and if this results in a voiced consonant the voiced consonant graph should be written (e.g., paard [IPA: part̚] - paarden [pardən] (English: horse - horses), otherwise the standard consonant (e.g., kat [kɑt̚] - katten [kɑt̚ən] (cat - cats)). All essential terms in the algorithm have an explicit and exhaustive description in the program with regards to the set of speech sounds, the categories of speech sounds, the corresponding orthographic elements, and the mapping operations. Consequently, the focus of attention remains continuously on the integration of letters and speech sounds.

Along with the learning of both consistent and inconsistent letter-speech sound mappings, the computer training provides a high exposure to letter-speech sound mappings at increasing levels of complexity. A typical example of an exercise during practice refers to the projection of individual words, speech sound by speech sound, on the computer screen under (progressive) time demands (see Figure 3.2 in previous chapter). The child is asked to pronounce the word sound by sound (and in the end the whole word), guided by the time-constraints of the graphemic presentation rate. During

presentation, the whole word is projected faintly on the screen to allow anticipation (cf., Legge, Mansfield, & Chung, 2001). During a practice session, specific letter-speech sound mappings or clusters of mappings (e.g., all long vowels) are presented, matching those addressed in the preceding instruction part. Practice is adjusted to the individual rate of acquisition by adapting time-constraints to the level of the child's performance.

The training program was provided by well-instructed junior psychologists, on a one-to-one basis for 45-min sessions. The training frequency was two sessions per week.

ERP Measurement

Procedure and equipment. The EEG recording took place in a video-controlled and soundproof room with temperature regulated by an air-conditioning system. There was no exposure to sunlight and the lightning of the room allowed a uniform and glare-free illumination. Participants and lab assistants were together at all times in the room while the experimenter controlling the recording, subject performance and stimuli presentation was in an adjacent room. Participants were seated at approximately 80 cm distance from the computer screen and the lab assistant sat behind at a distance that safely avoided any possible distraction or interference on the visual field of the participant. At both arms of the participant's chair response buttons were placed. The experiment lasted around 16 minutes including pauses, and it was part of a longer experimental session (around 2 hours long). There were short pauses between blocks and longer breaks (around 5 minutes long) between experiments. The length of these pauses and breaks varied according to the needs of the participants and all of them received a present at the end of the experimental session. The stimuli were presented using an ASUS VW22U (resolution 1680x1050) monitor with a Dell Optiplex 760 dual-core 3.0GHz computer and an ATI HD 6570, 2Gb graphic card. The software used to present the stimuli was Presentation (Version 14.4, www.neurobs.com).

The ERP data were collected using a 64 channels Biosemi ActiveTwo system (Biosemi, Amsterdam, Netherlands). EEG was recorded DC (low-pass: 5th order sync digital filter) with a 1024 Hz sample rate. The Biosemi system uses two additional electrodes (Common Mode Sense [CMS] and Driven Right Leg [DRL]) located to the left and right of POz, respectively, as recording reference and ground (see www.biosemi.com/faq/cms&drl.htm for details). The 64 electrodes were distributed across the scalp according to the 10-20 International system and applied using an elastic electrode cap (Electro-cap International Inc.). Electrode sites across the scalp are presented in Figure 2.1 (chapter 2) and the electrodes used in the analyses are highlighted. In addition, six external Flat-Type Active electrodes were used, four of which recorded vertical and horizontal electro-oculogram (EOG) and two were placed at mastoids for off-line reference.

Stimuli. Strings of words and symbols were used in the experiment (see Appendix A for the list of the stimuli used). 80 bi-syllabic Dutch words were selected using estimates of age of acquisition (AOA). Estimates of AOA were based on two published ratings; (1) vocabulary estimates of 6-year-olds (Schaerlaekens et al., 1999), (2) AOA of Dutch words (Ghyselinck et al., 2000), and a subsequent student/parent familiarity rating of the selected words. The current selection criterion was motivated by a study indicating that AOA is a more sensitive index of lexical familiarity than either word frequency or neighborhood density when examining developmental change in visual word recognition (Garlock et al., 2001). Short vs. long strings contained 4 or 5 letters and long strings contained 6 and 7 letters. 80 symbol strings were created by converting the previous words into a special font: "3elementSymbols-1600" (P.L. Cornelissen, personal communication October 2011) with a similar number of line elements and comparable spatial frequency and contrast characteristics to actual letters (Pammer et al., 2004). To avoid symbols resembling the fixation cross, the letters 'z' and 'y' were replaced by 's' and 'u' in the symbol strings. Short vs. long strings contained 4 or 5 characters and long strings contained 6 and 7 characters.

Experimental design and Task. All stimuli were presented at the center of the screen with a visual angle subtending on average 1.5° x 6.4° (height x width), using the lower case font "Arial" in white on a black background, at a font size of 40 and bold. They were presented during 700 ms followed by a 1350 ms inter-stimulus interval (ISI) during which a white centered fixation cross was displayed. Blocks comprised 44 trials, four of which were target trials (i.e., immediate repetitions). The experiment had a 2x2 design with the experimental conditions String Length (short vs. long) and String type (word vs. symbol) evenly distributed in 8 trial blocks. 4 Word and 4 symbol blocks alternated pseudo-randomly across participants. The presentation of the targets was pseudo-randomized to avoid consecutive presentations of targets. The participants were instructed to press a button when they detected a target (i.e., when a stimulus was immediately followed by itself). An example of the stimuli used and a schematic of the design are shown in Figure 2.2 (chapter 2).

ERP preprocessing. All EEG data were preprocessed and analyzed with EEGLAB v.11.0.0.0b (Delorme & Makeig, 2004), an open source toolbox for Matlab (Mathworks, Inc.). When imported to EEGlab, the data were referenced to average mastoids, digitally filtered using a basic FIR filter (high pass 1 Hz and low pass 70 Hz), resampled to 256 Hz and epoched (from -500 to 1550 ms after stimulus onset). The baseline of each epoch was then corrected to remove residual activity differences prior to stimuli. This is done by subtracting the mean prestimulus activity (from -500 to 0 ms) from the waveform for each channel and epoch). Artifact removal was done in two steps. The first step consisted of visual inspection of the epochs to remove those epochs containing non-stereotyped artifacts such us head or muscle movements. Secondly, an Independent Component Analysis (ICA) was run using the 'runica' algorithm available in EEGlab (Makeig et al., 1997). The extended option was

used to perform a version of the infomax ICA algorithm (Lee et al., 1999) that results in a better detection of sources with sub-Gaussian distribution, such as line current artifacts and slow activity. The resulting 64 ICA components were pruned by visual inspection of their scalp map, time course and mean activity, in order to remove components related to artifacts like line noise, eye blinks and ocular movements. The data was then reconstructed on an average (SD) of 34.75 (4.73) ICA components in the typical readers group. In the dyslexic group the averages of ICA components kept for pre- and posttest, were 33.83 (8.05) and 29.83 (7.59) components, respectively. Spline interpolation was applied to channels with excessive artifacts (Perrin, Pernier, Bertrand, & Echallier, 1989). Pretest data from P10 and P9 were interpolated for three participants, from PO4 for two participants, and from O1 and O2 for one participant each; posttest data from PO3 was interpolated for five participants and from PO4 for one participant. After artifact removal by ICA a new baseline correction (-500 to 0 ms) was done. Afterwards, data were low-pass filtered to 30 Hz (48 dB/octave) and re-referenced to the average of the 64 scalp electrodes. Trials with responses (i.e., target trials and false alarms) were not included in the statistical analysis. The mean (SD) number of trials included in the analysis (after removal of artifacts and response epochs) in the typical readers group, for short words, long words, short symbols and long symbols were 78.95 (1.79), 78.95 (1.27), 73.90 (3.40) and 73.2 (4.11), respectively. The mean (SD) number of trials included in the analysis in the dyslexic group at pretest for short words, long words, short symbols and long symbols were 77.22 (4.57), 75.33 (4.54), 72.94 (4.71) and 70.50 (8.54) respectively; at posttest they were 79.39 (0.78), 78.78 (1.44), 75.50 (2.41) and 72.61 (5.37) respectively. Finally, individual subject averages were calculated for each experimental condition.

Statistical Analysis

Behavioral analysis. For all analyses, standardized scores were used instead of raw scores, in order to assess the child's position within the distribution of a normative sample. Due to reduced variance, no reliable norm scores were available for the accuracy measures of the three subtasks of the 3DM word reading; thus raw scores were used for these measures. The evaluation of potential training effects comprised the following sequence of steps.

First, one-way ANOVAs were performed to examine baseline differences. The outcome of this analysis should provide a first impression of group differences before evaluating training effects. Secondly, to examine potential training effects, a repeated measures ANOVA statistical analysis was performed in the dyslexic group with the within subjects factor *Training* (2 levels: pre- and posttest). Finally, in order to assess responsiveness to training participants were classified as responders or poor responders in terms of reading speed gains. For this purpose, we performed a median split on the pre-/posttest difference (Vellutino & Scanlon, 1996) for the standardized fluency scores of the 3DM word reading task. The total 3DM word reading fluency score was used, as it is a reliable and sensitive measure, which is part of a test battery widely used for diagnostic assessment of dyslexia in the

Netherlands (see Behavioral Measures). Control analyses were performed comparing responders and poor responders at pretest to confirm that the groups did not differ in their reading scores before the training.

ERP analysis. In a previous study, we obtained an N1 pattern in typical readers, characterized by an effect of hemisphere on word amplitudes that was absent in dyslexics (Fraga González et al., 2014). We first examined whether the same group difference was present using the current sample of dyslexics. A mixed-model ANOVA was performed on dyslexics and typical readers data at pretest, including the between subjects factor *Dyslexia*. The within subjects factors were the following. *String Type* (2 levels: words or strings of letter-like symbols); *String Length* (2 levels: short or long strings); *Hemisphere* (2 levels: right and left hemisphere); and *Electrode* (7 levels. Electrodes pairs at occipital, occipito-temporal and parietal locations were included; O1-O2, PO7-PO8, PO3-PO4, TP7-TP8, P9-P10, P7-P8, P5-P6). A follow-up analysis on dyslexics pretest data examined the specific pattern of responses in dyslexics. Peaks were detected by searching for the maximum amplitude value within the time ranges of 50-180 ms for P1, 175-300 ms for N1, and 250-400 ms for P2. The peak values of amplitudes (μV) and latencies (ms) were used in analysis. Greenhouse-Geisser correction of degrees of freedom was used to calculate *p* values when the assumption of sphericity was violated.

Training effects. The focus of current study was to examine training-induced changes in N1 amplitudes for words. We performed a repeated measures ANOVA on the dyslexics' data incorporating the factor *Training* to the within subject factors *String Length*, *Hemisphere* and *Electrode*. Then a follow-up analysis examined the specific pattern of ERP responses at pre- and posttest measurements, separately.

Relation to reading gains. We examined the relation between changes in N1 responses that previously discriminated between dyslexics and typical readers, and reading fluency gains in dyslexics after the training. Consequently, the left hemisphere sites (TP7, P9, P7, P5, PO7, PO3, and O1) were selected based on their proximity to the VWFA location (Tarkiainen et al., 1999). The pre-/posttest difference in N1 amplitudes for words was computed and averaged across the left hemisphere sites that showed higher sensitivity to training. A composite score of word reading fluency was computed by averaging the One-Minute Test score and the 3DM word reading scores for high frequency and low frequency words, all based on single-word reading as described in Fraga González et al. (2014). The pre-/posttest difference was computed for this composite score. A linear regression analysis was then performed relating the averaged pre-/posttest difference in N1 amplitudes for words to the composite reading fluency difference score. A control analysis was performed including the homologue electrode pairs at the right hemisphere.

Responsiveness. In order to account for responsiveness to intervention, we examined the effects of *Training* on N1 amplitudes for words only in the group classified as responders based on their reading

gains (see Behavioral Analysis). A subsequent control analysis evaluated the anticipated absence of a training effect in poor responders. Finally, an ANOVA was performed on pretest measurements with 'responsiveness' as a between subjects factor to examine whether initial N1 responses could predict response to intervention.

4.3 Results

Behavioral Results

Baseline characteristics. The results of the ANOVAs performed on the pretest data in reading accuracy and speed measures are shown in Table 4.1. The table shows a deficit in dyslexics that is mainly manifested in the reading fluency measures. The dyslexic group attained reasonably high levels of reading accuracy, although significantly lower than those of the typical readers. With regard to the letter-speech sound measures, only the fluency score associated with letter-speech sound identification discriminated between groups.

Training effects. The results of a repeated-measures ANOVA on the performance of the dyslexic group using Training as a within-subjects factor are presented in Table 4.2. The table shows significant gains after training for the main word reading measures. The training effects were less pronounced for accuracy measures, as it might be expected given the relatively high accuracy scores at pretest. The training effect was most pronounced for reading fluency measures, with the exception of the fluency measures derived from the 3DM pseudowords task and the One-Minute test where the gains in standardized scores did not reach significance. Finally, with regard to the tasks related to letter-speech sound mapping, dyslexics showed gains in both spelling accuracy and spelling fluency.

Responsiveness to training. Participants were classified as responders or poor responders based on the median of the post-pretest difference in the standardized total fluency score for the 3DM word reading task. The normative scores were T scores where 50 is the mean and 10 the standard deviation. The individual differences in reading fluency are plotted in Figure 4.1. The median of the differences in T scores was 3.50; the mean (SD) difference was 4.06 (3.63), range 0-11. ANOVAs, including Responsiveness as a between subjects factor, revealed that responders and poor responders did not differ in their initial reading scores, $ps > .221$ (see Table 4.3).

Table 4.2. Results of repeated measures ANOVA in dyslexics (n = 18) with training as within-subjects factor

	Pretest	Posttest	ANOVA		
	M (SD)	*M (SD)*	*F*	*p-value*	η^2
3DM Word reading - *accuracy* [a]					
High Frequency	92.02 (7.20)	96.48 (7.15)	6.56	.020	0.28
Low Frequency	82.96 (16.54)	91.12 (12.59)	9.71	.006	0.36
Pseudowords	70.72 (16.37)	78.33 (19.19)	2.61	.125	0.13
Total [T][b]	32.33 (12.76)	40.72 (14.10)	7.88	.012	0.32
3DM Word reading - *fluency* [T]					
High Frequency	30.50 (5.43)	35.67 (7.41)	29.76	.000	0.64
Low Frequency	31.11 (6.46)	34.89 (6.94)	19.58	.000	0.54
Pseudowords	30.78 (5.55)	32.89 (7.37)	3.73	.070	0.18
Total	29.83 (5.53)	33.89 (7.15)	22.58	.000	0.57
One-Minute Test -*fluency* [SS][c]	3.44 (1.82)	3.89 (2.30)	1.36	.260	0.07
Text Reading - *fluency*[T]	33.11 (5.66)	34.61 (6.36)	4.24	.055	0.2
Letter-speech sound associations [T]					
LSS identificacion - *accuracy*	43.83 (13.27)	45.94 (8.63)	0.43	.520	0.03
LSS discrimination - *accuracy*	45.72 (8.59)	47.67 (9.91)	1.1	.310	0.06
LSS identificacion - *fluency*	46.00 (7.06)	49.22 (10.65)	2.15	.161	0.11
LSS discrimination - *fluency*	51.83 (8.92)	55.11 (10.24)	2.78	.114	0.14
3DM Spelling - *accuracy*	36.11 (8.34)	44.33 (9.83)	19.21	.000	0.53
3DM Spelling - *fluency*	40.61 (8.30)	44.83 (10.90)	4.66	.046	0.22

Note. LSS = Letter-speech sound.
[a]Raw scores. [b] T scores (M = 50, SD = 10). [c] SS scores (M = 10, SD= 3).

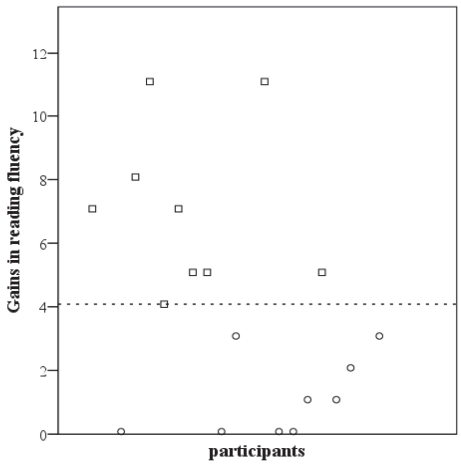


Figure 4.1. Individual differences in the gain in reading fluency (3DM standardized total score) in the dyslexic group (N = 18). The dashed line refers to the group median used to classify subjects as responders or poor responders.

Table 4.3. Descriptive statistics of reading scores in dyslexic responders and poor responders

	Responders	Poor Responders		
	M (SD)	*M (SD)*	*p*-value	η^2
N	9	9		
Sex ratio (m:f)	3:6	5:4		
Handedness (L:R)	1:8	2:7		
Age	9.13 (0.34)	8.97 (0.57)	.484	0.03
3DM Word reading - *accuracy* [a]				
High Frequency	91.93 (6.81)	92.11 (7.98)	.960	0.00
Low Frequency	85.85 (13.83)	80.07 (19.27)	.476	0.03
Pseudowords	69.64 (13.71)	71.80 (19.47)	.788	0.01
Total [T][b]	31.11 (12.62)	33.56 (13.54)	.697	0.01
3DM Word reading - *fluency* [T]				
High Frequency	30.56 (4.77)	30.44 (6.31)	.967	0.00
Low Frequency	31.89 (6.31)	30.33 (6.89)	.624	0.02
Pseudowords	30.00 (5.52)	31.56 (5.79)	.568	0.02
Total	29.56 (5.36)	30.11 (6.01)	.839	0.00
One-Minute Test -*fluency* [SS][c]	3.89 (1.76)	3.00 (1.87)	.000	0.75
Text Reading - *fluency*[T]	34.78 (4.99)	31.44 (6.06)	.000	0.71
Letter-speech sound associations [T]				
LSS identificacion - *accuracy*	43.11 (11.75)	44.56 (15.33)	.825	0.00
LSS discrimination - *accuracy*	46.78 (8.83)	44.67 (8.73)	.617	0.02
LSS identificacion - *fluency*	46.11 (6.85)	45.89 (7.69)	.949	0.00
LSS discrimination - *fluency*	49.33 (10.69)	54.33 (6.38)	.246	0.08
3DM Spelling - *accuracy*[T]	38.00 (9.68)	34.22 (6.78)	.352	0.05
3DM Spelling - *fluency*[T]	41.44 (9.74)	39.78 (7.08)	.683	0.01
Phoneme deletion -accuracy[T][*]	40.88 (8.44)	37.44 (10.38)	.470	0.04
3DM Naming speed scores[T][*]				
Letters	37.13 (6.36)	37.89 (9.12)	.846	0.00
Numbers	37.88 (8.77)	35.33 (8.75)	.559	0.02
Total	34.25 (8.26)	36.00 (10.58)	.712	0.01

Note. LSS = Letter-speech sound.
[a] Raw scores. [b] T scores (M = 50, SD = 10). [c] SS scores (M = 10, SD= 3).
[*] Data missing for one participant; Responders n = 8.

Experimental task performance. For the sake of completeness, we report the outcomes of analyses of group differences and training effects with regard to the accuracy and latency measures obtained from the experimental task. There were no differences in task performance between responders and poor responders, *ps* > .168.

Accuracy. The performance accuracy data were not normally distributed. Thus, an independent samples Mann-Whitney-U test was performed to examine differences between dyslexics and typical readers at pretest. Furthermore, Wilcoxon's matched pairs signed-ranks test was used to examine differences in accuracy after training in the dyslexic group.

The percentage of correct responses (button presses to targets) at pretest was significantly larger in the typical readers relative to dyslexics, both for short words (U = 90.00, p = .008) and long words (U = 82.00, p = .004). The mean (SD) percentages of correct responses for short and long words in typical readers were, 89.38 (17.34) and 90.00 (9.60) respectively; while in dyslexics they were 74.31 (23.28) and 72.92 (22.79), respectively. Training did not alter the percentage of correct responses in dyslexics.

The percentage of false alarms (button presses to non-target stimuli) at pretest was significantly larger in dyslexics relative to typical readers for long words, U = 93.00, p = .010. The mean (SD) percentage of false alarms for long words in dyslexics and typical readers was 2.85 (4.75) and 0.38 (0.71), respectively. Finally, Wilcoxon's matched pairs signed-ranks test revealed that the percentage of false alarms in dyslexics was lower at posttest relative to pretest for long words (Z = 2.22, p = .026), and short symbols, (Z = 2.13, p = .033). The percentage of false alarms for long words at pre- and posttest was 2.85 (4.75) and 0.94 (1.26), respectively. For long words, the mean rank in favor for pretest was 9.00 and the mean rank in favor for posttest was 5.25. The percentage of false alarms for short symbols at pre- and posttest was 7.50 (5.78) and 4.39 (2.38), respectively. For short symbols, the mean rank in favor for pretest was 10.13 and the mean rank in favor for posttest was 6.30. The effect of training approached significance for short words, p = .054, indicating that the percentage of false alarms tended to be lower at post- relative to pretest for short words.

In brief, the percentage of correct responses to words was lower in dyslexics than in typical readers and this percentage did not change after training received by the dyslexics. Additionally, dyslexics at pretest emitted more false alarms to long words than typical readers. Finally, dyslexics' percentage of false alarms decreased after training for long words and short symbols.

Reaction times. Reaction times (RTs) of correct responses to target stimuli at pretest were subjected to a mixed-model ANOVA with the within-subject factors String Length and String Type, and the between-subject factor Dyslexia. None of the effects including the factor Dyslexia approached significance, *ps* > .189. Finally, a repeated-measures ANOVA was performed on the dyslexics' data including Training as a within-subject factor. The analysis revealed a significant three-way interaction

including the factors Training, String Type and String Length, F (1,17) = 6.45, p = .021, η^2 = 0.27. The effect indicated longer RTs at posttest relative to pretest for short words but not for long words, and for long symbols but not for short symbols. The mean (SD) RTs of correct responses for short words at pretest and posttest were 669.69 (238.36) and 803.92 (293.60) respectively, and for long symbol they were 582.16 (303.39) and 642.92 (248.11) respectively.

ERP Results

Training effects on N1 amplitudes. Figure 4.2 shows the ERPs and their scalp distribution (at mean peak latency for each group) for typical readers and dyslexics at pre- and posttest. N1 amplitudes discriminated between words and symbols in all groups.

Baseline. Our previous ERP study showed that N1 amplitudes for words were reduced at the left compared to the right hemisphere sites in typical readers but not in dyslexics (Fraga González et al., 2014). The current mixed-model ANOVA performed on N1 amplitudes revealed a significant three-way interaction effect including Dyslexia, Hemisphere and String Type, F (1,36) = 5.76, p = .022, η^2 = 0.14. A subsequent ANOVA on the dyslexic pretest data indicated that, consistent with our previous report, hemispheric differences in N1 amplitudes to words were absent, ps > .208, confirming that the group differences previously reported were present also in the current sample.

Training effects. A repeated-measures ANOVA including the within-subject factor Training was performed on N1 amplitudes to words. The analysis indicated that the effect of training failed to reach significance, ps > .133. In spite of the absence of a significant effect of training, we performed an ANOVA on the posttest data showing a marginally significant interaction between Hemisphere and Electrode, F (2, 42) = 2.99, p = .051, η^2 = 0.15. The interaction suggested a trend for reduced word amplitudes at the left relative to the right hemisphere that was more pronounced at P9 and P7 sites. This pattern comes close to the one obtained in typical readers. The N1 amplitudes for words at pre- and posttest are shown in Figure 4.3 for typical and dyslexic readers.

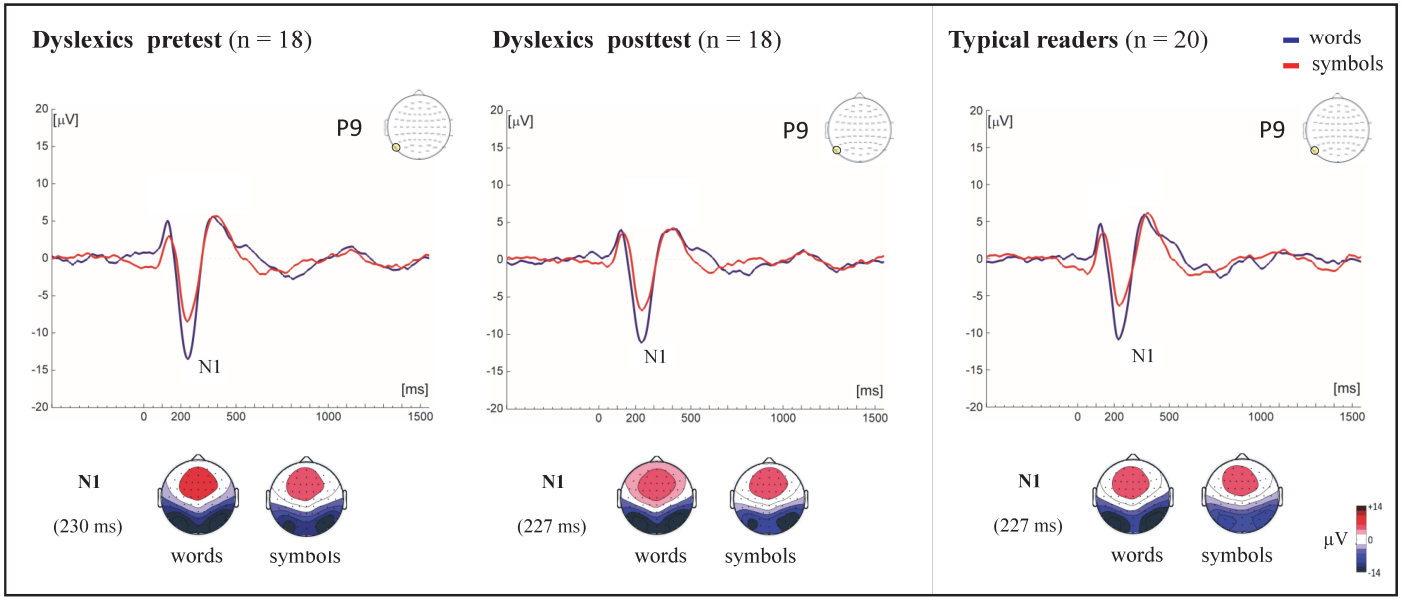


Figure 4.2. Group ERPs to word and symbol stimuli at P9. Topographical maps showing the course of neural activity following stimulus onset. Posterior activations and polarity are visible at peak latencies (group mean latencies).

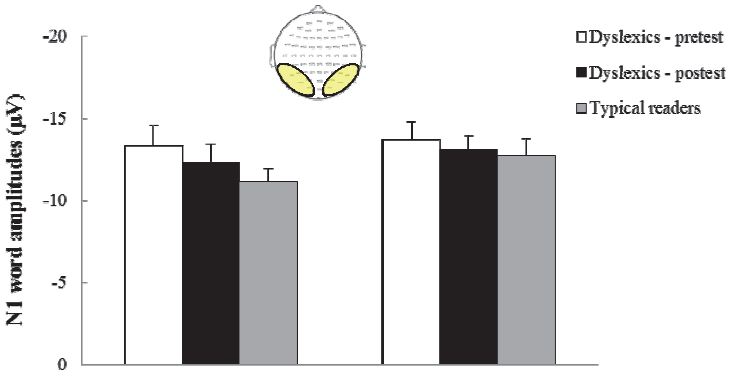


Figure 4.3. Mean N1 amplitude to words at left and right hemisphere sites in dyslexics in the pretest and posttest, and typical readers (pretest only). Left hemisphere amplitudes are averaged across TP7, P9, P7, P5, PO7, PO3 and O1 sites, and right hemisphere across their homologue pairs. Error bars show standard errors of the sample.

Relation to gains in reading fluency. We examined how individual differences in modulation of N1 responses related to gains reading fluency. The pre-/posttest difference in N1 amplitudes to words was averaged across the left hemisphere electrode sites most sensitive to training (P9, P7, PO7 and O1). This average was then included in a regression analysis relating the pre-/posttest differences to the composite score of reading fluency (see Statistical Analysis). The analysis showed a significant relation, $R = 0.53$, $R^2 = 0.28$, $\beta = -0.49$, $t = -2.49$, $p = .024$, plotted in Figure 4.4 This figure illustrates a positive relation between gains in reading fluency and the decrease in N1 amplitudes to words across the left hemisphere occipito-temporal region. This relation was not significant in a control analysis including right hemisphere sites, $p > .133$.

Responsiveness. Repeated measures ANOVA including the within subject factor Training were performed on N1 amplitudes for words in responders. Interestingly, the analysis revealed a significant main effect of Training, F (1, 8) = 7.30, $p = .027$, $\eta^2 = 0.48$, indicating reduced N1 amplitudes across both hemispheres for the posttest relative to the pretest. This result is shown in Figure 4.5. The responders mean (SD) amplitude for words at pre- vs. posttest were 15.70 (3.36) and 14.01 (2.87), respectively. The subsequent control analysis on the data obtained from poor responders did not reveal an effect of Training, $ps > .192$.

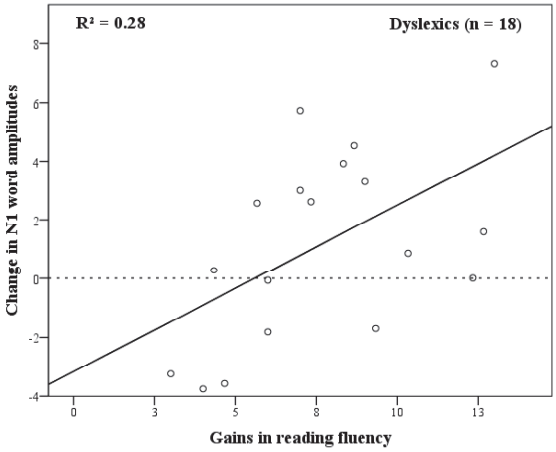


Figure 4.4. Linear regression between post-pretest change in N1 amplitudes to words at the left posterior electrodes (average of P9, P7, PO7 and O1) and gains in reading fluency (average of 3DM high and low frequency word reading and One minute test). A change towards positive values along the y-axis refers to a decrease in N1 amplitude.

Secondly, we examined whether initial N1 amplitudes could discriminate between responders and poor responders to training. The analysis revealed a significant main effect of Responsiveness, F (1, 16) = 6.34, p = .023, η^2 = 0.28, indicating larger word N1 amplitudes in responders relative to poor responders across both hemispheres (see Figure 4.5). The mean (SD) word amplitudes at pretest for responders and poor responders were 15.70 (3.36) and 11.30 (4.01), respectively.

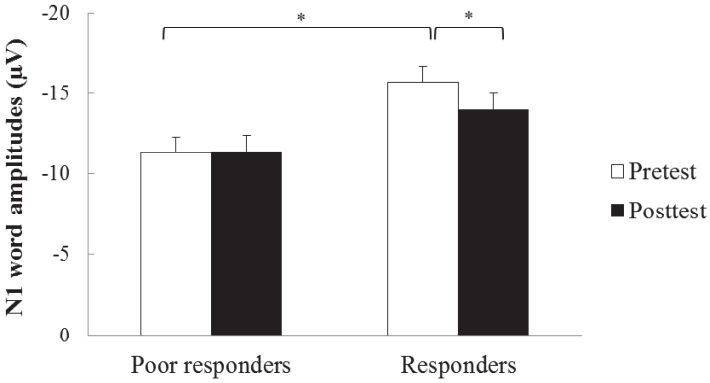


Figure 4.5. Mean N1 amplitudes for words averaged across all electrode pairs (O1-O2, PO7-PO8, PO3-PO4, TP7-TP8, P9-P10, P7-P8, P5-P6) for poor responders and responders. Open bars refer to pretest N1 amplitudes for words and filled bar to posttest amplitudes

4.4 Discussion

The aim of this study was threefold. First, we examined training effects on N1 responses. Previously, we found reduced N1 amplitudes for words at the left vs. right hemisphere in typical readers but not in dyslexics. We expected that this lateralized pattern would emerge in our dyslexic sample after training. The second goal of this study was to examine the relation between changes in N1 and reading fluency gains after training. Third, we expected to find differences in between those children who benefited from training and those who did not in their modulation of N1 amplitudes. Additionally, we examined whether initial N1 amplitudes could be used as predictor of intervention outcomes.

The analysis of reading measures showed gains after training that were more pronounced in word reading fluency measures than in accuracy measures. The current results are in line with our previous studies showing that training automation in letter-speech sound (LSS) mapping can successfully improve reading fluency in dyslexia (Tijms et al., 2003; Tijms, 2011). Knowledge of LSS correspondences is essential at the initial stages of reading acquisition as they enable to link spelling of written words to their pronunciation (Ehri, 2002). Importantly, automation of these associations appears to be crucial to enable the neural tuning required for fast and effortless word decoding, and demands much longer time than the initial passive knowledge of them (Blomert, 2005; Sprenger-Charolles et al., 2006). As a consequence, if letter-speech sound correspondences are not optimally automated, children fail to acquire typical levels of reading fluency. In relation to this, recent neuroimaging and cognitive studies of dyslexia suggest a deficit in LSS mapping fluency rather than in accuracy (Aravena et al., 2013; Blomert, 2011; Froyen et al., 2011). This might explain why conventional interventions for dyslexia, which are focused on accurate LSS learning without directly addressing automation, are still unable to efficiently improve reading fluency (Alexander & Slinger-Constant, 2004; Gabrieli, 2009; Wolff, 2011). The present training targeted both explicit knowledge and automaticity of LSS correspondences through intensive and repetitive practice, intended to account for the time demands of audiovisual integration (Froyen et al., 2009). The current improvements in reading fluency after this training demonstrate the utility of including automation in LSS mapping as a key remedial element to address the fluency barrier in dyslexia.

The primary goal of this study was to examine changes in N1 responses in dyslexics after training LSS mapping fluency. In a previous study we observed that N1 amplitudes for words were reduced at the left vs. right hemisphere in typical readers, while no lateralization effect was found in dyslexics (Fraga González et al., 2014). The present baseline analysis showed the same deviant pattern in N1 in the current sample of dyslexics, that is, dyslexics showed no lateralization effect in N1 amplitudes for words as opposed to typical readers. Importantly, this result suggests that previous findings were robust and reliable. The results were interpreted to suggest facilitated lexical access in typical readers that is absent or diminished in dyslexics. The interpretation that lower amplitudes in typical readers may reflect

less effortful decoding is supported by studies indicating lower responses in high frequency vs. low frequency words (Assadollahi & Pulvermüller, 2003; Hauk & Pulvermüller, 2004) and real words vs. pseudohomophones or pseudowords (Araújo, Faísca, Bramão, Reis, & Petersson, 2015). Moreover, two fMRI studies reported a lack of such orthographic familiarity effects in occipito-temporal regions in dyslexics relative to typical readers, in children (van der Mark et al., 2009) and adults (Wimmer et al., 2010). The later studies suggest that visual specialization at the whole-word level may be deficient in dyslexia. In this line, the lack of a left-lateralized reduction of N1 amplitudes in dyslexics in the current study may reflect more demanding /less facilitated word decoding in contrast to typical readers. This deficit is indicated by reading measures showing dysfunctional word reading in dyslexics (see Table 4.1). Additional support for the relation between magnitude of N1 amplitudes and decoding effort is provided by the association found in the present study between training effects on N1 and gains in reading, which is discussed below.

The overall analysis of training effects, including all dyslexic participants, failed to show changes on N1 amplitudes for words after the training. However, the separate analysis of the posttest data showed a response pattern in dyslexics that tended to be more similar to that of typical readers (see Figure 4.3). The pattern emerging in dyslexics after intervention showed reduced N1 amplitudes for words at the left hemisphere vs. right hemisphere, but only in some electrode sites. In line with the current trend, an ERP-source analysis study in dyslexic children found that N1 responses during a phonological, semantic and orthographic task, were initially equally distributed across hemispheres and became left-lateralized after a phonological training (Spironelli, Penolazzi, Vio, & Angrilli, 2010). However in that study, as opposed to the present results, the lateralization pattern showed by typical readers and by dyslexics after training consisted of stronger N1 responses at left vs. right hemisphere. Similarly, other neuroimaging remediation studies reported normalization after intervention, i.e., initially deviant responses in dyslexics became comparable to those in typical readers, in parieto-temporal areas (Aylward et al., 2003; Meyler, Keller, Cherkassky, Gabrieli, & Just, 2008; Shaywitz et al., 2004; Simos et al., 2007; Temple et al., 2003) and occipito-temporal areas (Aylward et al., 2003; Heim et al., 2014). Most of these studies reported larger responses in typical readers compared to dyslexics, which is in apparent discrepancy with the pattern of responses in the current study. However, differences in task, type of intervention and imaging techniques make difficult to explain differences across studies (Heim et al., 2014). Importantly, those studies, together with the current trend, provide with evidence for differences in brain responses between typical readers and dyslexics that are diminished after intervention.

The second finding of the current study pertains to the relation between the conjoint training effect on reading measures and N1 amplitudes. Larger gains in reading fluency were associated with larger reduction of N1 amplitudes for words at the left hemisphere (see Figure 4.4). No relation was found at

the right hemisphere. This finding supports the validity of N1 as a neural correlate of reading expertise; N1 responses in the left occipito-temporal electrode sites are proposed to reflect the activity of the VWFA which specializes for fast word recognition (Dehaene et al., 2015; McCandliss et al., 2003). Previously, studies linked N1 amplitudes and reading abilities in children and adults, with and without dyslexia (Fraga González et al., 2014; Korinth et al., 2012; Maurer et al., 2006, 2007). Importantly, it has been suggested that in typical reading acquisition, strong visual responses emerge after the first years of instruction and later become smaller and more left lateralized as expertise develops (Maurer et al., 2006). This inverted 'U' development of visual expertise is supported by the current association between a decrease in visual responses at the left hemisphere and improvements in reading fluency. This relation also supports the previously discussed interpretation of the lateralized pattern found in typical readers that relates lower neural responses to facilitated decoding.

In addition, the current training is focused on fluency of LSS associations, thus it is expected to directly influence the parieto-temporal system responsible for multisensory integration. Previous research has suggested that the multimodal association system for reading supports the specialization of visual areas (Sandak et al., 2004; Schlaggar & McCandliss, 2007). Accordingly, studies found that specialization of occipito-temporal areas to print was absent in kindergarten (Brem et al., 2010) but becomes apparent once children learn grapheme-phoneme correspondences (Maurer & Mccandliss, 2003). The present results are in line with such an interactive account, as the LSS training modulated visual N1 responses at the proximity of the VWFA. Interestingly, a recent study showed that selective attention to grapheme-phoneme correspondences during learning of a novel script lead to left-lateralization of N1 responses (Yoncheva, Wise, & McCandliss, 2015). In that study, Yoncheva and colleagues trained literate adults on two novel scripts with different learning requirements; one required to link each letter to a sound and the other required memorizing whole words and prevented grapheme-phoneme decoding. The grapheme-phoneme learning group showed larger N1 responses at the left vs. right hemisphere in a word verification task after training, but this pattern was absent in the whole-word learning condition (Yoncheva et al., 2015). Importantly, the results of Yoncheva and colleagues, as well as current findings underscore the interactive role of audiovisual mapping in shaping the specialization of visual areas.

Thirdly, this study looked at differential training effects on N1 between responders and poor responders Subjects were classified as responders or poor responders based on a median-split performed on standardized word reading fluency scores (see Behavioral Analysis). We chose word reading fluency for classification because of the focus on improving fluency of the current training. Regarding the training effects on N1, responders showed a bilateral decrease of N1 amplitudes for words after training. Interestingly, no effect of training was found in poor responders. In accordance with the previous interpretation relating smaller N1 amplitudes to less effortful decoding, the present

result may indicate facilitated reading in responders after training. Similarly, previous studies reported greater normalization of neural activity in responders relative to poor responders (Davis et al., 2011; Molfese et al., 2013; Odegard et al., 2008). In addition, one study found normalization in those participants showing larger improvements after training, while compensatory activity was found in those who did not improve reading (Simos et al., 2007). In the current results, responders did not show lateralization of N1 amplitudes, similarly to typical readers, at the posttest, thus indicating that neural abnormalities persist after training. This would be in in line with the behavioral results showing that despite significant gains in reading speed, responders still remain dysfluent in comparison with typical readers.

Most importantly, we examined the additional value of N1 in predicting treatment response. Interestingly, baseline N1 amplitudes for words could discriminate between responders and poor-responders, while both groups did not differ in their initial reading performance. N1 amplitudes in poor responders (which did not change after training) and were initially smaller relative to responders, while no group difference were found in any of the reading fluency or accuracy measures (see Table 4.3). The current pattern of findings is consistent with the results of a previous MEG study by Rezaie et al. (2011). The authors observed under-activation of the ventral occipitotemporal areas in struggling readers that did not benefit from an intervention in middle school compared to those who improved reading (Rezaie et al., 2011a). The authors suggested that lower activations in inadequate responders may relate to a more severe deficit in the overall functionality of the reading network that may prevent its adaptation after remediation. Moreover, that result was supported by another MEG study which also found N1 amplitudes across hemispheres to be lower in inadequate compared to adequate responders (Molfese et al., 2013). Similarly, the current finding of smaller bilateral N1 responses in the poor responders may indicate a more global deficit less responsive to remediation. In addition, strong visual responses are proposed to emerge after the first years of instruction reflecting coarse specialization to print (e.g., to letter vs. symbol) and to later become smaller and more left lateralized as expertise develops (Maurer et al., 2006). The stronger visual responses in the initial stages of acquisition have been suggested to relate to early perceptual learning and top-down predictions from phonological areas (Price & Devlin, 2011). Accordingly, in the present study, the initially smaller N1 amplitudes for words in poor responders may also indicate that they lag behind or follow a different trajectory than responders in their perceptual learning processes. This could explain why their visual responses do not sufficiently benefit from with visual system and LSS integration areas, which are arguably tackled by present training.

An alternative consideration of the initial N1 differences between responders and poor responders is that related to attentional strategies during the task. Previous research has demonstrated the role of attention in early visual components such as N1 (see review in Luck, Woodman, & Vogel, 2000). Thus

it is possible that initially larger N1 amplitudes in responders reflect different attentional processes (i.e. poorer orthographic processing) that facilitate reading once LSS mapping becomes automated. Interestingly, a previous ERP study found that paying attention to orthographic cues may enhance early visual responses relative to when phonological cues are attended (Ruz & Nobre, 2008). Further, phonological processing during task might not be sufficiently constrained in visual paradigms such that in the present study (Kronschnabel et al., 2013). Several studies, showed that occipito-temporal responses can be modulated by phonological or semantic processing during task (Price & Devlin, 2011; Twomey, Kawabata, Price, & Devlin, 2011) and by differences in the way stimuli are encoded during learning (Song, Hu, Li, Li, & Liu, 2010; Yoncheva et al., 2015).

At this point, it is important to note that neither responders nor poor responders showed lateralization effects of N1 amplitudes to words in contrast to typical readers. In relation to this, Okumura and colleagues examined the influence of attention on N1 responses in adults in a Japanese syllabic and transparent script (Okumura, Kasai, & Murohashi, 2014; Okumura et al., 2015). The first study showed that N1 amplitudes for words were not left lateralized when stimuli were task irrelevant and presented in rapid sequences (Okumura et al., 2014). That result was interpreted to reflect restricted linguistic processing during the task. A second study, requiring more active attention to stimuli, found left-lateralized N1 responses to words that became bilateral when intercharacter spacing was enlarged so as to require serial reading (Okumura et al., 2015). That result was interpreted to indicate diminished phonological processing when a serial application of attention was required due to large intercharacter spacing. Similarly, a fMRI study suggested an increasing influence of dorsal attentional mechanisms in the visual system when word reading difficulty was manipulated (Laurent Cohen, Dehaene, Vinckier, Jobert, & Montavont, 2008). Additionally, as discussed above, lateralization of visual responses were also found to be sensitive to attention to grapheme-phoneme vs. whole-word when encoding stimuli (Yoncheva et al., 2015). Collectively, these studies suggest that besides VWFA specialization for reading, attention and decoding strategies have a significant impact in lateralization and strength of N1 responses. In view of this, the fact that the initial N1 differences between responders and poor responders were found across both hemispheres favors the possibility that more general visual attentional strategies may have contributed to this result.

An apparent limitation of the current study refers to its design. The present design did not allow for disentangling the effects of training from those related to the passage of time. It is unlikely, however, that the passage of time would provide an explanation for the current pattern of results. First, and most importantly, both responders and poor responders were measured at the same time points and thus were equally susceptible to be influenced by the time elapsed between tests. Although this does not exclude the possibility of different sensitivities to time between the groups, overall, general maturation is unlikely to provide a convincing explanation for the observed changes in N1. Secondly, we presented

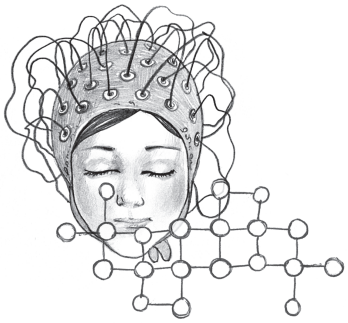
high frequency words that are already well known also for dyslexics thus adaptation of neural responses to these overlearned and already familiar stimuli within less than half a year do not seem the most likely explanation for the observed changes in N1 (Maurer et al., 2005). Thirdly, it has been suggested that the strongest changes in visual responses take place in the earlier stages of reading acquisition, thus before the current age (Brem et al., 2010; Maurer et al., 2005; Price & Devlin, 2011). Moreover, a previous longitudinal study indicated that visual specialization to print may emerge under several years of reading instruction, i.e. from kindergarten to 2nd grade (Maurer et al., 2006).

Conclusion

The present study demonstrates the sensitivity of N1 amplitudes for words as neural marker for intervention responsiveness in dyslexics. First, we found a trend towards normalization of N1 responses showing a pattern that became more similar between typical readers and dyslexics in the posttest. Secondly, the association between left-lateralized decrease in N1 amplitudes and gains in reading fluency credits the validity of N1 as a neural measure of reading ability. Thirdly, we found a dissociation between N1 and reading scores in their ability to discriminate between responders and poor responders at pretest, which illustrates the additional value of neural markers such as N1 in predicting treatment outcomes. In brief, the present results suggest that a well-stablished neural marker such as N1 are able to identify individual differences in treatment responsiveness that are not revealed by behavioral tests (Leppänen, 2013). These findings are in line with previous studies of reading accounting for the predictive value of neurophysiological responses to outcome of intervention (Brem et al., 2013; Hasko et al., 2014; Lemons et al., 2010; Molfese et al., 2013). Additionally, our results support the clinical potential of training LSS mapping fluency in dyslexia and the interaction between multimodal integration and visual specialization to print. The present study extends current evidence relating N1 specialization with reading expertise, and provides additional evidence for this relation in 3rd grade dyslexics that showed improvements after training LSS integration. Our results underscore the value of N1 in predicting treatment outcomes. Finally, our findings also underline the importance of accounting for individual differences in response to training within dyslexics.

Chapter 5

Graph Analysis of EEG Resting State Functional Networks in Dyslexic and Typically Reading Children



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Abstract

Neuroimaging research suggested abnormalities in the organization of functional networks in developmental dyslexia. The current study examined the differences in the topological properties of brain networks between dyslexics and typically reading children (3rd grade) using graph analysis. Minimum spanning tree graphs, derived from phase lag index (PLI) weighted connectivity matrices in EEG resting-state data, revealed group differences in the theta band. More specifically, relative to typical readers, neural network organization in dyslexics could be characterized by a lower leaf fraction, indicating less network integration, and higher diameter together with a trend for higher eccentricity, pointing to less communication between network nodes. Collectively, our findings point to a less efficient network configuration (more line-like tree) in dyslexics relative to the more proficient configuration (more star-like tree) in typical readers.

5.1 Introduction

Reading involves integrated functioning of complex brain networks. Distinct brain systems, mostly in the left hemisphere, have been proposed to specialize during reading acquisition (see a review in Schlaggar & McCandliss, 2007). Studies in developmental dyslexia revealed various disturbances of the brain networks implicated in reading. Studies using diffusion tensor imaging (DTI) to examine white matter properties of the main pathways that constitute the anatomical basis of the network reported reduced connectivity in dyslexia (for a review and meta-analysis Vandermosten, Boets, Wouters, & Ghesquière, 2012). Similarly, a score of functional magnetic resonance imaging (fMRI) studies in adults reported reduced connectivity of the reading network (e.g., Pugh et al., 2000; Quaglino et al., 2008; Schurz et al., 2014; Shaywitz et al., 2003; Stanberry et al., 2006; Van der Mark et al., 2011; but see Richards & Berninger, 2008) and other connectivity disturbances (Finn et al., 2014; R. C. Wolf et al., 2010). A recent MRI study examining the topological organization in Chinese dyslexic children revealed a less integrated network organization relative to typical readers, characterized by increased local processing and less long-range communication (Liu et al., 2015).

The goal of the current study was to examine functional network connectivity and organization in developmental dyslexia using the electroencephalogram (EEG). EEG studies examining functional connectivity during task performance yielded a mixed pattern of results. Some studies reported reduced or more diffuse EEG coherence in poor relative to typical readers (Dhar et al., 2010; Nagarajan & Mahncke, 1999) while other studies observed increased coherence in dyslexics compared to normal readers (Arns & Peters, 2007; Shiota et al., 2000) or a mixed pattern; that is, increased coherence for some EEG bands and reduced coherence for other bands (Marosi et al., 1995). In addition, fMRI studies on resting-state data revealed relations between resting-state functional connectivity across the reading network with reading abilities in children and adults (Koyama et al., 2011, 2013; Schurz et al., 2014; Zhang et al., 2014). Other studies linked the strength of resting-state connectivity between the visual word recognition areas and the dorsal attention network to age and reading skills (Vogel et al., 2012, 2014). The latter studies attest to the utility of resting-state data to characterize the functional reading network (Hampson et al., 2006; Koyama et al., 2010).

In the current study we used graph analysis, which allows for modeling the organization of resting-state whole-brain functional connectivity networks during development (Stam, 2014). A 'graph' refers to an abstract representation of a network, consisting of a set of nodes (vertices) and connections between them (edges). Various graph measures allow for characterizing graph topologies in terms of the efficiency of information transfer and an optimal balance between 'segregation' and 'integration' (see reviews in Bullmore & Sporns, 2009; Bullmore & Sporns, 2012). Thus, a 'small-world' network topology, characterized by a high clustering (related to high local connectedness and robustness) and a short path length (related to high global efficiency) has been proposed as a plausible configuration of

highly efficient brain networks (Bassett & Bullmore, 2006). This topology combines features from ordered or regular networks (high clustering) and random networks (short path length).

A recent development in graph theory refers to minimum spanning tree (MST) analysis (Stam et al., 2014). A tree is a loop-less sub-graph derived from a weighted connectivity matrix, with a fixed number of nodes and edges. The advantage of MST analysis over conventional graph procedures is that it minimizes bias when performing direct comparisons between groups and experimental conditions (Tewarie, Van Dellen, Hillebrand, & Stam, 2015). There are two extreme tree topologies; path- and star-like configurations. Path-like configurations consist of nodes that are all linked to two other nodes with the exception of the nodes at either end of the path. Nodes with only one link in a tree are referred to as 'leaf' nodes (or leaves) and the number of those nodes in a tree is the leaf number. Thus a path has a leaf number of two. In contrast, star-like configurations consist of a central node connected to all other nodes with only one link. Thus, a star consisting of N nodes has a leaf number of N-1. Many different tree topologies are in between the two extreme configurations and they can be characterized using a variety of metrics (review in Van Mieghem, 2014). We will apply the tree measures that have been applied previously in EEG studies (see Methods section below).

The MST analysis has been successfully applied to EEG data from different populations. A relatively early study indicated that patients with left vs. right temporal epilepsy could be reliably discriminated in terms of large scale functional networks emerging just prior to the onset of seizures (Lee, Kim, & Jung, 2006). More recently, Fraschini et al., 2014 examined the effects of vagal nerve stimulation in patients with pharmaco-resistant epilepsy. MST analysis yielded a clear differentiation between responders vs. non-responders. Vagal nerve stimulation shifted the network towards a more star-like network architecture in responders but not in non-responders. Van Diessen et al., 2014 examined the effect of sleep deprivation on EEG networks in children diagnosed with focal epilepsy. MST analysis revealed a shift to a more path-like topology after sleep deprivation in children with focal epilepsy whereas a shift towards a more star-like configuration was observed in controls. Vourkas et al., 2014 performed a MST analysis on the EEG recorded in children with mathematical difficulties and typical controls during the performance of tasks with increasing difficulty. Although group differences were absent in this study the MST parameters suggested a more centralized and integrated network layout in the alpha bands of the EEG with increasing task demands. Most relevant to the present study, Boersma et al., (2013) applied MST analysis to resting-state EEG data of a large sample of 5- and 7-years old children. Developmental change was observed for the EEG alpha band. More specifically, the MST analysis yielded increases in diameter and eccentricity with advancing age while leaf number, degree and hierarchy decreased. This pattern of results was interpreted to suggest a more integrated network configuration in the 7- compared to the 5-years olds.

Collectively, the MST studies suggest MST analysis may provide a sensitive tool to assess condition or group differences in network configuration. The goal of the current study was to assess potential differences in network configuration between children with dyslexia and typically reading children. Previously, graph analysis of magnetoencephalogaphic (MEG) data in dyslexic children and controls showed task-dependent dysfunctional long- and short-range functional connectivity in the dyslexic children (Vourkas et al., 2011). Another graph analysis from the same group of MEG data obtained during rest revealed less organized network configuration in dyslexic children (Dimitriadis et al., 2013). The current study will extend these findings by focusing on resting state EEG data and by performing a MST analysis on these data. MST analysis goes beyond more conventional network analysis as (i) it allows an unbiased network representation; (ii) it provides a comparison between groups/conditions that is normalized; and (iii) it integrates features of small-worldness (clustering/ path length) and scale-freeness (hubs) (e.g., Tewarie et al., 2015).

5.2 Methods

Participants

Twenty-nine third-grade dyslexic children (Mean age = 8.46; SD= 0.40) were recruited from a nation-wide center for dyslexia in the Netherlands.[3] All dyslexic children had a percentile score of 10 or lower on a standard reading test and they participated in the EEG recordings before starting their treatment program at the center. A group of 15 third-grade, typical readers (8.75 ± 0.31 years old) was recruited from several primary schools attended by children with the same socio-demographical background as the dyslexic group (see Table 5.1 for group characteristics). They had no history of reading difficulties and had a percentile score of 25 or higher on standard reading tests (see below). All participants were native Dutch speakers, received two and a half years of formal reading instruction in primary education. Children with below average IQ (IQ < 85 on a non-verbal IQ-test), uncorrected sight problems, hearing loss, diagnosis of ADHD or other neurological or cognitive impairments were excluded. The study was approved by the Ethical Review Board of the University and all parents or caretakers signed informed consent before the children participated.

Behavioral Measurements

A series of tests was used to assess the reading skills of the participants (Gonzalez et al., 2014). The children took the tests at their school.

[3] The current participants are part of a larger sample of 62 children taking part in the EEG recordings. From the original data set, resting-state data was not available for 3 participants due to complications during recording. Moreover, data from 6 participants were excluded due to excessive artifacts. In the remaining data (N= 53), the inspection of individual peak frequencies in the average spectra indicated that for the majority of participants the peak frequency fell within the low alpha (8-10 Hz) and high alpha (10-13 Hz) range (see Spectral Power section). We discarded data from children with a peak frequency equal or lower than 8 Hz as this might bias subsequent analysis in the lower frequency bands. A total of 9 subjects were excluded; 5 dyslexics (N=29) and 4 typical readers (N = 15). Demographic characteristics and reading scores of the complete sample are included in Appendix C.

Word reading skills were measured using a Dutch version of the *One-minute test* (*Een-Minuut-Test*, EMT; Van den Bos, Spelberg, Scheepsma, & De Vries, 1999), a time-limited test consisting of a list of 116 unrelated words of increasing difficulty. The number of correctly read words within 1 minute serves as reading fluency score. Text reading fluency was assessed also using a test consisting of a coherent text of increasing difficulty. The children were asked to read the story out loud within 1 minute (*Schoolvaardigheidstoets Technisch Lezen;* de Vos, 2007). In addition, the 3DM battery of tests (test reliability information available in *Dyslexia Differential Diagnosis*; 3DM, Blomert & Vaessen, 2009) was individually administered. The scores of the following 3DM subtests were used. *Word Reading task*: contains visually presented high-frequency words, low-frequency words and pseudowords. Accuracy (% correct) and fluency (correct words in 1 minute) were measured. *Rapid automatized naming (RAN):* blocks of letters or numbers are presented and items have to be read as fast and accurately as possible. Fluency is the time in seconds needed to name a screen of 15 items. *Letter-speech sound (LSS) association tasks*: consist of identification and discrimination tasks. In the identification task an aurally presented speech sound has to be matched to one out of four visually presented letters. In the discrimination task the child has to judge whether the speech sound and letter on the screen are congruent or incongruent. *Computerized Spelling:* words are aurally presented and visually displayed on screen with missing letters. Participants have to select the missing letter out of four alternatives. For the last two subtests, accuracy (% correct) as well as response time (sec/item) is measured.

Finally, the *RAVEN Coloured Progressive Matrices* was used to obtain an estimate of fluid IQ (RAVEN CPM; Raven, Raven, & Court, 1998) and the Child Behavior Checklist (CBCL) was completed by the parents to exclude any additional behavioral problems (Achenbach et al., 2008).

Table 5.1. Sample characteristics and descriptive statistics showing reading accuracy and fluency scores

	Typical Readers	Dyslexics		
	M (SD)	*M (SD)*	*p*-value	η^2
N	15	29		
Sex ratio (m:f)	6:9	16:13		
Handedness (L:R)*	2:10	2:27		
Age	8.75 (0.31)	8.96 (0.40)	.088	0.07
RAVEN - IQ test [a]	6.70 (1.51)	7.11 (1.51)	.395	0.02
3DM Word reading - *accuracy* [b]				
High Frequency	99.28 (1.05)	93.10 (5.93)	.000	0.27
Low Frequency	98.32 (2.54)	86.31 (14.48)	.003	0.19
Pseudo	88.70 (8.48)	73.33 (17.43)	.003	0.20
Total [T][c]	51.40 (8.00)	33.72 (12.58)	.000	0.37
3DM Word reading - *fluency* [T]				
High Frequency	54.27 (7.58)	31.38 (6.14)	.000	0.74
Low Frequency	56.80 (8.98)	32.07 (6.46)	.000	0.72
Pseudo	54.93 (9.71)	30.93 (6.37)	.000	0.70
Total	55.93 (9.51)	31.00 (5.40)	.000	0.75
One-Minute Test -*fluency* [SS][d]	12.07 (2.94)	3.97 (1.97)	.000	0.74
Text Reading - *fluency*[T]**	55.27 (8.41)	33.21 (6.30)	.000	0.70
3DM Spelling - *accuracy*[T]	51.73 (8.62)	36.21 (6.70)	.000	0.51
3DM Spelling - *fluency*[T]	54.33 (9.90)	36.55 (6.01)	.000	0.57
3DM Phoneme deletion - *accuracy* [T]**	53.73 (8.39)	39.61 (8.32)	.000	0.41
Letter-speech sound associations [T]				
L-SS identificacion - *accuracy*	46.87 (8.65)	43.34 (12.99)	.350	0.02
L-SS discrimination - *accuracy***	50.80 (10.28)	44.43 (9.63)	.050	0.09
L-SS identificacion - *fluency*	51.53 (7.67)	41.79 (6.97)	.000	0.30
L-SS discrimination - *fluency***	51.73 (7.36)	45.46 (8.95)	.025	0.12
3DM Naming speed scores[T]**				
Letters	50.93 (6.95)	36.57 (8.05)	.000	0.45
numbers	52.73 (10.67)	36.21 (8.50)	.000	0.43
Total	50.80 (7.73)	35.54 (9.15)	.000	0.42

[a] C scores (M = 5, SD = 2).[b] Raw scores. [c] T scores (M = 50, SD = 10). [d] SS scores (M = 10, SD= 3)
*Data missing for 3 participants; Typical N = 12. ** Data missing for one participant; Dyslexics N = 28.

Procedure and Equipment

EEG recordings were taken within a period of around 4 months and took place in a video-controlled, dimly lit and air conditioned laboratory room. The participant and a lab assistant were together at all times in the room while the experimenter controlling the recording was in an adjacent room. The 2 minutes eyes-closed resting-state baseline was recorded at the beginning of a longer experimental session (around 2 hours long, including visual and audiovisual tasks). Children were instructed to keep their eyes closed and, when ready, to make a button press to initiate the eyes-closed resting state EEG recording. Participants were monitored at all times to ensure they complied to the instructions during the baseline recording.

EEG Recording and Signal Processing

The EEG data were collected using a 64 channels Biosemi ActiveTwo system (Biosemi, Amsterdam, Netherlands). EEG was recorded DC (low-pass: 5th order sync digital filter) with a 1024 Hz sample rate. The Biosemi system uses two additional electrodes (Common Mode Sense [CMS] and Driven Right Leg [DRL]) creating a feedback loop to replace the conventional ground electrode (see www.biosemi.com/faq/cms&drl.htm for details). The CMS electrode served as online reference. The 64 electrodes were distributed on the scalp according to the 10-20 International system and applied using an elastic electrode cap (Electro-cap International Inc.). Six external Flat-Type Active electrodes were used; four electrodes for recording the vertical and horizontal electro-oculogram (EOG) and two electrodes were placed at mastoids for off-line reference.

Continuous EEG data were imported in EEGLAB v.11.0.0.0b (Delorme & Makeig, 2004), an open source toolbox for Matlab (Mathworks, Inc.), using the averaged mastoids as initial off-line reference. A two minutes long epoch was selected, time-locked to the button press indicating the start of the eyes-closed resting-state recording.

The 2 min EEG epoch was imported in Brain Vision Analyzer (Version 2.0.1.5528, © Brain Products) for further preprocessing. After importing, spline interpolation was applied to channels with excessive artifacts. In the typical readers group, interpolation was applied to data from 10 subjects (a maximum of 5 electrodes in one subject); in the dyslexic group interpolation was applied to data from 8 subjects (a maximum of 5 electrodes in one subject). Data were segmented in 30 epochs of 4 s (4096 sample points per epoch). The epochs were visually inspected for eye blinks or muscle artifacts. For each subject 10 artifact-free epochs were selected and exported to ASCII files. The artifact-free epochs of 4 s were imported in Brainwave v0.9.117 (developed by C.S.; freely available at http://home.kpn.nl/stam7883/brainwave.html) where data were re-referenced to the average of all scalp channels before performing spectral power analysis, functional connectivity and MST metrics.

For the analysis of connectivity strength (measured with phase lag index; see Functional Connectivity section), besides mean connectivity, the following sub-averages were calculated: frontal (including the electrodes Fp1, Fp2, AF3, AF4, AF7, AF8, F1, F2, F3, F4, F5, F6, F7 and F8); central (including the electrodes FC1, FC2, FC3, FC4, FC5, FC6, C1, C2, C3, C4, C5, C6, CP1, CP2, CP3, CP4, CP5 and CP6); temporal (including the electrodes FT7, FT8, T7, T8, TP7 and TP8) and parietal-occipital (including the electrodes O1, O2, PO3, PO4, PO7, PO8, P1, P2, P3, P4, P5, P6, P7, P8, P9 and P10). The mean connectivity between the electrodes included in each sub-average was calculated. These sub-averages were chosen to examine strength of both short-range and long-range connectivity across broad cortical regions that previous studies have found relevant to reading and dyslexia. Note that the graph measures, which are the main focus of the present analysis, were derived from the complete connectivity matrix including the 64 scalp electrodes.

Spectral Power

Spectral power was calculated for all EEG channels using Fast Fourier Transformation (FFT) in Brainwave, with a frequency resolution of 1 / 4 s = 0.25 Hz. The relative power values were calculated for the following frequency bands: delta (0.5-4 Hz), theta (4-8 Hz), alpha (8-13 Hz), beta (13-30 Hz) and gamma (30-48 Hz). The broad alpha range was used instead of the lower alpha (8-10 Hz) and upper alpha (10-13 Hz) as some participants showed an average peak frequency within the upper alpha range. Power values were averaged over epochs.

Functional Connectivity

The Phase Lag Index (PLI) was used to calculate functional connectivity between all 64 electrodes for each frequency band separately. The PLI measures phase synchronization based on the asymmetry of the distribution of instantaneous phase differences between two signals, which is determined using the analytical signal based on the Hilbert transformation (Stam, Nolte, & Daffertshofer, 2007). The PLI is less sensitive to common sources since the zero-lag synchronization is removed from the analysis (Porz, Kiel, & Lehnertz, 2014). Furthermore, the PLI quantifies the relative phase distribution's asymmetry; that is, that the likelihood that the phase difference $\Delta\phi$ will be in the interval $-\pi < \Delta\phi < 0$ is different from the likelihood that it will be in the interval $0 < \Delta\phi < \pi$. This implies the presence of a consistent, nonzero phase difference ('lag') between two time series. The distribution is expected to be symmetric if there is no coupling or if the median phase difference is equal to or centers around a value of 0 mod π. The PLI is obtained from time series of phase differences $\Delta\phi\ (t_k)$, k=1…N by means of:

$$\mathrm{PLI} = |\langle \mathrm{sign}[\sin(\Delta\phi(t_k))]\rangle|$$

Here sign is the signum function. The PLI ranges between 0 and 1. A PLI of zero indicates either no coupling or coupling with a phase difference centered around 0 (mod π). A PLI of 1 indicates

perfect phase locking at a value of $\Delta\phi$ different from 0 (mod π). The stronger this nonzero phase locking is, the larger PLI will be.

Minimum Spanning Tree

The Minimum Spanning Tree (MST) sub-graph was calculated for each PLI matrix. A schematic of the analytic steps is shown in Figure 5.1. The MST is a unique sub-graph based on a weighted matrix that connects all nodes of the network but does not contain circles or loops. The MST always contains $m = N\text{-}1$ links, where N is the number of nodes. The MST was constructed by applying Kruskal's algorithm (Kruskal, 1956). This algorithm orders the distance of all links in an ascending order followed by the construction of the MST with the link of the shortest distance, and then adding the following shortest distance link until all nodes are connected in a loop-less sub-graph. If adding a new link results in the formation of a cycle, this link is skipped. In the current case, we use a maximum spanning tree, which is equivalent to an MST based upon 1-PLI, which represents the sub-network with maximum connectivity.

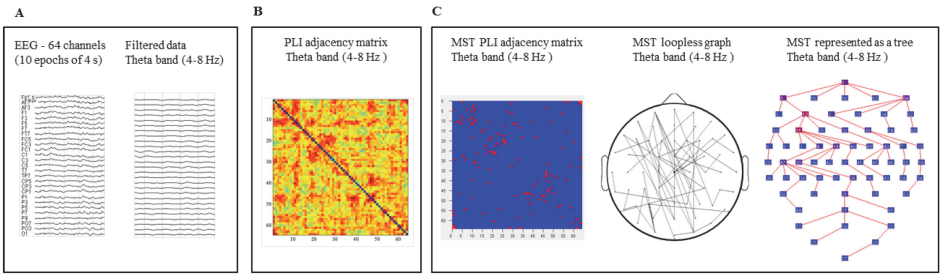


Figure 5.1. Schematic of the graph analysis. First, artifact-free epochs are filtered for each frequency band (A). Secondly, the functional connectivity matrix based on Phase Lag Index (PLI) is calculated for each frequency band and epoch (B). Finally, the Kruskal's algorithm is applied to obtain the Minimum Spanning Tree (MST) matrix (C-left); the resulting loopless graph is displayed on a scalp projection (C-middle) and as a tree (C-right). The tree view shows the hierarchical structure of the graph starting from an arbitrary root node (in this case FP1), the color map of the nodes from blue to red represents lower to higher betweenness centrality. For illustrative purposes this figure shows the MST obtained from the PLI matrix averaged across epochs and subjects of the typical readers group (N = 15).

MST metrics provides information about the topological properties of the tree. The following tree measures were used in this study: Degree, leaf number, betweenness centrality (BC), eccentricity, diameter, hierarchy (T_h), and degree correlation (R). The measures are summarized in Table 5.2 and examples of tree topologies with increasing leaf number are presented in Figure 5.2 (a detailed description in Stam et al., 2014). The degree of a node is its number of connections (edges), and the leaf fraction (L) represents the number of nodes on the tree with degree = 1. The leaf number has a lower bound of 2 and upper bound of $N\text{-}1$. The leaf number presents an upper bound to the diameter of the MST, which is the largest distance between any two nodes of the tree. The upper limit of the diameter is $d = m\text{-}L + 2$, which implies that the largest possible diameter will decrease with the increasing leaf

number. Eccentricity of a node is defined as the longest distance between that node and any other node and is low if this node is central in the tree. The BC of a node *u* is the number of shortest paths between any pair of nodes *i* and *j* that are running through *u,* divided by the total number of paths between *i* and *j*. The BC value ranges between 0 and 1 since it is a fraction. The BC relates to the importance of a node within the network. The nodes with the highest BC have the highest load. For instance, in a star-like tree, the central node has a BC of 1 and it could be easily overloaded, while the leaf nodes have a BC of 0. Degree, eccentricity and BC are different measures for relative nodal importance and may indicate the critical nodes in a tree.

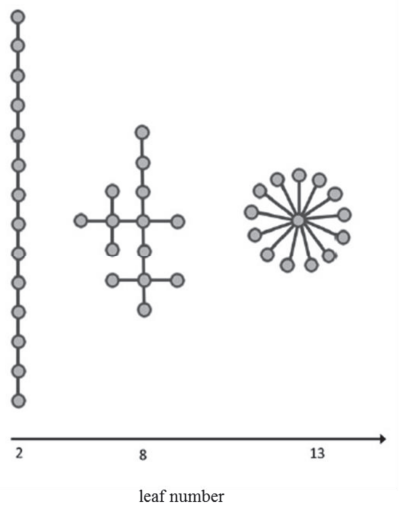


Figure 5.2. Examples of trees for increasing leaf number including the two extreme forms of trees. In this illustration, all of them have 14 nodes (circles) and 13 edges (lines). On the left a line-like tree with the lowest possible leaf number which is 2. The middle example shows a tree configuration with eight leaf nodes. On the right, a star-like tree with the highest possible leaf number which equals the number of edges.

For a tree topology to result in optimal network performance, it should conform to two criteria. Firstly, efficient communication would require a small diameter. Secondly, the tree topology would require preventing overload of hub nodes by setting a maximal BC_{max} for any tree node. The balance between these two criteria is reflected by the tree hierarchy (T_h) measure (Boersma et al., 2013), which is defined as:

$$T_H = \frac{L}{2mBC_{max}}$$

To assure T_h ranges between 0 and 1, the denominator is multiplied by 2. If $L = 2$ (line-like topology), and m approaches infinity, then T_h approaches 0. If $L = m$ (star-like topography), then T_h approaches 0.5. For leaf numbers in between these extreme values, T_h has higher values.

Finally, the degree correlation is an index of whether the degree of a node is correlated with the degree of its neighboring vertices to which it is connected. A positive degree correlation indicates that the graph is assortative; if the degree correlation is negative the graph is called disassortative. The degree correlations can be quantified by computing the Pearson correlation coefficient of the degrees of pairs of nodes connected by an edge. Interestingly, most social networks tend to be assortative, while most technological and biological networks tend to be disassortative (Newman, 2003).

Table 5.2. MST measures summary

N	Nodes	Number of nodes in MST
M	Links	Number of links in the MST
	Degree	Number of neighbors for a given node in the MST
L	Leaf fraction	Fraction of nodes with degree = 1 (leafs) in the MST.
D	Diameter	Largest distance between any two nodes of the tree.
	Eccentricity	Longest distance between a reference node and any other node
BC	Betweenness Centrality	Fraction of all shortest paths that pass through a particular node
K	Kappa	Measure of the broadness of the degree distribution (degree divergence)
Th	Tree Hierarchy	A hierarchical metric that quantifies the trade-off between large scale integration in the MST and the overload of central nodes
R	Degree correlation	Correlation between the degrees of a node and the degree of the neighboring vertices to which it is connected

Statistical Analysis

One-way ANOVAs were used for group comparisons in behavioral measures, relative power, PLI averages and MST measures. Prior to analysis, the PLI and MST measures were transformed to their natural logarithm, y=ln (x), to obtain normal distributions. For the behavioral analyses, standardized scores were used instead of raw scores, in order to assess the child's position within the distribution of a normative sample. Due to reduced variance, no reliable norm scores were available for the accuracy measures of the three subtasks of the 3DM word reading; thus raw scores were used for these measures. Additionally, for the MST measures, Bonferroni correction for multiple comparisons was applied to *p* values for each frequency band. Finally, to examine the relation between tree-derived measures and reading, regression analysis was performed in dyslexics and typical readers separately for the MST measures in which we found group differences and the main reading scores.

The same set of analyses was performed on the data of a sub-sample of 15 randomly selected dyslexics to evaluate whether different sample sizes dyslexic children (n=29) and controls (n=15) had any effect in the group differences. The main pattern of results reported below did not change and it is presented in Appendix C.2.

5.3 Results

Behavior

The results of the ANOVAs for reading accuracy and speed measures are shown in Table 5.1. The table shows a deficit in dyslexics that is mainly manifested by substantial differences in the reading fluency measures. The dyslexic group attained reasonably high levels of accuracy, although significantly lower than those of the typical readers. With regard to the letter-speech sound measures, only the fluency scores were sensitive to group differences.

Spectral Power and Functional Connectivity

The power spectra averaged across all electrodes for each group are shown in Figure 5.3. Typical readers and dyslexics both showed prominent peak frequencies in the alpha band, which did not differ between groups. The ANOVAs performed on the relative power values in each frequency band revealed no significant differences between groups. For each frequency band outliers and extreme values in relative power were detected and excluded for the subsequent analyses of connectivity and graph measures. Outliers and extreme values were defined based on 1.5 inter-quartile range steps. Accordingly, for the theta band 2 subjects from the dyslexic group were excluded (N = 27). For the alpha band 1 subject from the dyslexic group was excluded (N= 28). No outliers or extreme values were detected in the delta, beta or gamma band.

The PLI total values and sub-averages were calculated for each frequency band. The ANOVAs yielded no significant differences in functional connectivity (total network or sub-networks) between groups (all *p*'s >.05). The total PLI values for each frequency band are presented in Tables 5.3 and 5.4.

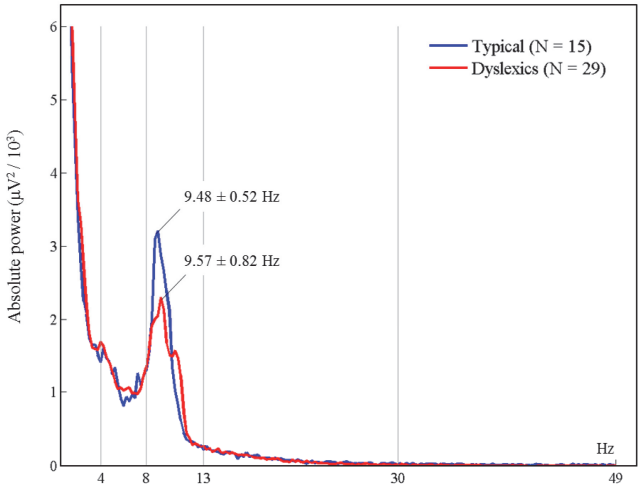


Figure 5.3. Power spectra averaged across 64 EEG scalp channels for typical readers and dyslexics.

MST Analysis

MST analysis yielded significant between group effects in the theta band (see Table 5.3 and Figure 5.4). Leaf fraction, reflecting the integration of information within the network, was significantly lower in dyslexics relative to typical readers, F (1, 40) = 10.24, p = .003, η^2 = 0.20. The group effect on diameter, representing the efficiency of communication between the nodes, was significant also, F (1, 40) = 4.27, p = .045, η^2 = 0.10, indicating higher diameter in dyslexics relative to typical readers. The group effect on eccentricity, relating to node centrality, just fell short of significance, F (1, 40) = 3.47, p = .070, η^2 = 0.08, suggesting a trend for higher eccentricity in dyslexics compared to typical readers. These group differences are displayed in Figure 5.5. Collectively these results indicate a less integrated network organization in dyslexic children compared to controls.

Table 5.3. PLI average and MST measures

		Typical Readers N = 15		Dyslexics N =29				
		M	*(SD)*	*M*	*(SD)*	*F*	*p* value	η^2
Delta	PLI	0.202	(0.012)	0.207	(0.013)	1.94	.171	0.04
	Degree	0.163	(0.022)	0.160	(0.022)	0.31	.580	0.01
	Leaf	0.583	(0.012)	0.576	(0.020)	1.37	.248	0.03
	Eccentricity	0.168	(0.010)	0.170	(0.011)	0.36	.552	0.01
	Kappa	3.551	(0.259)	3.501	(0.270)	0.37	.543	0.01
	Diameter	0.216	(0.013)	0.219	(0.014)	0.33	.568	0.01
	BC	0.704	(0.026)	0.698	(0.033)	0.32	.577	0.01
	Degree Correlation	-0.325	(0.030)	-0.321	(0.039)	0.22	.643	0.00
	Hierarchy	0.418	(0.015)	0.417	(0.023)	0.03	.865	0.00
Theta[a]	PLI	0.176	(0.008)	0.174	(0.009)	0.70	.408	0.02
	Degree	0.152	(0.011)	0.148	(0.015)	0.86	.359	0.02
	Leaf	**0.584**	**(0.013)**	**0.569**	**(0.015)**	**10.31**	**.003***	**0.20**
	Eccentricity	*0.169*	*(0.011)*	*0.174*	*(0.008)*	*3.47*	*.070*	*0.08*
	Kappa	3.415	(0.149)	3.341	(0.165)	2.14	.151	0.05
	Diameter	**0.216**	**(0.015)**	**0.224**	**(0.011)**	**4.27**	**.045**	**0.10**
	BC	0.701	(0.022)	0.696	(0.023)	0.49	.489	0.01
	Degree Correlation	-0.327	(0.037)	-0.319	(0.031)	0.55	.463	0.01
	Hierarchy	0.419	(0.015)	0.412	(0.016)	2.13	.152	0.05
Alpha[b]	PLI	0.209	(0.033)	0.200	(0.037)	0.68	.413	0.02
	Degree	0.187	(0.028)	0.185	(0.033)	0.11	.744	0.00
	Leaf	0.623	(0.030)	0.609	(0.027)	2.59	.115	0.06
	Eccentricity	*0.154*	*(0.013)*	*0.160*	*(0.011)*	*2.86*	*.098*	*0.07*
	Kappa	3.967	(0.398)	3.892	(0.466)	0.37	.545	0.01
	Diameter	*0.197*	*(0.018)*	*0.206*	*(0.015)*	*3.22*	*.080*	*0.07*
	BC	0.713	(0.025)	0.712	(0.032)	0.03	.862	0.00
	Degree Correlation	-0.345	(0.028)	-0.352	(0.038)	0.29	.593	0.01
	Hierarchy	0.441	(0.018)	0.432	(0.024)	1.74	.194	0.04

Bold text represents significant results ($p < 0.05$); italic text represents results at trend level;
* Significant after Bonferroni correction at $p < 0.006$. [a] Two outliers based on spectral power excluded; Dyslexics N = 27.[b] One outlier based on spectral power excluded; Dyslexics N = 28.
MST, minimum spanning tree; PLI, phase lag index; BC, betweenness centrality.

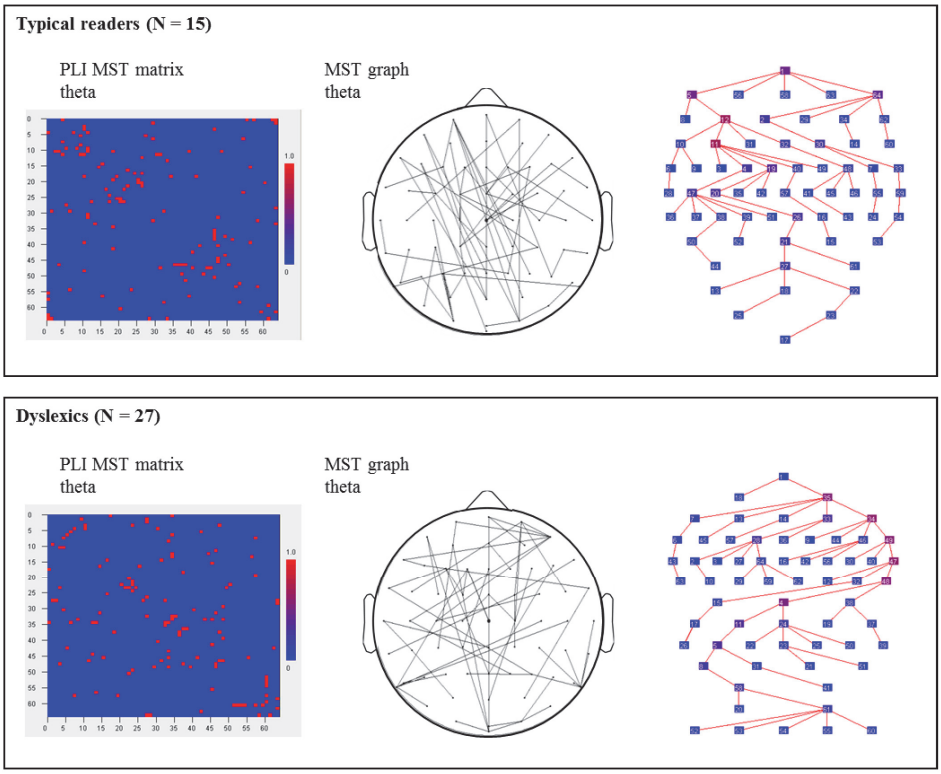


Figure 5.4. MST matrices (left panels) and MST graph in scalp view (center panel) and tree view (right panel) for the theta band for typical readers (above) and dyslexics (below). For illustrative purposes the MST algorithm was performed on the averaged PLI matrices.

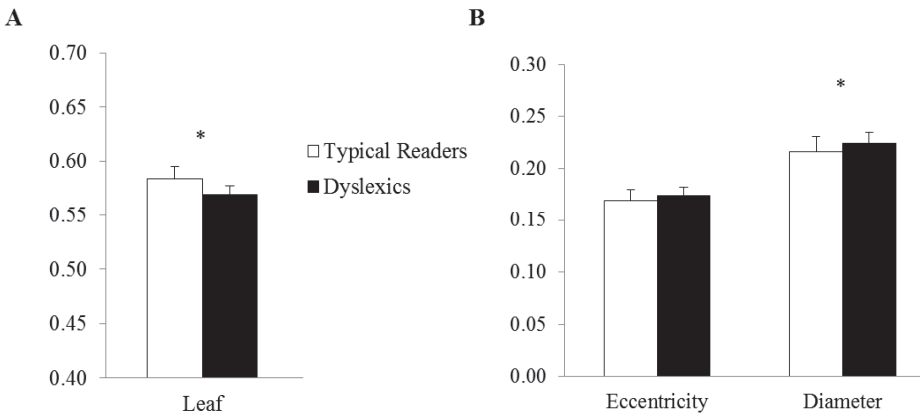


Figure 5.5. Group averages in the theta band for (A) leaf fraction, (B) eccentricity and diameter measures of the MST. Open bars refer to typical readers and filled bars to dyslexics. * $p < 0.05$.

For the alpha band, the group effects on diameter and eccentricity just failed to reach significance, p = .080 and p = .098, respectively, suggesting trends for higher diameter and eccentricity in dyslexics relative to typical readers. Finally, for the gamma band, the ANOVA revealed a somewhat higher hierarchy in typical readers relative to the dyslexic children but this effect just failed to reach significance, F (1, 40) = 3.89, p = .055, η^2 = 0.09. Group effects in all other measures and frequency bands were not significant, ps > .124. Moreover, there were no significant correlations between MST measures and reading performance.

Table 5.4. PLI average and MST measures

		Typical Readers N = 15		Dyslexics N =29				
		M	*(SD)*	*M*	*(SD)*	*F*	*p* value	η^2
Beta	PLI	0.099	(0.006)	0.101	(0.010)	0.43	.514	0.01
	Degree	0.160	(0.019)	0.162	(0.019)	0.09	.770	0.00
	Leaf	0.582	(0.018)	0.580	(0.022)	0.07	.796	0.00
	Eccentricity	0.168	(0.010)	0.168	(0.009)	0.00	.958	0.00
	Kappa	3.516	(0.244)	3.542	(0.275)	0.08	.773	0.00
	Diameter	0.216	(0.013)	0.216	(0.012)	0.06	.811	0.00
	BC	0.691	(0.026)	0.702	(0.021)	2.28	.138	0.05
	Degree Correlation	-0.319	(0.027)	-0.316	(0.040)	0.18	.675	0.00
	Hierarchy	0.425	(0.015)	0.417	(0.020)	1.72	.197	0.04
Gamma	PLI	0.092	(0.006)	0.091	(0.006)	0.04	.840	0.00
	Degree	0.224	(0.041)	0.214	(0.061)	0.69	.410	0.02
	Leaf	0.637	(0.034)	0.621	(0.038)	2.04	.160	0.05
	Eccentricity	0.152	(0.011)	0.158	(0.015)	2.02	.162	0.05
	Kappa	4.587	(0.875)	4.468	(1.381)	0.41	.528	0.01
	Diameter	0.196	(0.014)	0.205	(0.019)	2.31	.136	0.05
	BC	0.725	(0.027)	0.725	(0.032)	0.00	.942	0.00
	Degree Correlation	-0.366	(0.031)	-0.356	(0.040)	0.89	.350	0.02
	Hierarchy	*0.443*	*(0.020)*	*0.431*	*(0.016)*	*3.89*	*.055*	*0.09*

Bold text represents significant results (p < 0.05); italic text represents results at trend level; MST, minimum spanning tree; PLI, phase lag index; BC, betweenness centrality.

5.4 Discussion

The present study examined the topological characteristics of brain networks in dyslexics and typical readers by applying MST analysis to eyes-closed resting state EEG. The MST method should correct for potential bias in comparing networks (Stam et al., 2014). Our results showed a clear dissociation between PLI connectivity analyses vs. MST analyses of network organization. That is, the PLI analyses failed to reveal connectivity differences between groups whereas the MST analyses yielded between groups differences in network organization as revealed in the theta band. This pattern of findings

presents another illustration of the differences between connectivity vs. network analysis of EEG data (see also Stam & van Straaten, 2012). More specifically, the MST analysis showed for dyslexic children a smaller leaf fraction indicating less network integration compared to controls. In addition, there was a significant group difference for diameter and a trend for eccentricity suggesting less communication between nodes of the network in dyslexic compared to typical readers. In terms of the extreme tree topologies, the current pattern of results suggests a more path-like configuration in dyslexic children and a more star-like topology in typically reading children.

The current group difference in network topology is indicative of a less integrated network configuration in dyslexic children compared to controls (Olde Dubbelink et al., 2014; Stam et al., 2014). This finding is in accordance with previous functional connectivity studies suggesting a disrupted network structure and mixed patterns of connectivity abnormalities in dyslexia (Frye, Liederman, McGraw Fisher, & Wu, 2012; Koyama et al., 2013). A relevant consideration when interpreting the current results is the relation between MST measures and more conventional graph metrics pertaining to network models such as small-world and scale-free networks. Tewari et al. (2015) examined this relation by performing an extensive and systematic series of simulation studies. We observed for dyslexic children a lower leaf fraction and a trend for higher diameter relative to controls. Tewarie et al., (2015) observed that these two measures are strongly related to path length. MST leaf was negatively related to path length. More specifically, MST leaf was low for trees derived from regular networks and increased as these networks became more random. MST diameter, on the other hand, was positively related to path length. That is, diameter increased as networks became more regular. This finding is consistent with a recent study that examined the topology of structural networks in Chinese dyslexics in which a longer path length was observed for dyslexics relative to controls (Liu et al., 2015). Interestingly, in the Tewari et al. (2015) simulation study, MST leaf fraction and diameter were also strongly related to the 'scale freeness' of the network. In particular, leaf fraction increased from regular to random networks and it was much larger for scale-free networks. Accordingly, the current results may also indicate a deviation from scale-free topologies that is larger in dyslexics compared to typical readers. A scale-free topology is indicative of the presence of highly connected hub nodes in the network (Stam, 2014). In this regard, the current findings may suggest dysfunctional hub nodes in dyslexia.

It should be emphasized that the main group differences in network organization were found in the theta band. The present results are consistent with previous research on functional and scaling aspects of oscillatory activity. Regarding general properties of the brain as an oscillatory system, research suggests that slow oscillations such as theta recruit large networks whereas higher frequencies are more confined to smaller networks (Buzsáki & Draguhn, 2004). Further, it is proposed that synchronous activity of lower frequency bands such as theta, mediate long range integration between

processes involving several cortical areas (A. Von Stein & Sarnthein, 2000). More specifically, theta frequencies have been related to long range interactions during top-down processes such as working memory retention (A. Von Stein & Sarnthein, 2000). In relation language-specific functions, it has been suggested that synchronous theta activity may play an important role in speech processing (Luo & Poeppel, 2007; Poeppel, Idsardi, & van Wassenhove, 2008) and language comprehension (Bastiaansen, Oostenveld, Jensen, & Hagoort, 2008). Finally, the findings of current study support previous evidence suggesting abnormalities in theta oscillations in developmental dyslexia (Arns & Peters, 2007; Goswami, 2011; Klimesch, 1999; Marosi et al., 1995; Spironelli, Penolazzi, & Angrilli, 2008).

The current results showed also a between-group effect in the gamma band that just fell short of significance. The dyslexic children showed a lower tree hierarchy than controls. It should be noted, however, that the gamma band in scalp EEG recordings may be strongly affected by muscle artifact (Whitham et al., 2007). Consequently, a previous study using graph analysis excluded the higher frequency gamma band from analysis (Lee et al., 2010). In this regard, we hesitate to interpret the current findings for the gamma band, the more so because we are dealing with child data that are typically more affected by muscle artifact compared to adult participants.

The MST metrics of the EEG obtained during rest did not relate to the reading measures differentiating children with dyslexia from controls. Previously, Dimitriades et al., (2013) did observe a positive relation between local efficiency of temporo-parietal networks in the beta band of the resting-state EEG and word reading measures in children with reading difficulties but not in typical controls. Similarly, Vourkas et al. (2011) reported significant correlations between graph metrics and phonological decoding ability but this relation was obtained for task-related EEG. In view of the limited studies available to date we are reluctant to interpret the current absence of a relation between reading ability measures and MST metrics. Future studies should examine the potential relations between these measures more systematically by comparing both resting-state and task-related EEG measures.

There are a few limitations to the current study. First, the current study used a modestly sized EEG montage (64 electrodes). Although MST metrics are not affected by connectivity strength and network density, some measures are sensitive to network size. Thus, our results should be replicated by using a high-density electrodes array, or preferably MEG source space networks, to assess relative nodal importance in network performance. Secondly, although PLI is more robust than other connectivity measures to methodological problems such as volume conduction (Stam et al., 2007), it is yet unclear how interpolation may affect connectivity measures. At some instances we had to resort to interpolation and the potential effects of interpolation should be examined more systematically. The current assessment of this issue suggests that, in view of the limited number of interpolations, it seems unlikely that interpolation impacted the connectivity weights. Moreover, a control analysis including

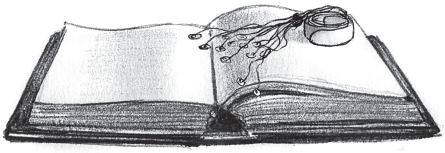
only participants without interpolated data continued to show the between-groups effect on leaf number. The results of the control analysis are reported in Appendix C.3. Finally, the PLI sub-averages differed in the number of electrodes and we cannot exclude the possibility that between-group differences in signal-to noise ratio might have affected our MST metrics. It should be noted, however, that the Tewarie et al. (2015) simulation studies indicated that the MST metrics are quite robust to noise.

General Conclusion

The current MST analysis of potential differences in network topologies between dyslexic children vs. typical controls indicated a more path-like topology in dyslexics compared to typical readers for the EEG theta band. This finding suggests a less integrated network configuration in dyslexia. More specifically, the current results might indicate less efficient long-range connections in dyslexics, which would be in line with evidence suggesting disrupted connectivity between the distant cortical areas of the reading network (Sandak et al., 2004). Future studies employing MST analysis might want to adopt a longitudinal perspective in examining the developmental trajectories of network organization during reading acquisition. Furthermore, it would be of considerable interest to examine how functional network organization is changed following reading intervention (e.g., Koyama et al., 2013).

Chapter 6

General Discussion



This thesis began by introducing the main cognitive and neural processes involved in reading acquisition, followed by a concise review of behavioral and neuroimaging studies of dyslexia. This review resulted in several key-issues that have been addressed in the current thesis. A first study examined specialization for visual word recognition using brain-potentials analysis in dyslexics and typical readers. Next, the effects of training automation of letter-speech sound mapping on reading fluency were examined and training outcomes were related to initial mapping skills. Subsequently, we examined changes in neural activity vis-à-vis reading gains after training and investigated neural predictors of responsiveness to intervention. Thereafter, we studied global organization of functional brain networks in dyslexics and typical readers. Finally, this thesis ends with a discussion on effective intervention programs for dyslexia, the utility and limitations neuroimaging studies, and future directions for educational neuroscience.

6.1 Improving Reading Fluency in Dyslexia

The primary goal of this project was to gain insights on how reading fluency can be effectively improved in dyslexia. Thus, an essential element was the assessment of a cognitive intervention. **Chapter 3** of this dissertation consists of a randomized controlled trial evaluating reading gains after 34 individual training sessions of 45 minutes over a five months period. The theoretical framework which inspired the training used in our studies postulates a failure to adequately automate letter-speech sound correspondences as the main deficit hindering reading fluency acquisition in dyslexics (Blomert, 2011).

Dyslexics in our study showed a much more pronounced deficit in reading fluency rather than in accuracy, for both word reading as well as letter-speech sound association tasks. That was expected given the age of participants (in 3rd grade of school) and the relatively high orthographic transparency of Dutch language used in the study; previous studies showed high levels of accuracy attained after the first few years of instruction and especially in transparent orthographies (de Jong & van der Leij, 2003; Landerl et al., 1997; Yap & Leij, 1993). In relation to letter-speech sound associations, our results were in line with previous research showing that dyslexic children in 3rd grade already present a relatively advance knowledge of this correspondences but they still may not be capable of using them for fluent reading (Vaessen & Blomert, 2010).

Importantly, in our study dyslexics that followed the letter-speech sound integration training showed larger gains in reading compared to the control dyslexics who did not received any special intervention (waiting-list group). Those gains, as expected from the baseline characteristics, were more pronounced for reading fluency than for accuracy scores. Interestingly, although effective remediation of reading accuracy have been previously demonstrated (Alexander & Slinger-Constant, 2004; Galuschka, Ise, Krick, & Schulte-Körne, 2014; Tijms, 2011), previous evidence for fluency improvements is less robust. Most traditional interventions, inspired by the notion of a phonological

awareness deficit underlying dyslexia, are more focused on accurate learning of letters and speech sound correspondences rather than on their automatic integration (Alexander & Slinger-Constant, 2004; Gabrieli, 2009; Wolff, 2011). Those interventions typically include phoneme awareness and phonemic decoding practice. In contrast, the training in our study aims to obtain letter-speech sound mapping automation besides instruction and practice of accurate correspondences. Thus, the beneficial training effects on reading support the notion of a deficit in automation of letter-speech sound correspondences in dyslexia. These results also suggest that dyslexics may need extra training to improve fluency but that in fact they are able become fluent readers.

Secondly, the outcome measures of the study in chapter 3 could be characterized by three latent factors which were: word reading, letter-speech sound fluency and letter-speech sound accuracy. The baseline deficits of dyslexics were manifested for the three factors. The separate factors for fluency and accuracy of letter-speech sound mapping are in line with previous studies and support that adequate knowledge of these correspondences is not sufficient to develop reading fluency (Blomert, 2011; Vaessen & Blomert, 2010). Most importantly, the training led to significant gains in the word reading factor. This suggests that more robust and automatic letter-speech sound associations can facilitate effective learning of automatic word identification in dyslexics (Ehri & Saltmarsh, 1995). The gains in word reading after the training further support the notion of a multisensory integration deficit underlying dyslexia (Blau et al., 2010; Blomert, 2011; Froyen et al., 2011). The dyslexic groups however, did not differ in gains in the two letter-speech sound mapping factors, perhaps due to insufficient sensitivity of the letter-speech sound measures (Vaessen & Blomert, 2010) or insufficient statistical power in the sample. Alternatively, it is possible that the training improved reading fluency by supporting other processes not reflected in the letter-speech sound tasks performance, such as visual word specialization. This is supported by the suggestion that the development of grapheme-phoneme integration areas may support the specialization of visual areas for fast recognition of words, which also plays a role in fluent reading (McCandliss et al., 2003; Pugh et al., 2013).

Additionally, our study showed that the rate of improvement for the word reading factor was faster in trained dyslexics compared to typical readers, while this difference was absent in untrained dyslexics. The lack of differences between the untrained group and typical readers suggest that without specialized training dyslexics do not tend to catch up with those with higher reading skills. This is supported by previous studies demonstrating a relatively high stability in reading abilities across elementary grades (Aunola et al., 2002; Juel, 1988; Parrila et al., 2004; Wagner et al., 1997). This result underlines the need for early and specialized intervention in dyslexia.

Furthermore, partial correlations suggested that reading fluency gains were related to initial differences in LSS mapping fluency in the waiting-list group, but not in the training group or in typical readers. This result shows that without special training reading fluency development is constrained by

letter-speech sound association processes, supporting Blomert's (2011) suggestion that deficits in automatizing multisensory mapping may underlie fluency deficits in dyslexia. A possible interpretation is that dyslexics in 3rd grade might rely strongly on phonological decoding, similarly to typical readers during the initial stages of reading, unless specific training is provided (Maurer et al., 2011).

To summarize, the study described in chapter 3 demonstrated that a relative short but intensive training in letter-speech sound mapping fluency can significantly improve word reading fluency in dyslexia. Recent neurophysiological and neuroanatomical studies have shown a deficit in the crossmodal integration of letters and speech sounds in a temporo-parietal network in dyslexia (Kronschnabel et al., 2014; Wallace, 2009; Žarić et al., 2014). Notably, this deviant processing of letters and speech sounds in these multisensory areas has been reported in dyslexic children even if they attained adequate knowledge of letter-speech sound correspondences (Blau et al., 2010; Froyen et al., 2009). Based on these brain findings, a theoretical account of dyslexia has been postulated that states that a failure to develop automatic letter-speech sound integration will first and for all result in an impairment in the acquisition of fluent reading skills (Blomert, 2011). Using a behavioral intervention paradigm, we provided support for this account by showing that (a) letter-speech sound mapping knowledge was not associated with reading fluency gains, (b) letter-speech sound mapping fluency was strongly correlated with fluency gains in untrained dyslexics, but not in trained dyslexics, and (c) an intensive training addressing the automation of letter-speech sound mappings produced reading fluency improvements.

Further research should examine at a more detailed level which mechanisms are involved in producing these gains (e.g. visual specialization). In addition, attaining reading fluency is a long process and previous studies have shown that even non-impaired readers may take years to become fluent readers (Vaessen & Blomert, 2010). Thus, long term training efficiency should be addressed in future studies. The results of our study, together with those reported in Aravena et al. (2013), illustrate the clinical potential of the letter-speech sound mapping framework for remediation programs in dyslexia.

Individual Differences in Response to Remediation

Despite the demonstrated advantages of including instructional elements such as phonological skills and letter-speech sound mapping in dyslexia treatments, most programs hardly remediate reading fluency deficits. In addition, a large proportion of variance in intervention response remains unexplained. Consequently, response to intervention (RTI) is often used as indicator of severity of impairments (Fletcher & Vaughn, 2009; Snowling & Hulme, 2011) and the identification of individual factors predicting training outcomes has become an important focus on current research.

A substantial part of intervention research has focused on cognitive factors that may predict reading outcomes after intervention. Phonological awareness seems to be one of the strongest predictor of

reading performance (Mann & Wimmer, 2002; Wagner et al., 1997). Importantly, a previous remediation study in poor readers in first grade found that children showing lower performance in phonologically-based skills would also present more difficulties to improve after a remediation program (Vellutino et al., 2006; Vellutino & Scanlon, 1996) Additionally, rapid naming skills appear to predict a unique part of the variance in reading fluency deficits in dyslexia (Landerl & Wimmer, 2008). Consequently, some authors have argued for differentiated subtypes of reading disabilities based on these two main cognitive factors (M. Wolf & Bowers, 1999). The 'double deficit hypothesis' postulates different subgroups of dyslexics characterized by either poor phonological skills, slow naming or a combination of both deficits. Accordingly, the subgroup presenting a double deficit would result in a more serious impairment that is harder to remediate. This theory assumes that phonological and rapid naming deficits are relative independent, which is partially supported by the rather modest correlation between both skills across studies (see meta-analysis in Swanson & Trainin, 2003). Moreover, it has been suggested that the deficit in naming speed may better account for reading fluency impairments than the only phonological deficits (see Peterson & Pennington, 2012 for an overview). In addition, some studies have indicated that impairments in rapid serial naming in dyslexia may relate to deficits in more domain-general processes such as visual (see review in Valdois, Bosse, & Tainturier, 2004). However, the mechanisms underlying a deficit in naming and the role of phonological skills in such a deficit remain rather unspecific and challenged by other experimental findings (Peterson & Pennington, 2012). In relation to this, the results of a study in a large sample of dyslexic children did not support the notion of an independent naming deficit in dyslexia (Vaessen, Gerretsen, & Blomert, 2009). Interestingly, the authors proposed that both naming and phonological processing speed may relate to a common underlying process of integrating written and spoken speech associations. Accordingly, they suggested that the unique value of naming speed in predicting reading fluency may be explained by the fact that naming tasks require fast audiovisual integration which is not always present in traditional phonological awareness tasks.

In sum, differences in cognitive profiles of dyslexics, especially regarding phonological and naming skills are relevant to the examination of response to intervention. In addition to these factors, a number of demographic variables (e.g. socio-economic status) together with instructional factors have been identified as predictors of individual differences (Vellutino et al., 2006). However, these variables do not sufficiently explain why a relatively large percentage of poor readers are not able to improve reading after specialized intervention. In this regard, the identification of neurocognitive aspects underlying reading impairments and response to intervention is currently gaining relevance in dyslexia research.

6.2 The Utility of Neurocognitive Markers in the Remediation of Dyslexia

Neurocognitive studies of dyslexia can provide with new theoretical insights of the underlying causes of dyslexia and inspire new interventions. In addition, remediation neuroimaging studies are useful for various reasons. They allow for assessing whether a treatment leads to neurocognitive changes and they provide with an opportunity to test theoretical prediction on processes underlying reading impairments. The following paragraphs summarize and discuss the findings of our two brain-potentials studies focused on visual N1 specialization for words. Subsequently, we summarize the results of our whole-brain functional networks analysis and discuss the potential of that type of EEG analysis to account for the interactive nature of the reading network in development.

Visual Word Recognition

N1 as a correlate of reading (dys) fluency. In the **chapter 2** of this thesis we examined neurophysiological responses during a visual word recognition task in dyslexics and typically reading children in 3rd grade. The study focused on left occipito-temporal N1 responses to words vs. symbol strings as they were previously suggested to reflect visual specialization to print at the Visual Word Form Area (VWFA). We found print sensitivity of N1, showing larger amplitudes for words than for symbol strings, in both dyslexics and typical readers. Most interestingly, there was a group difference in the pattern of N1 responses to words, which were smaller at left vs. right hemisphere sites in typical readers but were similar across hemispheres in the dyslexic group. This group difference was interpreted to indicate facilitated or less effortful word decoding in typical readers, resulting in smaller N1 amplitudes, relative to dyslexics. Importantly, we found an association between N1 amplitudes for words at the left hemisphere and reading fluency in the dyslexic group but not in the typical readers group. We interpreted this finding to indicate stronger reliance on visual processing in dyslexics relative to typical readers.

Regarding N1 word specificity, the results of our study suggested that some degree of visual specialization for print is present in dyslexics in 3rd grade. This was indicated by the enhanced N1 amplitudes for words relative to false fonts across groups. This is consistent with a previous study reporting similar letter sensitivity in N1 in dyslexics (Hasko et al., 2013). Such coarse specialization is expected given the advance level of letter knowledge in 3rd grade in both dyslexics and typical readers. Furthermore, our behavioral results showed relatively high levels of reading accuracy in dyslexics, which presented larger deficits in reading fluency measures. This seems to be a common finding in dyslexia studies involving language with relative shallow orthographies such as German or Dutch (Frith et al., 1998; Landerl et al., 1997; Paulesu et al., 2001). In typical readers, longitudinal data indicates that

N1 sensitivity to print vs. symbol strings emerges in the majority of children from kindergarten to 2nd grade (Maurer et al., 2006)

Most interestingly, typical readers in our study showed reduced N1 amplitudes for words at the left hemisphere compared to the right hemisphere, and that pattern was not found in the dyslexic group. This finding is in apparent discrepancy with previous studies showing a reduced difference in N1 response to words vs. symbols in dyslexics relative to controls. A potential interpretation of this result relates to specialization of the VWFA. Accordingly, lower responses to words at the left hemisphere in typical readers may reflect facilitated lexical access. This idea is supported by studies reporting lower N1 responses to high vs. low frequency words (Assadollahi & Pulvermüller, 2003; Hauk & Pulvermüller, 2004) and to real words vs. pseudohomophones or pseudowords (Araújo et al., 2015). Those studies suggest that words that are easier to retrieve elicit lower visual responses in expert readers. Interestingly, such orthographic familiarity effects were found absent in impaired relative to typical readers, in children (van der Mark et al., 2009) and adults (Wimmer et al., 2010). The results of those studies were interpreted to indicate a failure to develop adequate word-level specialization in dyslexics. In line with this, the findings in our study of a lack of left-lateralized reduction of N1 amplitudes in dyslexics may indicate more effortful or demanding visual decoding relative to typical readers. The notion that dyslexics may benefit less from word-level specialization would be consistent with the impairments shown by the word reading tests, and with the experimental task performance which was less accurate in dyslexics relative typical readers.

Importantly, longitudinal data suggest an inverted 'U' developmental trajectory of visual responses, that become increasingly stronger at the initial stages of reading acquisition to later decline with increasing expertise (Maurer et al., 2011; Price & Devlin, 2011). Accordingly, a study in typical readers reported larger and more bilateral word-specific N1 amplitudes in children in 2nd grade compared to adults (Maurer et al., 2006). Similarly, a decrease in N1 amplitudes was reported from 2nd to 5th grade in typical readers while an opposite trend was observed in dyslexics (Maurer et al., 2011). Thus, in our study, the pattern of responses in the dyslexic group may present higher resemble to that of typical readers in earlier stages of reading acquisition. This idea is supported by the association found in the dyslexic group between word reading fluency and N1 amplitude enhancement for words vs. false font strings at the left hemisphere. Previous studies found similar results collapsing both groups of typical and dyslexic readers (Maurer et al., 2006, 2007) and in typical readers (Korinth et al., 2012). In our study, the relation between N1 amplitudes at the left hemisphere and reading fluency was found in dyslexics but not in the typical readers group. This supports the notion of a stronger reliance on visual processing in dyslexics, which might be comparable to typical readers during earlier stages of reading acquisition.

So far the findings of our study have been mainly interpreted based on the notion of a deficit in the VWFA specialization in dyslexics. However, an important alternative interpretation may consider attentional factors and their influence on early visual ERPs such as N1.

Attentional influences on N1. Previous research has indicated an important role of attention modulation in early visual components such as N1 (see review in Luck, Woodman, & Vogel, 2000). For instance, stimuli typically elicit stronger N1 responses when presented at attended compared to unattended locations (see reviews in Luck et al., 2000; Vogel & Luck, 2000). Importantly, some studies have suggested strong functional interactions between the occipito-temporal systems for reading (i.e., the VWFA) and dorsal systems related to spatial and feature attention (Vogel et al., 2012). In the context of reading tasks, a previous study reported larger N1 amplitudes when the task required attention to orthography compared to phonological or semantic features (Ruz & Nobre, 2008). Similarly, a recent study emphasized the role of attentional focus while learning an artificial script (Yoncheva et al., 2015). That study found that attention to grapheme-phoneme when encoding led to left-lateralization of N1 responses while attention to whole-words lead to right-lateralization during when the learnt words were presented. Moreover, in relation to lateralization, Okumura and colleagues examined in two recent studies how N1 responses were influenced by attention in adults using a Japanese syllabic and transparent script (Okumura et al., 2014, 2015). The first of those studies showed a bilateral enhancement of N1 amplitudes for words relative to control symbols when stimuli were task irrelevant and rapidly presented (Okumura, Kasai, & Murohashi, 2014). The authors interpreted the lack of lateralization effects on N1 as the consequence of restricted linguistic processing during the task (i.e., detecting the color change of a fixation cross). The second study used a task that required more active attention to stimuli (i.e., detecting color change of target stimuli) and found left-lateralized enhancement of N1 responses to words (Okumura et al., 2015). Interestingly, in that study, N1 enhancement for words became bilateral when intercharacter spacing was sufficiently enlarged so that the whole words could only be decoded by serial reading. The authors interpreted this finding to indicate diminished influence of phonological processing when performing serial reading. In this line, an fMRI study manipulated word decoding difficulty (i.e., via visual degradation) and found that increased difficulty lead to increased activations at both posterior visual and dorsal attentional regions (Laurent Cohen et al., 2008).

Collectively, the studies reviewed above suggest that besides VWFA specialization for reading, attention and decoding strategies could account, at least in part, for the group differences found in our study. Bilateral responses in dyslexics and reduced amplitudes at the left vs. right amplitudes in typical readers might thus relate to group differences in attentional focus during task (e.g., serial reading vs. whole word reading, respectively). The association between reading fluency and left N1 amplitudes for words in dyslexics but not in typical readers may also relate to differences in visual attention during

reading (e.g., more allocation of attentional resources to orthographic features in dyslexics). In relation to this, the behavioral results of experimental task performance may also be reflecting deviant allocation of visual attention in dyslexics, which showed a lower rate of correct responses to symbol strings relative to typical readers. Finally, deficits in visual-spatial attention processing in dyslexia have been reported in previous behavioral studies (Facoetti, Paganoni, Turatto, Marzola, & Mascetti, 2000; Valdois, Bosse, & Tainturier, 2004).

To conclude, our study presented in chapter 2 provided evidence for differences in N1 word responses between dyslexic and typical readers. Both groups showed N1 enhancement for words vs. symbol strings, but in typical readers the N1 amplitude for words was reduced over the left relative to the right hemisphere sites. This effect was absent in dyslexic readers. Our study differed from previous research with regard to the symbol strings used to assess the efficiency of word processing. The pattern of results suggests that the symbol strings used in our study might provide a sensitive tool for assessing N1 word specialization in dyslexic readers. This is supported by the relation observed between the N1 word-specific amplitudes and reading speed measurements in the dyslexic group. The findings in chapter 2 were followed up by a longitudinal analysis to assess whether the apparent deficit in visual word specialization in dyslexic children decreases when they attain higher levels of reading fluency (i.e., following a remediation program). The subsequent study provides additional insight on the sensitivity of N1 to intervention response.

N1 sensitivity to remediation and prediction of treatment success. The study presented in **chapter 4** constituted a continuation of our two previous studies discussed above. This study had three main goals; first, it aimed at examining whether the pattern of N1 responses reported in chapter 2 would change in dyslexics after a training focused on letter-speech sound integration (that training is evaluated in detail in the behavioral study in chapter 3). Second, we investigated the association between longitudinal changes in N1 and reading fluency gains after training. Such gains were anticipated based on the results of our behavioral study (see above and chapter 3). Third, because not all children benefitted equally from the training, we examined differences in modulation of N1 amplitudes between children who responded to training and those who did not. The latter analysis also examined initial N1 differences that could help predicting training responses.

The behavioral analysis performed in this study yielded findings that are comparable to the results of our behavioral study reported in chapter 3. This pattern of findings was anticipated as both studies employed the same training program for overlapping samples of participants. The dyslexic group presented deficits that were more pronounced in reading fluency rather than in accuracy scores. The training led to significant gains for the main word reading measures, but the training effects were less pronounced for accuracy measures, as it might be expected given that they presented relatively high accuracy scores at pretest. The training effect was most pronounced for reading fluency measures, with

the exception of the fluency measures derived from the 3DM pseudowords task and the One-Minute test where the gains in standardized scores did not reach significance. With regard to letter-speech sound mapping, dyslexics showed gains in both spelling accuracy and spelling fluency.

In our study in chapter 4, dyslexics at pre-test showed the same pattern of responses as in our previous brain-potentials analysis (see chapter 2); that is, N1 amplitudes for words did not differ across hemisphere, in contrast to typical readers who presented reduced amplitudes at the left vs. right hemisphere. Although the training analysis failed to yield significant results, the separate analysis in the posttest data showed that dyslexics' responses tended to be more similar to those previously found in typical readers; after training, dyslexics showed reduced N1 amplitudes for words at the left vs. right hemisphere, but only in some electrode sites. This emerging pattern is in line with an ERP-source analysis study in dyslexic children showing N1 responses that were initially equally distributed across hemispheres and became left-lateralized after a phonological training (Spironelli et al., 2010). In that study, however, lateralization consisted of larger N1 amplitudes at the left relative to the right hemisphere, showing a pattern opposite to that in our study. Normalization of neural responses, characterized by activations that increase with reading improvements is reported in multiple neuroimaging studies examining parieto-temporal (Aylward et al., 2003; Meyler, Keller, Cherkassky, Gabrieli, & Just, 2008; Shaywitz et al., 2004; Simos et al., 2007; Temple et al., 2003) and occipito-temporal activations (Aylward et al., 2003; Heim et al., 2014). The apparent discrepancy with the pattern of responses in our study is presumably due to methodological differences across studies in task, type of intervention and imaging technique (Heim et al., 2014). Importantly, those studies, together with the trend in our study, provide with evidence for differences in brain responses between typical readers and dyslexics that are diminished after intervention.

The second finding of our study related to the association found between the decrease of N1 amplitudes for words at the left hemisphere and gains in reading fluency after training. That association supports the notion of an inverted 'U' development of visual expertise, according to which strong visual responses to print emerge after the first years of reading instruction to later become smaller and more left-lateralized with increasing reading expertise (Maurer et al., 2006). Importantly, the association found in our study supports the role of N1 as a neurocognitive correlate of VWFA specialization for reading and extends our previous finding relating N1 amplitudes with reading rate in dyslexics (see chapter 2), similarly to other studies in adults and children (Korinth, Sommer, & Breznitz, 2012; Maurer et al., 2006, 2007). Ultimately, our findings support the previously discussed interpretation of the lateralized pattern found in typical readers that relates lower neural responses to facilitated decoding. In addition, the training used in chapters 3 & 4 is focused on letter-speech sound integration fluency, which would arguably have a direct influence on the multisensory integration systems at parieto-temporal brain areas. The association between reading gains after training and left occipito-temporal

responses supports an interactive account suggesting the influence of multimodal areas in the specialization of the VWFA (Sandak, Mencl, Frost, & Pugh, 2004; Schlaggar & McCandliss, 2007). Accordingly, a recent study showed that selective attention to grapheme-phoneme correspondences during learning of a novel script lead to left-lateralization of N1 responses (Yoncheva et al., 2015). Similarly to our findings, the results of that study underscore the interactive role of audiovisual mapping in shaping the specialization of visual areas.

Thirdly, we found a significant training effect on N1 in the group of subjects classified as improvers (based on a median-split on standardized word reading delta scores) but not in the group of poor improvers. N1 amplitudes for words bilaterally decreased after training in the group of improvers, supporting the notion that smaller amplitudes may in general reflect less effortful decoding. Further, this result is in line with previous studies reporting differential effects in normalization of neural activity between responders and poor responders (Davis et al., 2011; Molfese et al., 2013; Odegard et al., 2008). In our study however, N1 amplitudes in improvers did not show the lateralization pattern found of typical readers, which may indicate persistent neural abnormalities. This would be consistent with the reading scores indicating that dyslexics remained dysfluent relative to typical readers despite substantial improvements after training.

Most relevant to the role of N1 as a potential predictor of treatment outcomes, the group of dyslexics that responded to training presented significantly larger amplitudes for words at pretest compared to poor-improvers. Importantly, the initial difference between improvers and poor-improvers was not evident from the pertinent reading scores. That finding is consistent with a previous MEG study that reported lower N1 amplitudes across hemisphere in inadequate relative to adequate responders to intervention (P. J. Molfese et al., 2013). Similarly, another MEG study also reported under-activation of ventral occipito-temporal areas in struggling readers that did not benefit from a remediation program in contrast to those who improved reading (Rezaie et al., 2011). The authors interpreted that results to indicate a more severe and global deficit in the reading network that prevented adaptation in non-improvers. This may also be a valid interpretation of our results indicating smaller N1 amplitudes across hemispheres, which were not modulated by training in the group of poor improvers relative to improvers. Additionally, that finding could also relate to differences between improvers and poor improvers in their level of visual specialization. As described in the previous section, longitudinal data suggested that visual responses are stronger and more bilateral after the first years of instruction, possibly reflecting coarse specialization to print (e.g., letter vs. symbol; Maurer et al., 2006). Thus, initially smaller N1 amplitudes for words in poor improvers may indicate a different or lagged developmental trajectory in perceptual expertise relative to the improvers group.

Alternatively, it might be possible that dyslexics resorted to different attentional strategies during the task in attempting to compensate for their reading difficulties. At this point it should be noted that

there were no lateralization effects on N1 amplitudes for words in neither improvers nor poor improvers. Interestingly, as discussed in previous section, previous studies reported absence of N1 lateralization when stimuli were not relevant to the task or when serial decoding was required for reading (Okumura et al., 2014, 2015). Accordingly, the fact that the initial N1 differences between improvers and poor improvers were found across both hemispheres seems to favor the possibility that more general visual attentional strategies may have contributed to our results.

An apparent limitation of the study presented in chapter 4 refers to its design which does not allow for disentangling the effects of training from those related to the passage of time. However, both improvers and poor improvers were equally susceptible to be influence by the time elapse between ERP measurements. Second, the high frequency words presented were already well known by the participants, thus familiarity effects in neural responses do not seem the most likely explanation as the stimuli are already overlearned. Third, the strongest changes in visual specialization are proposed to occur in earlier stages of reading acquisition and to take place under several years of instruction, i.e., from kindergarten to 2nd grade (Maurer et al., 2006). Furthermore, the results of our randomized controlled trial (see chapter 3) demonstrated that dyslexics would not show significant improvements in reading fluency without special training.

To conclude, the findings presented in chapter 4 supported the notion that N1 can be used to identify individual differences in reading improvement after training that are not revealed by behavioral tests. This is in line with previous studies including neurophysiological responses as predictor of response to intervention (Brem et al., 2013; Hasko et al., 2014; Lemons et al., 2010; P. J. Molfese et al., 2013). Additionally, our results further supported the clinical potential of training LSS mapping fluency. In relation to this, our findings also account for the interaction between multisensory integration areas (arguably tackled by our training) and the specialization of visual areas (reflected in N1). Finally, our study underlines the value of N1 in predicting treatment outcomes and the importance of taking into account individual differences within dyslexics when evaluating interventions.

Limitations of N1 as marker of visual specialization. The previous ERP studies (in chapters 2 & 4) provided evidence for the sensitivity of N1 to reading fluency impairments in dyslexia and to individual differences in reading improvements after training. A limitation of these studies, related to interpretation of findings, refers to the influence of additional processes besides orthographic visual processing. The paradigm in those studies, using an implicit word recognition task, may not sufficiently constrain allocation of attentional resources and cognitive strategies during task, which can influence early visual components (this is discussed more extensively in the section *Attentional influences on N1*). Indeed, in many of the studies examining occipito-temporal responses to print in dyslexics, the experimental tasks allow for phonological processing of stimuli in addition to orthographic processing (see review in Richlan, Kronbichler, & Wimmer, 2011). This has been emphasized in a previous study

which intended to restrict as much as possible top-down effects of phonological processing by combining short stimulus duration at high presentation rate with a low-level detection task (Kronschnabel et al., 2013). The study showed that even restricting high-order processing, dyslexics showed deficit in print sensitivity of the occipito-temporal areas. The authors interpreted the finding as supporting deficits at bottom-up orthographic processing stages in dyslexics. It is then important to consider task influences when interpreting ERP results based the functionality of VWFA.

Besides experimental considerations, it is important to appreciate that reading is an intrinsically cross-modal process that requires interaction between different brain areas which specialize for reading. For this reason studies are increasingly focusing on connectivity between different regions of the reading network. More recently, the focus of some studies has shifted towards more global measures of network organization. The latter approach was investigated in chapter 5, which is discussed in the following paragraph.

6.3 Network Analysis of the Functional Reading Systems

Previous studies suggested a number of mixed functional connectivity abnormalities as well as disturbances in network organization in dyslexia (Frye et al., 2012; Koyama et al., 2013). The study in **chapter 5** examined the large-scale topological characteristics of brain networks in dyslexics and typical readers by applying the minimum spanning tree (MST; a recently developed graph analysis) to eyes-closed resting state EEG. The MST method was introduced to allow unbiased group network comparisons by establishing a fixed number of links between the nodes (Stam et al., 2014). The MST algorithm was applied to the functional connectivity matrices including all 64 scalp channels, for different frequency bands. The resulting 'tree' represents the subnetwork with maximum strength of connectivity from which graph-derived measures are analyzed. We found a clear dissociation between PLI connectivity analysis and MST analysis of network organization; while the groups did not differ in strength of connectivity, the MST analysis revealed differences in network organization for the theta band (4-8 Hz). The MST measure *leaf fraction* was smaller in dyslexic children, indicating less network integration, compared to typical readers. In addition, there was a significant group difference for diameter and a trend for eccentricity suggesting less communication between nodes of the network in dyslexic compared to typical readers. In terms of the extreme tree topologies, the pattern of results found in our study suggests a more path-like configuration in dyslexic children and a more star-like topology in typically reading children.

An important consideration is how the MST measures relate to conventional graph metrics. In an extensive series of simulations Tewarie et al. (2015) observed that both leaf fraction and diameter are negatively and positively related, respectively, to path length. Thus, our results are consistent with a recent study that examined the topology of structural networks in Chinese dyslexics in which a longer

path length was observed for dyslexics relative to controls (Liu et al., 2015). In addition, MST leaf fraction and diameter are also related to the 'scale freeness' of the network; in particular, leaf fraction largely increases for scale-free networks (Tewarie et al., 2015). Accordingly, our results may also indicate a deviation from scale-free topologies that is larger in dyslexics compared to typical readers. A scale-free topology is indicative of the presence of highly connected hub nodes in the network (Stam, 2014). In this regard, our findings may suggest dysfunctional hub nodes in dyslexia.

Interestingly, we only found group differences in network organization in the theta band. This is consistent with previous research on functional and scaling aspects of oscillatory activity. Regarding general properties of the brain as an oscillatory system, research suggests that slow oscillations such as theta recruit large networks whereas higher frequencies are more confined to smaller networks (Buzsáki & Draguhn, 2004). Further, it is proposed that synchronous activity of lower frequency bands such as theta, mediate long range integration between processes involving several cortical areas (A. Von Stein & Sarnthein, 2000). More specifically, theta frequencies have been related to long range interactions during top-down processes such as working memory retention (A. Von Stein & Sarnthein, 2000). In relation to language-specific functions, it has been suggested that synchronous theta activity may play an important role in speech processing (Luo & Poeppel, 2007; Poeppel et al., 2008) and language comprehension (Bastiaansen et al., 2008). Finally, our findings support previous evidence suggesting abnormalities in theta oscillations in developmental dyslexia (Arns & Peters, 2007; Goswami, 2011; Klimesch, 1999; Marosi, Harmony, & Becker, 1995; Spironelli, Penolazzi, & Angrilli, 2008).

The MST metrics of the EEG obtained during rest did not relate to the reading measures differentiating children with dyslexia from controls. Previously, Dimitriades et al., (2013) did observe a positive relation between local efficiency of temporo-parietal networks in the beta band of the resting-state EEG and word reading measures in children with reading difficulties but not in typical controls. Similarly, Vourkas et al. (2011) reported significant correlations between graph metrics and phonological decoding ability but this relation was obtained for task-related EEG. In view of the limited studies available to date we are reluctant to interpret the absence in our results of a relation between reading ability measures and MST metrics. Future studies should examine the potential relations between these measures more systematically by comparing both resting-state and task-related EEG measures.

Our MST analysis of differences in network topologies between dyslexic children vs. typical controls was suggestive of a less integrated network configuration in dyslexia in the EEG theta band. The results might indicate less efficient long-range connections in dyslexics, which would be in line with evidence suggesting disrupted connectivity between the distant cortical areas of the reading network (Sandak et al., 2004). Future studies employing MST analysis might want to adopt a longitudinal perspective in examining the developmental trajectories of network organization during

reading acquisition. Furthermore, it would be of considerable interest to examine how functional network organization is changed following reading intervention (e.g., Koyama et al., 2013). Finally, future studies should perform MST analysis during task (e.g. letter-speech sound mapping) to advance our understanding of how network configuration metrics relate to reading skills.

6.4 General Conclusions

The studies presented in this thesis contribute to our understanding of dyslexics' deficits and their remediation. In addition the current ERP and EEG findings advance our knowledge of the brain systems implicated in reading and the functional organization of neural connectivity characterizing dyslexic children. First, our behavioral study supported the notion of a failure to integrate letter-speech sounds as a core deficit in dyslexia. Most importantly, it showed that intensively training fluency in audiovisual integration can substantially improve reading fluency even in a relatively short intervention. Second, our brain potential studies underscored the importance of visual specialization for fast word recognition for reading fluency in dyslexics in 3rd grade. Additionally, our longitudinal ERP study suggested that visual responses during reading can provide with additional predictions of treatment success. Further, these studies also illustrated the supportive role of multisensory integration systems on the development of visual specialization. Finally, the interactive nature of reading was taken into consideration in chapter 5, which illustrated how the examination of global organization of functional networks may provide with additional information on the neural deficits underlying dyslexia.

Appendices

Appendix A

Appendix to Chapters 2 & 4:

Stimuli used in ERP studies of visual word recognition

Dutch word	Translation	Symbol string	N. characters
baby	baby	**babu**	4
café	cafe	**café**	4
cola	coke	**cola**	4
foto	photo	**foto**	4
kade	quay	**kade**	4
kano	canoe	**kano**	4
kilo	kilo	**kilo**	4
kiwi	kiwi	**kiwi**	4
lade	tray	**lade**	4
lego	lego	**lego**	4
mama	mom	**mama**	4
menu	menu	**menu**	4
papa	papa	**papa**	4
paté	pate	**pateé**	4
pony	pony	**ponu**	4
beker	cup	**beker**	5
bezem	broom	**besem**	5
boter	butter	**boter**	5
deken	blanket	**deken**	5
hamer	hammer	**hamer**	5
haven	port	**haven**	5
hotel	hotel	**hotel**	5
kamer	room	**kamer**	5
kever	beetle	**kever**	5
lepel	spoon	**lepel**	5
luier	diaper	**luier**	5
molen	mill	**molen**	5
nagel	nail	**nagel**	5
panda	panda	**panda**	5
patat	chips	**patat**	5
pinda	peanut	**pinda**	5
raket	rocket	**raket**	5
regel	line	**regel**	5
tafel	table	**tafel**	5
tegel	tile	**tegel**	5
veter	lace	**veter**	5
vogel	bird	**vogel**	5
wagen	car	**wagen**	5
zadel	saddle	**sadel**	5
zomer	summer	**somer**	5

Dutch word	Translation	Symbol string	N. characters
bakker	baker	**bakker**	6
ballon	balloon	**ballon**	6
banaan	banana	**banaan**	6
danser	dancer	**danser**	6
deksel	cover	**deksel**	6
dokter	doctor	**dokter**	6
gordel	belt	**gordel**	6
hengel	fishing rod	**hengel**	6
honing	honey	**honing**	6
kameel	camel	**kameel**	6
karton	cardboard	**karton**	6
koffer	suitcase	**koffer**	6
koning	king	**koning**	6
kuiken	chick	**kuiken**	6
ladder	ladder	**ladder**	6
mantel	mantle	**mantel**	6
matras	mattress	**matras**	6
modder	mud	**modder**	6
papier	paper	**papier**	6
wekker	alarm	**wekker**	6
borstel	brush	**borstel**	7
citroen	lemon	**citroen**	7
dochter	daughter	**dochter**	7
fabriek	factory	**fabriek**	7
fornuis	stove	**fornuis**	7
gordijn	curtain	**gordijn**	7
hamster	hamster	**hamster**	7
kapster	hairdresser	**kapster**	7
kantoor	office	**kantoor**	7
kasteel	castle	**kasteel**	7
ketting	chain	**ketting**	7
lichaam	body	**lichaam**	7
matroos	sailor	**matroos**	7
parkiet	parakeet	**parkiet**	7
pinguin	penguin	**pinguin**	7
pistool	pistol	**pistool**	7
potlood	pencil	**potlood**	7
pudding	pudding	**pudding**	7
sandaal	sandal	**sandaal**	7
yoghurt	yoghurt	**uoghurt**	7

Appendix B

Appendix to Chapter 3: Touchscreen Used in Letter-Speech Sound Integration Training

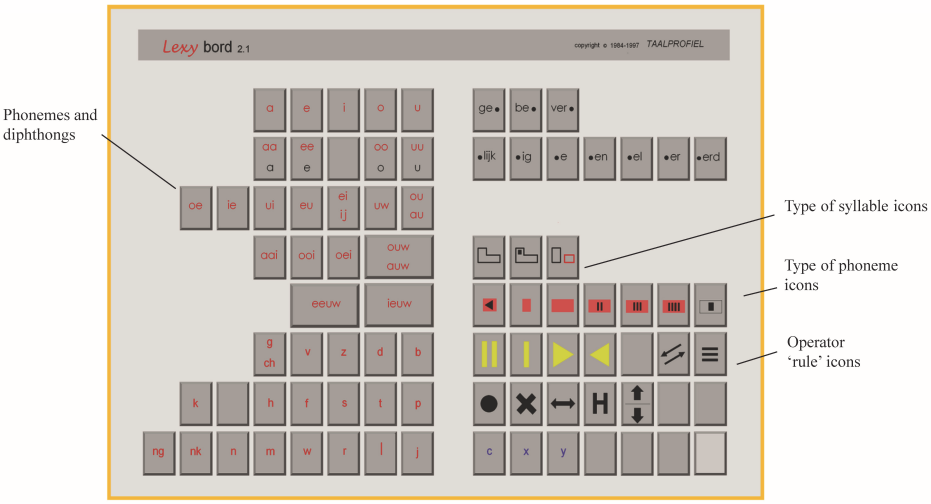


Figure B.1. Illustration of the touchscreen used in training

Appendix C

Appendix to Chapter 5: Graph Analysis of EEG Resting State Functional Networks in Dyslexic and Typically Reading Children

Appendix C.1. Descriptive Statistics of Complete Sample

Participants

Third-grade dyslexic children (N = 34; 9.03 ± 0.43 years old) were recruited from a nation-wide center for dyslexia in the Netherlands. All of them had a percentile score of 10 or lower on a standard reading test and they participated in the EEG recordings before starting their treatment program at the center. A group of 19 third-grade, typical readers (8.74 ± 0.31 years old) was recruited from several primary schools attended by children with the same sociodemographical background as the dyslexic group (see Appendix Table C.1 for group characteristics).

Table C.1. Descriptive statistics showing reading accuracy and fluency scores in the complete sample.

	Typical Readers	Dyslexics		
	M(SD)	*M(SD)*	*p*-value	η^2
N	19	34		
Sex ratio (m:f)	8:11	19:15		
Handedness (L:R)*	2:14	5:29		
Age	8.74 (0.31)	9.03 (0.43)	.012	0.12
RAVEN - IQ test [a]	7.02 (1.53)	7.17 (1.42)	.733	0.01
3DM Word reading - *accuracy*[b]				
HF	99.07 (1.13)	93.18 (5.62)	.000	0.29
LF	97.22 (3.32)	86.48 (13.60)	.001	0.18
Pseudo	86.89 (9.67)	72.85 (17.68)	.002	0.17
Total [T][c]	49.11 (9.13)	33.47 (12.38)	.000	0.31
3DM Word reading - *fluency* [T]				
HF	52.84 (7.78)	31.38 (5.89)	.000	0.71
LF	54.68 (9.26)	32.00 (6.33)	.000	0.69
Pseudo	52.95 (9.7)	30.74 (6.41)	.000	0.66
Total	53.89 (9.59)	30.88 (5.39)	.000	0.71
One-Minute Test -*fluency* [SS][d]	11.53 (2.89)	3.85 (1.96)	.000	0.72
Text Reading - *fluency*[T]**	54.58 (8.24)	33.36 (5.99)	.000	0.70
3DM Spelling - *accuracy*[T]	50.05 (9.05)	36.47 (7.20)	.000	0.41
3DM Spelling - *fluency*[T]	54.79 (8.87)	37.59 (6.83)	.000	0.55
Letter-speech sound associations [T]				
L-SS identification - *accuracy*	46.68 (7.82)	43.18 (12.25)	.266	0.02
L-SS discrimination - *accuracy***	50.05 (9.48)	43.88 (9.89)	.032	0.09
L-SS identification - *fluency*	52.84 (7.27)	42.82 (7.15)	.000	0.32
L-SS discrimination - *fluency***	52.11 (6.81)	46.64 (9.55)	.033	0.09
3DM Naming speed scores[T]**				
Letters	49.79 (7.22)	36.61 (7.80)	.000	0.42
numbers	50.16 (10.99)	37.21 (8.52)	.000	0.31
Total	49.42 (7.88)	35.97 (9.10)	.000	0.37

[a] C scores (M = 5, SD = 2).[b] Raw scores. [c] T scores (M = 50, SD = 10). [d] SS scores (M = 10, SD= 3).
*Data missing for 3 participants; Typical N = 16. ** Data missing for one participant; Dyslexics N = 33

Appendix C.2. Control Analysis on Equal Sample Sizes

Participants

Fifteen dyslexic children (9.01 ± 0.44 years old) were randomly selected from a sample recruited from a nation-wide center for dyslexia in the Netherlands. All of them had a percentile score of 10 or lower on a standard reading test and they participated in the EEG recordings before starting their treatment program at the center. A group of 15 third-grade, typical readers (8.75 ± 0.31 years old) was recruited from several primary schools attended by children with the same sociodemographical background as the dyslexic group (see Table C.2 for group characteristics).

Table C.2. Descriptive statistics showing reading accuracy and fluency scores in a random sample of 15 dyslexics.

	Typical Readers	Dyslexics		
	M(SD)	*M(SD)*	*p*-value	η^2
N	15	15		
Sex ratio (m:f)	6:9	7:8		
Handedness (L:R)*	2:10	2:13		
Age	8.75 (0.31)	9.01 (0.44)	.070	0.11
RAVEN - IQ test [a]	6.70 (1.51)	7.07 (1.64)	.530	0.01
3DM Word reading - *accuracy* [b]				
High Frequency	99.28 (1.05)	93.77 (4.17)	.000	0.47
Low Frequency	98.32 (2.54)	86.53 (15.00)	.006	0.24
Pseudo	88.70 (8.48)	76.17 (16.04)	.012	0.20
Total [T][c]	51.40 (8.00)	36.13 (10.76)	.000	0.41
3DM Word reading - *fluency* [T]				
High Frequency	54.27 (7.58)	33.07 (6.08)	.000	0.72
Low Frequency	56.80 (8.98)	33.27 (5.93)	.000	0.72
Pseudo	54.93 (9.71)	32.53 (6.41)	.000	0.67
Total	55.93 (9.51)	32.20 (5.12)	.000	0.72
One-Minute Test -*fluency* [SS][d]	12.07 (2.94)	4.40 (2.29)	.000	0.70
Text Reading - *fluency*[T]	55.27 (8.41)	35.43 (4.99)	.000	0.69
3DM Spelling - *accuracy*[T]	51.73 (8.62)	35.13 (5.00)	.000	0.60
3DM Spelling - *fluency*[T]	54.33 (9.90)	37.47 (5.48)	.000	0.54
3DM Phoneme deletion - *accuracy* [T]**	53.73 (8.39)	39.40 (5.96)	.000	0.51
Letter-speech sound associations [T]				
L-SS identification - *accuracy*	46.87 (8.65)	44.67 (11.91)	.567	0.01
L-SS discrimination - *accuracy***	50.80 (10.28)	43.86 (9.24)	.067	0.12
L-SS identification - *fluency*	51.53 (7.67)	43.40 (8.04)	.008	0.22
L-SS discrimination - *fluency***	51.73 (7.36)	47.71 (5.98)	.120	0.09
3DM Naming speed scores[T]				
Letters	50.93 (6.95)	39.13 (6.03)	.000	0.47
numbers	52.73 (10.67)	39.53 (6.94)	.000	0.37
Total	50.80 (7.73)	40.00 (6.78)	.000	0.37

[a] C scores (M = 5, SD = 2).[b] Raw scores. [c] T scores (M = 50, SD = 10). [d] SS scores (M = 10, SD= 3)

Results

MST analysis. The group analysis on MST measures found significant group effects in the theta band (see Table C.3). Leaf fraction - reflecting the integration of information within the network - was significantly lower in dyslexics relative to typical readers, F (1, 28) = 8.95, p = .006, η^2 = 0.24. Further, the group effect on diameter just fell short of significance, F (1, 28) = 4.11, p = .052, η^2 = 0.13, indicating a trend for higher diameter in dyslexics, relative to typical readers. We did not find significant correlations between any of these measures and reading. Finally, in the gamma band, the ANOVAs revealed a group effect on hierarchy, F (1, 28) = 5.57, p = .025, η^2 = 0.17, suggesting higher hierarchy in typical readers relative to dyslexics (see Table C.4). No significant group effects were found for any of the other MST measures or other frequency bands, ps > .124.

Table C.3. PLI average and MST measures in a random sample of 15 dyslexics.

		Typical Readers N = 15		Dyslexics N =15				
		M	*(SD)*	*M*	*(SD)*	*F*	*p* value	η^2
Delta	PLI	0.202	(0.012)	0.206	(0.009)	1.46	.246	0.05
	Degree	0.163	(0.022)	0.170	(0.019)	0.91	.347	0.03
	Leaf	0.583	(0.012)	0.582	(0.013)	0.05	.825	0.00
	Eccentricity	0.168	(0.010)	0.167	(0.011)	0.32	.859	0.00
	Kappa	3.551	(0.259)	3.613	(0.246)	0.47	.497	0.02
	Diameter	0.216	(0.013)	0.215	(0.015)	0.03	.873	0.00
	BC	0.704	(0.026)	0.714	(0.038)	0.69	.415	0.02
	Degree Correlation	-0.325	(0.030)	-0.320	(0.037)	0.22	.643	0.01
	Hierarchy	0.418	(0.015)	0.412	(0.025)	0.55	.465	0.02
Theta	PLI	0.176	(0.008)	0.176	(0.010)	0.01	.924	0.00
	Degree	0.152	(0.011)	0.146	(0.013)	1.84	.186	0.06
	Leaf	**0.584**	**(0.013)**	**0.569**	**(0.015)**	**8.95**	**.006**	**0.24**
	Eccentricity	*0.169*	*(0.011)*	*0.174*	*(0.006)*	*3.08*	*.090*	*0.10*
	Kappa	3.415	(0.149)	3.331	(0.146)	2.52	.124	0.08
	Diameter	*0.216*	*(0.015)*	*0.225*	*(0.008)*	*4.11*	*.052*	*0.13*
	BC	0.701	(0.022)	0.696	(0.020)	0.45	.508	0.02
	Degree Correlation	-0.327	(0.037)	-0.317	(0.028)	0.59	.450	0.02
	Hierarchy	0.419	(0.015)	0.411	(0.014)	2.18	.151	0.07
Alpha	PLI	0.209	(0.033)	0.198	(0.028)	0.82	.372	0.03
	Degree	0.187	(0.028)	0.190	(0.034)	0.03	.856	0.00
	Leaf	0.623	(0.030)	0.612	(0.030)	1.12	.300	0.04
	Eccentricity	0.154	(0.013)	0.160	(0.010)	2.08	.160	0.07
	Kappa	3.967	(0.398)	3.980	(0.508)	0.00	.991	0.00
	Diameter	0.197	(0.018)	0.206	(0.014)	2.12	.157	0.07
	BC	0.713	(0.025)	0.710	(0.029)	0.09	.761	0.00
	Degree Correlation	-0.345	(0.028)	-0.355	(0.047)	0.30	.591	0.01
	Hierarchy	0.441	(0.018)	0.435	(0.026)	0.54	.468	0.02

Note. Bold text represents significant results ($p < 0.05$); italic text represents results at trend level. MST, minimum spanning tree; PLI, phase lag index; BC, betweenness centrality

Table C.4.PLI average and MST measures in a random sample of 15 dyslexics.

		Typical Readers N = 15		Dyslexics N =15				
		M	*(SD)*	*M*	*(SD)*	*F*	*p* value	η^2
Beta	PLI	0.099	(0.006)	0.100	(0.006)	0.24	.625	0.01
	Degree	0.160	(0.019)	0.162	(0.014)	0.12	.732	0.00
	Leaf	0.582	(0.018)	0.583	(0.020)	0.03	.875	0.00
	Eccentricity	0.168	(0.010)	0.170	(0.009)	0.37	.547	0.01
	Kappa	3.516	(0.244)	3.547	(0.220)	0.15	.704	0.01
	Diameter	0.216	(0.013)	0.219	(0.012)	0.64	.431	0.02
	BC	0.691	(0.026)	0.699	(0.020)	0.90	.352	0.03
	Degree Correlation	-0.319	(0.027)	-0.325	(0.036)	0.22	.645	0.01
	Hierarchy	0.425	(0.015)	0.421	(0.018)	0.45	.510	0.02
Gamma	PLI	0.092	(0.006)	0.090	(0.006)	0.26	.612	0.01
	Degree	0.224	(0.041)	0.225	(0.061)	0.01	.910	0.00
	Leaf	0.637	(0.034)	0.622	(0.039)	1.38	.250	0.05
	Eccentricity	0.152	(0.011)	0.158	(0.016)	1.30	.263	0.04
	Kappa	4.587	(0.875)	4.618	(1.510)	0.03	.867	0.00
	Diameter	0.196	(0.014)	0.205	(0.020)	1.73	.198	0.06
	BC	0.725	(0.027)	0.736	(0.029)	1.03	.318	0.04
	Degree Correlation	-0.366	(0.031)	-0.354	(0.038)	1.06	.313	0.04
	Hierarchy	**0.443**	**(0.020)**	**0.427**	**(0.016)**	**5.57**	**.025**	**0.17**

Note. Bold text represents significant results ($p < 0.05$).
MST, minimum spanning tree; PLI, phase lag index; BC, betweenness centrality

Appendix C.3. Control Analysis: Only Participants without Interpolated Electrodes

Participants

21dyslexic children (9.08 ± 0.36 years old; 13 boys, 8 girls) were recruited from a nation-wide center for dyslexia in the Netherlands. All of them had a percentile score of 10 or lower on a standard reading test and they participated in the EEG recordings before starting their treatment program at the center. A group of 7 third-grade, typical readers (8.73 ± 0.29 years old; 2 boys, 5 girls) was recruited from several primary schools attended by children with the same sociodemographical background as the dyslexic group. An ANOVA revealed that the age difference was significant, F (1, 42) = 5.54, p = .026, η^2 = 0.18, suggesting that dyslexics were slightly older than typical readers.

Results

MST analysis. The results of the group analyses on MST measures are presented in Tables A.5 and A.6. In the delta band, the strength of degree correlation - index of whether the degree of a node relates to the degree of its neighbors- was lower in dyslexics than in typical readers, F (1, 28) = 4.26, p = .049, η^2 = 0.14. In the theta band, leaf fraction - reflecting the integration of information within the network - was significantly lower in dyslexics relative to typical readers, F (1, 28) = 6.34, p = .019, η^2 = 0.21. Further, in the alpha band, there were trends for higher diameter and eccentricity in dyslexics relative to typical readers, F (1, 28) = 3.21, p = .085, η^2 = 0.11, and F (1, 28) = 2.98, p = .097, η^2 = 0.11, respectively. In the beta band, a trend for higher diameter in dyslexics vs. typical readers was also found, F (1, 28) = 3.21, p = .081, η^2 = 0.11. Finally, in the gamma band, the ANOVAs revealed a group effect on hierarchy, F (1, 28) = 4.78, p = .038, η^2 = 0.16, suggesting higher hierarchy in typical readers relative to dyslexics. No significant group effects were found on any of the other MST measures for the other frequency bands, $ps > .108$.

Table C.5. PLI average and MST measures for subjects without interpolated electrodes.

		Typical Readers N = 7		Dyslexics N =21				
		M	*(SD)*	*M*	*(SD)*	*F*	*p* value	η^2
Delta	PLI	0.200	(0.012)	0.205	(0.012)	0.83	.374	0.03
	Degree	0.160	(0.020)	0.160	(0.022)	0.00	.994	0.00
	Leaf	0.580	(0.011)	0.573	(0.018)	0.89	.354	0.03
	Eccentricity	0.168	(0.010)	0.168	(0.011)	0.00	.980	0.00
	Kappa	3.539	(0.175)	3.503	(0.276)	0.15	.705	0.01
	Diameter	0.217	(0.012)	0.217	(0.015)	0.01	.916	0.00
	BC	0.703	(0.035)	0.706	(0.034)	0.04	.852	0.00
	Degree Correlation	**-0.343**	**(0.030)**	**-0.311**	**(0.036)**	**4.26**	**.049**	**0.14**
	Hierarchy	0.417	(0.020)	0.410	(0.019)	0.57	.455	0.02
Theta [a]	PLI	0.175	(0.004)	0.173	(0.008)	0.53	.474	0.02
	Degree	0.152	(0.009)	0.146	(0.014)	1.03	.319	0.04
	Leaf	**0.584**	**(0.014)**	**0.568**	**(0.015)**	**6.34**	**.019**	**0.21**
	Eccentricity	0.172	(0.012)	0.175	(0.006)	0.76	.391	0.03
	Kappa	3.393	(0.117)	3.318	(0.151)	1.49	.234	0.06
	Diameter	0.221	(0.017)	0.225	(0.008)	0.80	.379	0.03
	BC	0.697	(0.030)	0.692	(0.018)	0.28	.602	0.01
	Degree Correlation	-0.327	(0.040)	-0.320	(0.030)	0.19	.664	0.01
	Hierarchy	0.422	(0.019)	0.413	(0.015)	1.56	.224	0.06
Alpha [b]	PLI	0.191	(0.030)	0.193	(0.033)	0.01	.934	0.00
	Degree	0.189	(0.037)	0.180	(0.027)	0.49	.490	0.02
	Leaf	0.622	(0.030)	0.607	(0.028)	1.48	.235	0.06
	Eccentricity	*0.154*	*(0.015)*	*0.162*	*(0.010)*	*2.98*	*.097*	*0.11*
	Kappa	3.985	(0.512)	3.836	(0.424)	0.62	.440	0.02
	Diameter	*0.197*	*(0.020)*	*0.209*	*(0.013)*	*3.21*	*.085*	*0.11*
	BC	0.720	(0.032)	0.707	(0.030)	0.08	.776	0.00
	Degree Correlation	-0.359	(0.020)	-0.355	(0.043)	0.99	.328	0.04
	Hierarchy	0.435	(0.017)	0.433	(0.027)	0.14	.712	0.01

Note. Bold text represents significant results ($p < 0.05$); italic text represents results at trend level.
[a] Two outliers based on spectral power excluded; Dyslexics N = 19.[b] One outlier based on spectral power excluded; Dyslexics N = 20. MST, minimum spanning tree; PLI, phase lag index; BC, betweenness centrality

Table C.6. PLI average and MST measures for subjects without interpolated electrodes.

		Typical Readers N = 7		Dyslexics N =21				
		M	*(SD)*	*M*	*(SD)*	*F*	*p* value	η^2
Beta	PLI	0.099	(0.006)	0.101	(0.011)	0.16	.696	0.01
	Degree	0.164	(0.020)	0.161	(0.020)	0.14	.711	0.01
	Leaf	0.589	(0.010)	0.576	(0.021)	2.65	.116	0.09
	Eccentricity	0.163	(0.009)	0.170	(0.010)	2.77	.108	0.10
	Kappa	3.553	(0.224)	3.509	(0.276)	0.18	.676	0.01
	Diameter	*0.209*	*(0.012)*	*0.219*	*(0.013)*	*3.29*	*.081*	*0.11*
	BC	0.694	(0.031)	0.700	(0.020)	0.35	.562	0.01
	Degree Correlation	-0.308	(0.025)	-0.308	(0.041)	0.00	.951	0.00
	Hierarchy	0.428	(0.019)	0.415	(0.021)	2.25	.146	0.08
Gamma	PLI	0.091	(0.005)	0.091	(0.006)	0.07	.793	0.00
	Degree	0.235	(0.044)	0.209	(0.061)	1.84	.187	0.07
	Leaf	0.645	(0.038)	0.618	(0.039)	2.64	.116	0.09
	Eccentricity	0.150	(0.012)	0.159	(0.016)	1.35	.257	0.05
	Kappa	4.820	(1.115)	4.374	(1.433)	1.17	.290	0.04
	Diameter	0.194	(0.016)	0.206	(0.020)	1.63	.213	0.06
	BC	0.731	(0.021)	0.725	(0.030)	0.23	.633	0.01
	Degree Correlation	-0.373	(0.034)	-0.351	(0.041)	1.66	.209	0.06
	Hierarchy	**0.445**	**(0.020)**	**0.428**	**(0.016)**	**4.78**	**.038**	**0.16**

Note. Bold text represents significant results ($p < 0.05$); italic text represents results at trend level.
MST, minimum spanning tree; PLI, phase lag index; BC, betweenness centrality.

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Submitted Articles

Fraga González, G., van der Molen, M.J.W., G., Žarić, G., Bonte, M., Tijms, J., Blomert, L., Stam, C.J., Van der Molen, M.W. (under review). Graph Analysis of EEG Resting State Functional Networks in Dyslexic and Typically Reading Children.

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Summary

The ability to read is essential to attain society's literacy demands. Unfortunately, a significant percentage of the population experiences major difficulties in mastering reading and spelling skills. Individuals diagnosed with developmental dyslexia are at severe risk for adverse academic, economic, and psychosocial consequences, thus requiring clinical intervention. To date, there is no effective remediation for the lack of reading fluency, which remains as the most persistent symptom in dyslexia.

Reading involves visual decoding of learned alphabetic symbols to access word meanings and pronunciations. In alphabetic orthographies, the elements of spoken language – speech sounds or phonemes – are associated to the letters or clusters of letters – graphemes. Effectively establishing these associations is essential to connect spelling of written words to their pronunciation and meaning. The adequate mapping of letters and speech sounds ultimately enables the development of sight word reading, that is, automatic and accurate word reading from memory. Neuroimaging research suggests that two posterior brain systems, in the left parieto-temporal and occipito-temporal regions, are involved in the development of letter-speech sound integration and automatic visual word recognition, respectively.

A recent theoretical account of dyslexia, based on evidence from behavioral and neuroimaging studies, proposes a failure to integrate letters and speech sounds as the most proximal cause for reading impairments. The present work combines this theoretical framework with recent advances in our knowledge of the brain networks specialized for reading. This thesis aims at identifying factors involved in the failure to develop fluent reading as well as factors of treatment success in addressing the 'fluency barrier' in dyslexia. To fulfill this goal, we used a longitudinal design including both behavioral and neurophysiological measures in dyslexics at 3rd grade of school.

In **chapter 2** we examined brain potentials in dyslexics and typically reading children during a visual word recognition task. The study focused on left occipito-temporal N1 responses to words vs. symbol strings as they reflect visual specialization to print, which is proposed to become increasingly important after the first stages of reading instruction. We found print sensitivity of N1, showing stronger responses for words than for symbol strings, in both dyslexics and typical readers. Most interestingly, there was a group difference in the pattern of N1 responses to words, which were smaller at left vs. right hemisphere sites in typical readers but were similar across hemispheres in the dyslexic group. This group difference was interpreted to indicate facilitated or less effortful word decoding in typical readers, resulting in smaller N1 amplitudes, relative to dyslexics. Importantly, we found an association between N1 amplitudes for words at the left hemisphere and reading fluency in the dyslexic group but not in the

typical readers group. We interpreted this finding to indicate stronger reliance on visual processing in dyslexics relative to typical readers.

In **chapter 3** we provide a behavioral evaluation of training fluency of letter-speech sound associations in dyslexics. This is done by means of a randomized controlled trial (RCT) design that allow us to compare pre-posttest reading scores in dyslexics following the training with an untrained group of dyslexics and a control group of typical readers. We pay special attention to reading fluency gains and how they relate to initial levels of letter-speech sound mapping skills. The training-group of dyslexics showed significant improvements in reading that were not limited to accuracy skills, but also extended to reading fluency. They also improved at a faster rate than typical readers. Further, the reading fluency gains were strongly correlated to initial letter-speech sound mapping fluency in untrained dyslexics but not in the training-group, suggesting that the latter overcame their initial mapping deficiency barrier. This conclusion concurs with reading development models in which the attainment of fluent letter-speech sound mappings are considered a critical step in the acquisition of fluent reading and, as suggested by neurophysiological evidence, in the development of a neural circuit for fast visual word recognition.

Given the beneficial effects of the present training and the relation of N1 neural responses with reading fluency found in our first analysis of brain potentials, **chapter 4** examines changes in N1 after training in dyslexics. The study in this chapter has a special focus on the relation between gains in reading fluency and 'normalization' of N1 responses to print. Additionally, we also examined whether initial N1 responses could discriminate between children who improved reading and those who would show poor reading improvements. We found a positive relation between gains in reading fluency and decrease of N1 responses at the left hemisphere. Interestingly, the initial N1 amplitudes were larger in improvers vs. poor-improvers, while they did not differ in their initial reading performance. The results support the sensitivity of N1 to reading fluency and its potential as a predictor of reading fluency acquisition.

In **chapter 5** we use resting state EEG to examine the organization of functional connectivity networks in dyslexia. In this study, we examine whole-brain network topologies in dyslexics and typical readers by means of a recently developed method based on graph theoretical analysis. We use a minimum spanning tree (MST) sub-graphs derived from connectivity matrices to characterize large-scale network properties related to integration of information and efficiency of communication within the network. The results showed that relative to typical readers, neural network organization in dyslexics could be characterized by a lower leaf fraction, indicating less network integration, and higher diameter together with a trend for higher eccentricity, pointing to less communication between network nodes. Collectively, our findings point to a less efficient network configuration (more line-like tree) in dyslexics relative to the more proficient configuration (more star-like tree) in typical readers.

Finally, **chapter 6** presents a summary of the findings of these studies and provides a neurocognitive interpretation of the main results. More general implications of neurophysiological research in the remediation of dyslexia are also discussed in this chapter. The studies in this thesis contribute to our understanding of reading deficits in dyslexia and their remediation. First, our behavioral study demonstrated the clinical potential of training fluency in letter-speech sound mapping, in support of the multisensory integration deficit account of dyslexia. Second, our brain potential studies underscored the role of visual specialization for fast word recognition in fluent reading and the potential use of occipito-temporal responses in predicting treatment success. Finally, our last study took into account the interactive nature of reading and examined global organization of functional brain networks, providing with additional information on the neural deficits underlying dyslexia.

Samenvatting

In de huidige geletterde maatschappij zijn adequate leesvaardigheden essentieel om succesvol te kunnen functioneren. Helaas ondervindt een aanzienlijk percentage van de bevolking ernstige problemen in het aanleren van lees- en spellingvaardigheden. Personen die gediagnosticeerd zijn met dyslexie hebben een verhoogd risico op negatieve academische, economische en psychosociale gevolgen, waardoor klinische interventie bij deze personen noodzakelijk is. Voor het gebrek aan leesvloeiendheid, het meest hardnekkige kenmerk van dyslexie, bestaat tot op heden echter geen effectieve aanpak.

Lezen is een proces waarbij aangeleerde alfabetische symbolen visueel worden gedecodeerd om toegang te krijgen tot de betekenis en uitspraak van woorden. In alfabetische orthografieën zijn de elementen van gesproken taal - spraakklanken of fonemen - verbonden met letters en letterclusters – grafemen. Het effectief vormen van deze letter-klank verbindingen is noodzakelijk om via de spelling van geschreven woorden toegang te krijgen tot uitspraak en betekenis. Het adequaat koppelen van letters en spraakklanken stelt een lezer uiteindelijk in staat tot het ontwikkelen van directe woordherkenning, oftewel het automatisch en accuraat herkennen van woorden vanuit het geheugen. Neuroimaging onderzoek suggereert dat twee posterieure hersensystemen - in de linker pariëtaal-temporale en occipitaal-temporale gebieden – betrokken zijn bij de ontwikkeling van respectievelijk de letter-spraakklank integratie en de automatische visuele woordherkenning.

Een recent theoretisch verklaringsmodel voor dyslexie, gebaseerd op bevindingen van zowel gedrags- en neuroimaging studies, veronderstelt het onvermogen om letters en spraakklanken te integreren als de meest proximale oorzaak voor leesproblemen. In het huidige proefschrift wordt dit theoretische verklaringsmodel gecombineerd met recente kennis over de hersennetwerken die gespecialiseerd zijn in lezen. Het proefschrift heeft als doel factoren te identificeren die een rol spelen in het onvermogen om letters en spraakklanken te integreren, en behandelfactoren te identificeren die succesvol zijn in het bestrijden van de leesvloeiendheid-barriere in personen met dyslexie. Om dit doel te bereiken, hebben we gebruik gemaakt van een longitudinaal onderzoeksdesign met zowel gedrags-en neurofysiologische maten bij dyslectici en gemiddelde lezers in groep 5.

In **hoofdstuk 2** onderzochten we hersen potentiëlen in dyslectici en gemiddelde lezers tijdens een visuele woordherkenning taak. Het onderzoek richtte zich op linker occipitaal-temporale N1 responsen op woorden ten opzichte van symboolreeksen. Deze reacties representeren visuele specialisatie voor geschreven tekst en hiervan wordt aangenomen dat dit steeds belangrijker wordt na de eerste fases van het leesonderwijs. Wij vonden dat gevoeligheid voor geschreven tekst, geoperationaliseerd als sterkere responsen op woorden dan voor symboolreeksen, in zowel dyslectici en gemiddelde lezers. De meest

interessante bevinding was een groepsverschil in het patroon van N1 responsen op woorden. Deze responsen waren kleiner in linker- ten opzichte van rechterhersenhelftgebieden in gemiddelde lezers, maar waren in beide hersenhelften van gelijke grootte in de groep dyslectici. Dit groepsverschil werd geïnterpreteerd als indicatie voor een soepeler of minder energie vergend woordherkenningsproces in gemiddelde lezers in vergelijking tot dyslectici, resulterend in kleinere N1 amplitudes. Van belang was dat we een associatie vonden tussen N1 amplitudes voor woorden in de linker hersenhelft en leesvloeiendheid in de dyslectische groep, maar niet in de groep gemiddelde lezers. Deze bevinding interpreteerden we als indicatie dat dyslectici een sterker beroep doen op visuele processen dan gemiddelde lezers.

In **hoofdstuk 3** presenteren we een gedragsevaluatie van een training gericht op vloeiendheid van letter-klank associaties in dyslectici. Dit wordt gedaan door middel van een gerandomiseerde gecontroleerde onderzoeksopzet (RCT) dat ons in staat stelt om pre-posttest leesscores van getrainde dyslectici te vergelijken met een ongetrainde groep dyslectici en een controlegroep van gemiddelde lezers. We besteden speciale aandacht aan verbetering in leesvloeindheid en aan de relatie hiervan met het aanvankelijke niveau van letter-klank vaardigheden. De groep getrainde dyslectici toonde significante verbetering in leesvaardigheid. Deze verbetering bleef niet beperkt tot leesnauwkeurigheid, maar betrof ook leesvloeiendheid. De verbetering in de groep getrainde dyslectici verliep ook sneller dan in de gemiddelde lezers. Bovendien bleek de verbetering in leesvloeiendheid sterk gecorreleerd met aanvankelijke vloeiendheid in letter-klank koppeling in de groep ongetrainde dyslectici, maar niet in de getrainde groep. Dit suggereert dat de getrainde groep hun aanvankelijke barrière, veroorzaakt door het onvermogen letters aan klanken te koppelen, had overwonnen. Deze conclusie sluit aan bij modellen van leesontwikkeling waarbij het beheersen van vloeiende letter-klank associaties wordt beschouwd als een cruciale stap in de ontwikkeling van leesvloeiendheid, en ook, zoals neurofysiologische bevindingen suggereren, in de ontwikkeling van een hersencircuit voor snelle visuele woordherkenning.

Vanuit de gevonden gunstige effecten van de training en de relatie tussen N1 responsen en leesvloeiendheid, bestuderen we in **hoofdstuk 4** hoe N1 responsen veranderen na de training in dyslectici. Het onderzoek in dit hoofdstuk is met name gericht op de relatie tussen verbeteringen in leessnelheid en 'normalisering' van N1 responsen op geschreven tekst. Daarnaast hebben we onderzocht of aanvankelijke N1 responsen onderscheid kunnen maken tussen kinderen waarbij de leesvaardigheid verbeterde tijdens de training en kinderen die weinig verbetering vertoonden. We vonden een positieve relatie tussen verbetering in leesvloeiendheid en afname van N1 responsen in de linker hersenhelft. Interessant hierbij_was dat de N1 amplitudes groter waren bij de kinderen die verbetering toonden ten opzichte van de kinderen die weinig verbetering toonden, terwijl deze groepen niet verschilden in aanvankelijke leesvaardigheid. De resultaten ondersteunen de assumptie dat N1

gevoelig is voor leesvloeiendheid en ook de potentie van de N1 als voorspeller voor de ontwikkeling van leesvloeiendheid.

In **hoofdstuk 5** maken we gebruik van rust EEG om inzicht te krijgen in de organisatie van functionele connectiviteitnetwerken bij dyslexie. In deze studie bestuderen we netwerk topologieen in het gehele brein bij dyslectici en gemiddelde lezers middels een recent ontwikkelde methode gebaseerd op grafiek theoretische analyse. We gebruiken *minimum spanning tree* (MST) sub-grafieken afgeleid van connectiviteit matrices om eigenschappen van grootschalige netwerken in kaart te brengen. Deze zijn gerelateerd aan integratie van informatie en efficiëntie van communicatie binnen het netwerk. De resultaten toonden aan dat, in vergelijking met gemiddelde lezers, de organisatie van neurale netwerken bij dyslectici werd gekenmerkt door een lagere *blad fractie*, wat een indicatie vormt voor minder integratie binnen het netwerk, en een hogere *diameter* in combinatie met een trend richting hogere *excentriciteit*, wat duidt op verminderde communicatie tussen netwerkknooppunten. Gezamenlijk wijzen deze bevindingen op een minder efficiënte netwerkconfiguratie (MST meer lijkend op een lijn) bij dyslectici ten opzichte van de meer bekwame configuratie (MST meer lijkend op een ster) bij de gemiddelde lezers.

Tot slot, presenteren we in hoofdstuk 6 een samenvatting van de bevindingen van deze studies en bieden we een neurocognitieve interpretatie van de belangrijkste resultaten. Meer algemene implicaties van neurofysiologische onderzoek voor de remediering van dyslexie worden hier ook besproken. De studies in dit proefschrift leveren een bijdrage aan ons begrip van de defecten in het leesproces bij dyslexie en de remediering hiervan. Ten eerste toont onze gedragsstudie het klinisch potentieel van het trainen van vloeiendheid in letter-klank associaties, en biedt daarmee ondersteuning voor het multisensorisch integratietekort verklaringsmodel van dyslexie. Ten tweede benadrukt onze studies naar hersenpotentiëlen de rol van visuele specialisatie voor snelle woordherkenning in vloeiend lezen en ook de mogelijkheid om occipitaal-temporale responsen te gebruiken om behandelsucces te voorspellen. Tenslotte, is in onze laatste studie rekening gehouden met het interactieve karakter van het leesproces en is de globale organisatie van functionele hersenennetwerken onderzocht. De bevindingen van deze studie bieden aanvullende informatie over de neurale tekorten die ten grondslag liggen aan dyslexie.

Resumen

La capacidad de leer de forma fluida es una habilidad esencial en la sociedad de la información. Desafortunadamente, un porcentaje significativo de la población presenta serias dificultades en la adquisición de habilidades de lectura y escritura. Los individuos diagnosticados con dislexia del desarrollo se encuentran en riesgo de padecer consecuencias académicas, económicas y psicosociales adversas, requiriendo por ello intervención clínica. Hasta la fecha, no hay un remedio efectivo para la falta de fluidez lectora, que continúa siendo el síntoma más persistente de la dislexia.

El proceso de lectura implica decodificar de forma visual una serie de símbolos alfabéticos para acceder al significado y la pronunciación de las palabras. En ortografías alfabéticas, los elementos del lenguaje oral (sonidos del habla o fonemas) se asocian con determinadas letras o grupos de letras (grafemas). El establecimiento de estas asociaciones de forma efectiva es esencial para conectar las formas ortográficas con su correcta pronunciación y significado, facilitando el desarrollo gradual de la capacidad de reconocimiento visual de palabras que, en última instancia, supone el acceso al léxico almacenado en la memoria de forma precisa y casi instantánea. La investigación en neuroimagen sugiere que dos sistemas posteriores en el cerebro, en las regiones parieto-temporal y occipito-temporal del hemisferio izquierdo, están relacionados respectivamente, con el desarrollo de las asociaciones grafema-fonema y con la especialización visual para el reconocimiento de palabras.

Basándose en evidencia de estudios comportamentales y de neuroimagen, un marco teórico reciente de la dislexia propone el fallo en la correcta integración de las asociaciones grafema-fonema como la causa más próxima de los problemas de lectura de los disléxicos. El presente trabajo combina este marco teórico con avances recientes en nuestro conocimiento de las redes neuronales especializadas en la adquisición de las habilidades lectoras. El objetivo de esta tesis es identificar factores implicados en las dificultades en el desarrollo de la fluidez lectora, así como otros factores que ayuden a predecir el éxito en las intervenciones en la dislexia. Para ello, este trabajo combina un diseño longitudinal, que incluye medidas comportamentales y neurofisiológicas en un grupo de niños disléxicos de 3° de primaria (grado 3).

El **capítulo 2** examina los potenciales evocados en disléxicos y lectores típicos durante una tarea de reconocimiento visual de palabras. El estudio se centra en las respuestas occipito-temporales en el hemisferio izquierdo, reflejadas en la amplitud de la respuesta N1, con latencia en torno a los 200 ms después la presentación estímulo visual. La amplitud de la respuesta N1 es comparada cuando palabras y cadenas de símbolos son presentados visualmente. Esta respuesta ha sido propuesta como uno de los

indicadores neurofisiológicos más relevantes de la especialización visual para el reconocimiento rápido de palabras, proceso que adquiere creciente importancia para la lectura después de las primeras etapas de instrucción. En este estudio encontramos que la respuesta N1 discrimina entre palabras y cadenas de símbolos, tanto en lectores típicos como en disléxicos, mostrando ambos respuestas más pronunciadas en los bloques de palabras. De forma más interesante, hallamos una diferencia entre los grupos en el patrón de respuestas N1 para palabras; estas respuestas fueron más reducidas en el hemisferio izquierdo, en comparación con el hemisferio derecho, en los lectores típicos, mientras que en los disléxicos las respuestas fueron comparables en ambos hemisferios. Esta diferencia fue interpretada como el reflejo de facilitación del procesamiento de palabras en el hemisferio izquierdo, en los lectores típicos, que no está presente en disléxicos. De forma más importante, encontramos una asociación entre las amplitudes de la respuesta N1 en el hemisferio izquierdo y la fluidez lectora en el grupo de disléxicos, pero no en el grupo de lectores típicos. Este resultado fue interpretado como indicativo de un mayor apoyo en el procesamiento visual durante la lectura en los lectores disléxicos.

El **capítulo 3** constituye una evaluación comportamental de un entrenamiento en la fluidez de las asociaciones letras-sonidos del habla (grafema-fonema) en un grupo de disléxicos. Utilizamos un diseño de prueba de control aleatorio para comparar las puntuaciones del pre y del post-test en un grupo de disléxicos, siguiendo una intervención con las de un grupo de disléxicos sin recibir entrenamiento especial, y un grupo de buenos lectores. Este estudio presta especial atención a las ganancias en fluidez lectora y su relación con los niveles iniciales de fluidez en las asociaciones grafema-fonema. El grupo que recibió el entrenamiento mostró mejoras significativas en las pruebas de lectura, que no se limitaron a las puntuaciones de precisión, sino que se extendieron a las de fluidez. Además, el grupo mejoró a un ritmo más rápido que el grupo de lectores típicos. Finalmente, encontramos una fuerte correlación entre las mejoras en fluidez lectora y los niveles iniciales de fluidez, en las asociaciones grafema-fonema en el grupo control de disléxicos sin entrenar, pero no en el grupo que siguió la intervención. Esto sugiere que los últimos superaron, en cierta forma, la barrera inicial de deficiencias en integración grafema-fonema. Esta conclusión coincide con los modelos del desarrollo lector**,** que consideran que la correcta automatización en las correspondencias grafema-fonema son un paso crítico en la adquisición de la fluidez lectora, y reciben el apoyo de evidencia neurofisiológica**,** sugiriendo que estos procesos favorecen el desarrollo de circuitos neurales para el procesamiento visual rápido de palabras.

Dados los efectos beneficiosos del programa de entrenamiento utilizado en este trabajo, así como la asociación entre la respuesta neurofisiológica N1 y la fluidez lectora, hallada en nuestro primer estudio, el **capítulo 4** evalúa cambios en la respuesta N1 en un grupo de disléxicos antes y después de seguir el entrenamiento. Este estudio está especialmente enfocado a la relación entre mejoras en fluidez lectora y la 'normalización' de las respuestas N1 en el hemisferio izquierdo. Adicionalmente, también examinamos si las respuestas N1 en el pre-test podrían discriminar entre niños que mejorar la lectura y

aquellos que presentaron escasas mejoras después de la intervención. Encontramos una correlación positiva entre las ganancias en lectura y la reducción en las respuestas N1, en el hemisferio izquierdo. De modo más interesante, las amplitudes del N1 iniciales fueron mayores en los niños que mejoraron, en comparación con aquellos que no se beneficiaron del entrenamiento, mientras que los grupos no se diferenciaban en las pruebas de lectura iniciales. Este resultado supone un apoyo adicional a la sensibilidad de N1 y su potencial como predictor de la adquisición de las habilidades de fluidez lectora.

En el **capítulo 5** utilizamos mediciones de EEG en estado de reposo para evaluar la organización de las redes de conectividad funcional en dislexia. Este estudio examina la topología a gran escala de las redes cerebrales en disléxicos y lectores típicos**,** a través de un método desarrollado recientemente, basado en el análisis teórico de grafos. Utilizamos un árbol de expansión mínima (mínimum spanning tree; MST), un sub-grafo derivado de la matriz general de conectividad funcional, que puede utilizarse para caracterizar propiedades de las redes relacionadas con la integración de la información, y la eficiencia en la comunicación entre los nodos. Los resultados mostraron que, en comparación con los lectores típicos, la organización de red en disléxicos puede caracterizarse por un número de hojas más bajo (medida que se asocia a una red menos integrada) y un mayor diámetro, además de una tendencia a mayor excentricidad (ambas medias relacionadas con menos comunicación entre los nodos de la red). En su conjunto, estos resultados sugieren una configuración de redes funcionales corticales menos eficiente, con una configuración más competente en los lectores típicos.

Finalmente, el **capítulo 6** presenta un sumario de los resultados de estos estudios y proporciona una interpretación neurocognitiva de los principales hallazgos. En este capítulo también se discuten las implicaciones más generales de la investigación neurofisiológica en el tratamiento de la dislexia. Los estudios de esta tesis contribuyen a nuestro entendimiento de los déficits de lectura en la dislexia y las posibles intervenciones para su mejora. En primer lugar, nuestro estudio comportamental demuestra el potencial clínico de entrenar la fluidez en la integración de letras con los sonidos del habla, coincidiendo con la aproximación teórica a la dislexia, basada en la idea un déficit en la integración multisensorial. En segundo lugar, nuestros de potenciales evocados subrayan el papel de la especialización visual para el reconocimiento rápido de palabras en la adquisición de la fluidez lectora, así como el potencial de emplear las respuestas occipito-temporales como predictores del éxito en el tratamiento. Para finalizar, nuestro último estudio toma en cuenta la naturaleza interactiva del proceso de lectura y examina la organización de las redes funcionales cerebrales, proporcionando información adicional sobre los posibles déficits a nivel neural subyacentes a la dislexia.

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