

BRAIN CONNECTIVITY DYNAMICS OF READING AND DYSLEXIA: TYPICAL
AND PERTURBED READING NETWORKS IN ADULTS AND CHILDREN

by

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Abstract

Developmental dyslexia is a language-based learning disability characterized by impaired reading speed and accuracy, poor spelling, and poor decoding abilities, despite normal intelligence. Neuroimaging investigations have identified brain regions critical for reading; few studies, however, have characterized how those regions interact to form networks and how those networks are perturbed in individuals with dyslexia. Advances in electroencephalography (EEG) analysis techniques now allow for intricate examination of these networks by focusing on individual frequency bands that comprise the brain signals. This study used EEG across several experiments to examine theta- and gamma-band connectivity patterns—first in the brains of adults, and then in dyslexic and typically-developing children during reading tasks. I investigated: 1) the ways in which the reading networks of typical and dyslexic readers differ, and 2) whether targeted reading interventions reduce these differences over time. Results show that dyslexic children generated greater occipito-temporal connectivity at critical time points in response to words and word-like stimuli, as well as increased engagement of higher-level language areas even for stimuli lacking linguistic content (e.g. consonant strings). After six months, the networks of dyslexic readers resembled those of their typically-developing counterparts for simple orthographic processing, but continued to utilize existing alternative pathways when engaging in higher-level language processes (e.g. phonology). This suggests that performance improvements in dyslexic readers are not necessarily related to changes to the typical left-lateralization of reading networks. These findings are in line with existing frameworks of dyslexia, and highlight the value of connectivity measures in understanding the neural underpinnings of word reading.

Lay Summary

Dyslexia is a learning disability in which reading speed and accuracy are impaired, despite normal intelligence. This research attempts to shed light on how reading skills develop in the brain, and how this development is altered in children with dyslexia.

By examining brainwaves, we investigated the development of brain networks and how reading-related brain areas send signals to each other to help make reading happen. This brain network communication offers insight as to which cognitive steps of the reading process are engaged at each moment.

Our results showed more neural communication in dyslexic children while reading, suggesting that they exerted additional resources to accomplish the same task compared to their “normal” classmates. However, after six months of training, dyslexic students’ reading scores improved and these improvements were correlated with a reduction in brain activity, suggesting that their brain networks became more efficient at reading. Based on the brain sites involved in this neural communication, dyslexic children seem to develop distinct networks rather than shifting to a “normal” network.

Preface

For this dissertation, I will often refer to myself in the first person with the understanding that I did not complete this work in isolation, but with the guidance and assistance of my supervisor, and with help from various collaborators. Since this dissertation is meant to illustrate my accumulated mastery of the topic at hand, I mean to indicate that each stage of this program of research—the experimental design, programming of tasks and stimuli, data collection and processing, and analysis—has been completed primarily by me, with exceptions listed below. This first-person referencing is in special consideration to the dissertation; any submission for publication would, of course, refer to our collective research group.

I prepared the content of this dissertation with guidance and minor edits from my supervisor, Dr. Lawrence M. Ward, and with input from Dr. Janet Werker and Dr. Todd Handy.

For the research presented in chapter 2, I designed the experiment as a variant of a similar earlier experiment originally designed by Dr. Ward and Dr. Urs Ribary (see Bedo et al., 2014). My contributions to this experiment include designing the stimuli, programming the stimulus presentation, preparing participants for EEG, collecting EEG data, and programming and executing the scripts for EEG processing and statistical analysis. The underlying methodologies for statistical analyses were developed with guidance from Dr. Ward.

Chapter 3 is a secondary analysis of data originally collected by Dr. Gerd Schulte-Körne's group at Ludwig-Maximilians-University Munich. These data were used in a previous publication from that group, published as: *Hasko, S., Groth, K., Bruder, J.*,

Bartling, J., & Schulte-Körne, G. (2013). The time course of reading processes in children with and without dyslexia: an ERP study. Frontiers in Human Neuroscience, 7(October), 570. All cognitive assessments were conducted by Dr. Schulte-Körne's group, who then subsequently used those results to classify participants as dyslexic readers or controls. EEG data were then collected as part of their experiment. Our own research group had no connection to the original study. We requested access to these data, which was granted after ensuring data privacy practices to keep the data anonymous. These raw data were then subjected to the same customized processing pipeline, designed and carried out by me, as in chapter 2. Moreover, I also interpreted and discussed these new results without consultation with Hasko, et al. who will, nonetheless, participate in eventual publication of the new results arising from these data.

Chapters 4 and 5 were based on data from a collaboration with colleagues at Simon Fraser University (SFU) as well as the Burnaby School District in Burnaby, British Columbia, as part of a pilot program investigating how schoolchildren with dyslexia process written words compared to typically developing children. Prior to EEG data collection, all reading assessments (Woodcock-Johnson Word Attack and Letter-Word Identification) were conducted by collaborators Dr. Dikla Ender-Fox from SFU and Janet Chow from the Burnaby School District, each of whom are specifically trained to administer such assessments. Additionally, educators at the Burnaby schools selected the students for participation in the study, and administered the FastForWord reading training that occurred between pre- and post-intervention experimental sessions. I designed the EEG experiment and programmed the stimuli, handled the on-site EEG data collection, and worked with the children as they participated. I processed the EEG data with custom

scripts that I developed, and carried out all analyses with guidance from Dr. Ward.

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CHAPTER 1: Introduction

Reading is one of the most important skills emphasized by modern educational systems. Children are taught core reading skills very early in life and society is constructed with the expectation that its citizens can quickly extract information from textual cues such as signs, notes, and books, among other things. It is, therefore, of great importance to understand cases in which children have severe challenges in learning to read (e.g. dyslexia), as these barriers impact their daily lives in significant ways. This dissertation aims to investigate just how these challenges in learning to read manifest in the brain, and how the brain changes as a result of specialized reading training.

Chapter 1 focuses on a review of relevant literature regarding the neural underpinnings of reading in the brain, and how these systems are affected by dyslexia. Then, I will discuss the importance of brain connectivity to understanding the developmental origins and dynamics of dyslexia, followed by an overview of my methodological approach to studying these topics.

Models of Reading

Before examining the neural signatures of dyslexia, it is critical to understand modern cognitive frameworks for reading so that we may then focus on the brain regions subserving the functions involved in word reading. To that end, I briefly describe here the two most prominent models of reading. And even though my research uses these models to inform the design and interpretation of the experiments presented here, my research does not directly bear on which of these models is correct.

Several cognitive models of reading have been proposed over the years in an

effort to describe visual word identification. These models must also attempt to capture all of the nuances and atypical processing documented by scientific research on the topic.

When reading a word, the brain attempts to use existing linguistic pathways whenever possible to speed up processing. Words that have been heavily practiced, or that have irregular spelling, utilize a direct route to the mental lexicon to retrieve their pronunciation (Dehaene. 2009). For example, a word like *fight* that does not follow conventional rules of written English, would make use of this pathway. On the other hand, words that are unfamiliar utilize an indirect “phonological” route, allowing readers to “sound out” the word in piecemeal fashion. Reading an entire passage then relies on the tight coordination of both of these pathways. This *dual-route* perspective of word identification is known as the Dual Route Cascaded model (DRC; Coltheart et al., 2001; Coltheart, 2006).

The primary competitor to the DRC viewpoint is the so-called connectionist perspective (Harm & Seidenberg, 1999, 2004; Seidenberg & McClelland, 1989), which leverages principles of parallel distributed processing (PDP) in neural networks.

The primary difference between DRC and connectionist perspectives is one of serial versus parallel processing. DRC models state that word reading is resolved serially by local orthographic processing units, such that an unfamiliar word is read letter-by-letter, each of which is converted to sound. The resulting sounds are then combined to produce a phonological representation of the word. In contrast, current connectionist models suggest that reading an unfamiliar word will activate orthographic units relevant to all of the letters simultaneously, then to be further refined down to the most probable candidate word.

Connectionist models are considered to more closely reflect neurobiological principles whereby individual features (e.g. a horizontal line and a vertical line) activate the relevant neural letter representations (e.g. the letter *T*). By doing this with every feature and letter, the model can then predict the identification of the word being read. The addition of reciprocal connections has resulted in this model resembling the top-down and bottom-up processing seen in many models of perception, further corroborating this perspective's resemblance to biological models. Even so, current DRC models tend to be more successful at resolving corner cases of word reading (e.g. position of grapheme irregularity and position-sensitive priming; Coltheart, 2006), and more closely resemble how children *learn* to read than do connectionist models. This may mean that connectionist models need further development (DRC frameworks have existed for several years longer), and not necessarily that the underlying connectionist principles are wrong, although others might argue otherwise (e.g., Coltheart, 2006).

This dissertation does not set out to prove or disprove either of the two models; rather, I use the models to guide expectations of brain activity and connectivity based on the field's current understanding of the relationships between cognition (e.g. phonology and semantics) and functional neuroanatomy associated with those functions. Presumably, the principles of these cognitive models will manifest in the brain activity in measurably distinct ways between typically-developing and dyslexic readers.

The Neural Correlates of Reading

Reading is a multi-stage process that involves the extraction of information from orthographic symbols (i.e. written language) and requires the engagement of multiple visual, auditory, and linguistic skillsets. Developmentally, this results in the emergence of

complex and nuanced systems of orthographic processing, semantics, pronunciation, grammar, and syntax that are all interconnected. In the brain of a typical reader, the process of reading spans across the entire left hemisphere – a collection of regions working in concert to convert visual information into an auditory code that is perceived as language, all of which requires substantial neural precision. Efforts to determine how the brain extracts linguistic information from orthography have yielded useful frameworks, especially with regard to impairments of such processing, as in dyslexia (Coltheart et al., 2001; Goswami, 2011; Lallier et al., 2016; Hancock et al., 2017; Harm & Seidenberg, 2004; Perry et al., 2007; Paulesu et al., 1996; Ramus, 2004).

Given that reading requires the utilization of several cognitive functions, extensive resources have gone into identifying brain regions responsible for handling the various aspects of reading written language. A useful characterization of orthographic processing – the stage at which signs and symbols are decoded as language, as opposed to other object categories (e.g. animals, places) – is particularly crucial for understanding how the brain accomplishes the task of reading. Once the orthographic information is decoded, it becomes accessible by other linguistic centers in the brain. Several studies now support the assertion that a region in left ventral occipito-temporal cortex (vOT), specifically in the left posterior fusiform gyrus, is critical for orthographic processing (Cohen et al., 2000; Dehaene et al., 2002; Eden et al., 2004; Hoeft et al., 2006; Jobard et al., 2003; Temple et al., 2002; Temple et al., 2003). The consistency with which this region responds specifically to orthographic stimuli has led some researchers to champion this region as being specialized for this task, naming it the visual word form area (VWFA; Cohen et al., 2000; Dehaene & Cohen, 2011). The neuroanatomical

location of the VWFA is advantageous from a network perspective, as it occupies a region of the brain directly between basic visual and high-level language processing centers in the brain, affording it efficient access to these regions.

In addition to the critical vOT region, several other regions in the brain play a crucial role in reading processes. Neuroimaging research has repeatedly shown that reading occurs predominantly across the left hemisphere in typical readers, although this does not preclude the involvement of the right hemisphere. After basic word form processing, several cortical sites allow for semantic access, including left anterior middle temporal gyrus (MTG; Price, 2012), left basal temporal areas, angular gyrus (AG; Price, 2012) and left inferior frontal gyrus (IFG, pars triangularis; McCandliss et al., 2003). At the stage of grapho-phonological conversion – converting the word forms into sounds – left MTG and STG (Vigneau et al., 2006), left IFG (pars opercularis), pre-central gyrus (PreCG; Vigneau et al., 2006), and left supramarginal gyrus (SMG; Hoeft et al., 2006; Vigneau et al., 2006) are engaged. The insights granted by the neuroimaging of reading processes in the brain have been highly influential in the development of brain-based reading frameworks. However, just as researchers investigate the regions and mechanisms that govern typical reading functions, they also seek out the mechanisms that underlie disruptions in reading – particularly those responsible for the emergence of dyslexia.

Reading, Phonology, and Dyslexia

Developmental dyslexia is a learning disability characterized by impaired reading speed and accuracy, poor spelling, and poor decoding abilities despite having normal intelligence. Dyslexia affects 3-7% of schoolchildren (Lindgren et al., 1985; Goswami,

2008) and is generally accompanied by deficits in phonological processing ability, in addition to a variety of subtle auditory processing problems. By far, the most prominent theories of dyslexia revolve around deficits in phonology, the processing of speech sounds. Phonology is the focal cognitive impairment in dyslexia while other aspects of language such as semantics, syntax, and articulation remain essentially intact (Dehaene, 2009; Ramus, 2004; Shaywitz & Shaywitz, 2005; Wolf, 2008). In order to produce words, we string together sequences of phonemes (e.g. /b/, /a/, /t/) to produce complete words (e.g. *bat*). In learning to read, children must gain awareness of the ability to pull words apart into their component phonemes, and moreover, learn that these speech sounds are mapped onto letters.

Support for the phonological deficit explanation of dyslexia is plentiful. Children and adults with dyslexia show marked deficits in general phonological awareness (Badian, 1998; Blachman et al., 1999; Bradley & Bryant, 1983; Brady et al., 1994; Cardoso-Martins, 1995; Cronin & Carver, 1998; de Jong & van der Leij, 2002; Duncan & Seymour, 2000; Goswami & Bryant, 1990; Hulme et al., 2002; Lukatela et al., 1995; Lundberg et al., 1991; Tunmer & Nesdale, 1985) in addition to impairments in processing various aspects of phonology, such as the discrimination of rapidly occurring sounds (Doelling et al., 2014; Hari & Kiesila, 1996; Hari & Renvall, 2001), and auditory frequency discrimination (Baldeweg et al., 1999). As well, individuals with dyslexia show difficulties in the manipulation, repetition, and evaluation of phonological components such as in rhyming (Duncan & Seymour, 2000; Hatcher & Hulme, 1999; Hulme, 2002; Maclean et al., 1987) and verbal short-term memory (Mann, 1984; Rohl & Pratt, 1995).

The phonological deficit perspective is further corroborated by neuroimaging research. Using positron emission tomography (PET) scanning, Paulesu and colleagues (1996) were among the first groups to show differences in brain activations between individuals with dyslexia and typical readers. Using word rhyming and verbal short-term memory tasks, they found that individuals with dyslexia use approximately the same regions as controls for phonological processing, but do so in an uncoordinated manner. In typical readers, both tasks activated Broca's and Wernicke's area simultaneously, whereas dyslexic brains selectively activated one or the other, depending on the task. Additionally, in a fMRI study comparing letter-case judgments (control) to non-word rhyming (phonological processing), typical readers showed increased activation in the angular gyrus (AG) and superior temporal gyrus (STG), while dyslexic subjects showed no difference in activation between the tasks (Shaywitz et al., 1998). Subsequent neuroimaging experiments have consistently yielded the same result – individuals with dyslexia show decreased activation in left hemispheric phonological processing regions such as STG, AG, SMG, and middle frontal gyrus (MFG) compared to controls (Eden et al., 2004; Hoeft et al., 2006; Temple, 2002; Temple et al., 2001).

In addition to differences in regional activation, the timing of neural responses in dyslexia seems to be perturbed, as well. Event-related potential experiments testing phonological processing have shown longer latencies for the N400 ERP component in individuals with dyslexia compared to controls (Moisescu-Yiflach & Pratt, 2005; Russeler et al., 2007). When examining the underlying oscillatory frequency responses to linguistic stimuli, it has been shown that dyslexic participants exhibit less consistent entrainment to auditory stimuli when listening to sentences (Doelling et al., 2014); if the

timing of neural activity is impaired when parsing linguistic content, this may account for lower reading performance, as these processes share similar brain networks.

These deficits hinder the learning and mapping of sounds to orthography, which burdens the system charged with constantly coding and decoding phonological information from these symbols. This idea is further supported by the improvements in reading performance gained by training and remediation programs that emphasize the practice of phonics and phonemic awareness to improve fluency and comprehension (Byrne et al., 2000; Hatcher et al., 1994; Temple et al., 2003). Dyslexic children that engage in remediation programs focused on phonological awareness show notable improvements in reading performance, both in fluency and accuracy, suggesting an important role for phonology in dyslexia. As well, these performance gains are matched by neuroimaging results showing increases in cortical activity in left fusiform (VWFA), IFG, and temporo-parietal cortex, as well as right STG and IFG areas following training (Eden et al., 2004; Temple et al., 2003).

Critically, not only do dyslexic readers show altered activation in the traditional left hemispheric reading network, but rather, they show a complete functional restructuring of the reading network, recruiting multiple right hemispheric analogs to compensate for perturbed left hemisphere language processing (Hoeft et al., 2006; Hoeft et al., 2010; Temple et al., 2002; Temple et al., 2003). A wide variety of studies have shown this right hemisphere recruitment in dyslexic readers, from observations of fMRI signals (Baillieux et al., 2009; Eden et al., 2004; Hoeft et al., 2011; van der Mark et al., 2009), white matter tractography (Carter et al., 2009; Casanova et al., 2010; Darki et al., 2012; Wang et al., 2017), gray matter volume (Beaton, 1997; Preston et al., 2014), and

cortical oscillations (Lehongre et al., 2011; Lehongre et al., 2013; Zaric et al., 2017).

Studies of gray matter volume in dyslexia show significantly greater cortical volume in the right STG, specifically the planum temporale (Beaton, 1997), an auditory processing region usually lateralized to the left hemisphere. The result may seem counterintuitive at first given that more cortical processing power is generally useful. However, many have theorized that a lack of asymmetry indicates a lack of linguistic specialization, and therefore a lack of network precision or efficiency (Dehaene-Lambertz et al., 2006; Morillon et al., 2010).

In addition to problematic phonological processing, low-level sensory deficits suggest that other neurocognitive systems may contribute to dyslexia (Galaburda et al., 1994; Goswami, 2011; Hancock et al., 2017; Lehongre et al., 2011; Lehongre et al., 2013; Livingstone et al., 1991; Stein, 2001). Supporting this idea, an anatomical and histological investigation of dyslexic brains found evidence of neural disorganization in thalamic nuclei critical for auditory and visual processing (Galaburda et al., 1985). In these classic studies, Galaburda and colleagues recorded the existence of displaced neuronal malformations surrounding language areas, predominantly along the Sylvian fissure of the left hemisphere, offering a potential neurobiological origin for the phonological impairments commonly seen in dyslexia (Figure 1.1).

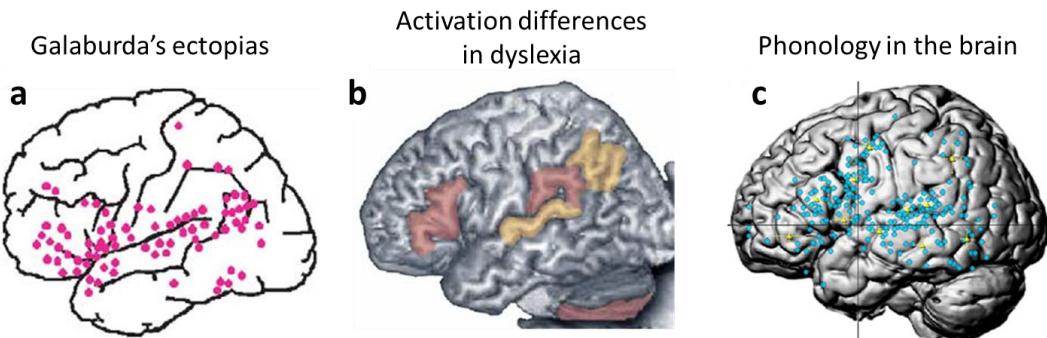


Figure 1.1. Overlap among ectopic neurons, brain activity during a reading task, and regions involved in phonological processing. (a) Documented locations of neuronal ectopias (Ramus, 2003); (b) activation differences between dyslexic and typical readers (Eckert, 2004); (c) a meta-analysis of phonological processing in the brain (each blue dot represents a single study; Vigneau et al., 2006). Figures adapted with permission.

Of particular interest to these morphological findings in the peri-Sylvian cortex, the temporal aspects of auditory processing (e.g. rise-time discrimination) seem to be especially challenging for individuals with dyslexia (Casini et al., 2017). For example, dyslexic children show significantly poorer performance in a non-linguistic beat-rhythm task compared to typically developing readers (Goswami et al., 2013). Similarly, dyslexic adults showed significant impairments in a syllable stressing task compared to non-impaired readers – a relationship predicted by rise-time discrimination ability (Leong et al., 2010).

The physiological correlates of this problematic auditory processing have been investigated, as well. EEG studies have shown reduced entrainment effects in the auditory cortex of dyslexic readers to auditory stimuli at low frequencies (<4 Hz), implicating the impairment of delta (1-4 Hz) oscillations as a contributor to the neural basis of dyslexia (Cutini et al., 2016; De Vos et al., 2017; Molinaro et al., 2016; Power et al., 2017; Soltesz et al., 2013). Lehongre and colleagues (2011) presented readers with phonemic auditory stimuli sampled at various rates. In this study, dyslexic readers

showed impaired neural entrainment to auditory stimulation sampled at a rate of ~30 Hz, while showing improved performance at higher rates, suggesting an oversampling of information by the auditory cortex as a contributor to the linguistic problems seen in dyslexia. Some have offered a competing framework for this evidence, however, suggesting that these same results could be the residual effects of a broader attentional deficit (Vidyasagar, 2013; Vidyasagar & Pammer, 2010). Reconciling these disparate viewpoints continues to be a challenge.

Brain Connectivity in Reading and Dyslexia

In modern cognitive neuroscience, it is widely accepted that human cognition and behaviour arise from the communication within and between diverse and disparate neural networks. Given the distributed nature of reading processes in the brain (i.e. disparate regions handle distinct sub-processes), understanding how information is propagated in the reading network is critical for understanding the underlying mechanisms involved in reading, and importantly, understanding the ways in which reading processes are disrupted (e.g. dyslexia).

Functional connectivity studies using fMRI have shown significant correlations between the left vOT cortex and left AG in typical readers, but not in dyslexic readers (Horwitz et al., 1998). In the same study, it was shown that control subjects had significantly correlated activity between the left AG and left IFG regions, while the dyslexic subjects showed no such correlation (Figure 1.2). The same research group later found that in dyslexic adults, orthographic processing regions showed greater functional connectivity to AG in the right hemisphere than in the left hemisphere during a reading task (Figure 1.3; Pugh et al., 2000). A similar pattern was seen during a rhyming task,

which increased functional connectivity between left and right IFG in dyslexic participants (Frye et al., 2010). Also using a rhyming task, Cao and colleagues (2007) found a weaker modulatory effect (causal influence) from left IFG to left IPL in children with reading difficulties. Taken together, these results indicate impaired connectivity between language areas in the left hemisphere for dyslexic readers, as well as increased connectivity between hemispheres and in some cases increased intra-hemispheric connectivity in the right hemisphere. These results further the suggestion that dyslexic readers have a less lateralized reading network, utilizing more of the right hemisphere compared to typical readers.

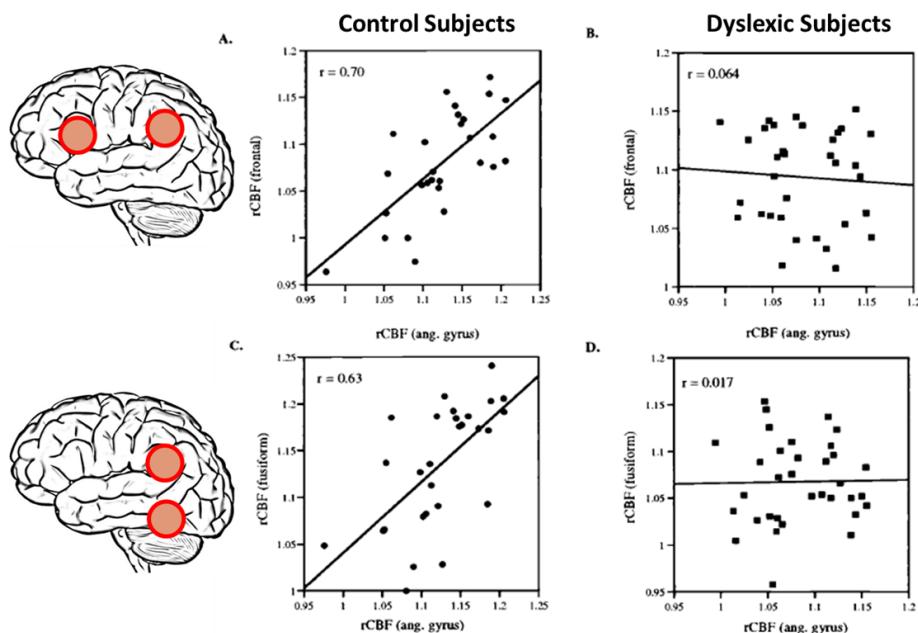


Figure 1.2. Functional connectivity and dyslexia. Brain activity was measured from dyslexic and control groups using PET during a reading task. (Top) During the reading task, brain activity between left angular gyrus and left inferior frontal cortex was significantly correlated in control subjects, but showed no such correlation in dyslexic subjects. (Bottom) Brain activity between left angular gyrus and left fusiform cortex was significantly correlated in control subjects, but not in dyslexic subjects. These findings begin to illustrate widespread network disorganization in the left hemisphere of dyslexic individuals (Horwitz et al., 1998). Figures adapted with permission.

Just as important as the regions engaging in communication is the *timing* of these interactions. Reading is a *fast* process; experienced readers can read several words in the span of a single second. Thus far, little research has investigated reading network connectivity at this temporal scale. To that end, the analysis of neural oscillations has been touted as a potentially fruitful avenue for understanding the fast dynamics of brain networks.

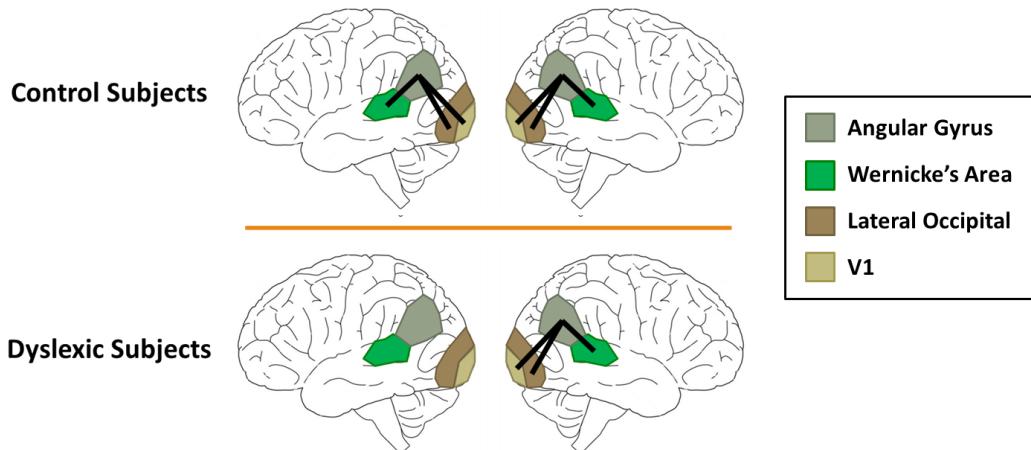


Figure 1.3. Left- and right-hemispheric functional connectivity and dyslexia. Brain activity was measured from dyslexic and control groups using fMRI during a reading task involving nonword rhyming (e.g. *LEET/JEET*). (Top) During the reading task, typical readers showed significant correlations between angular gyrus and occipital and temporal regions in both left and right hemisphere. (Bottom) Dyslexic readers exhibited similar connectivity patterns in the right hemisphere, but showed no such correlations in the left hemisphere. These results further offer insight into how the integration of visual and linguistic information may be perturbed in the left hemisphere, relying predominantly on the right hemisphere occipito-temporal network (Pugh et al., 2000). Figures adapted with permission.

Neural Oscillations and Connectivity

Even with the insights provided by traditional neuroimaging connectivity studies,

efforts to understand the connectivity dynamics of word reading have thus far fallen short in capturing the moment-to-moment neural interactions that govern successful reading, much less how those interactions become perturbed in dyslexia. To that end, my dissertation emphasizes the connectivity dynamics of reading at a scale of tens to hundreds of milliseconds by analyzing oscillatory brain activity.

Evidence has been mounting for a theory of neural communication that capitalizes on the oscillatory behavior of brain regions to send fast and dynamic messages throughout brain networks (Buszaki & Draguhn, 2004; Fries, 2005; Sauseng & Klimesch, 2008; Varela et al., 2001). With respect to reading, some emerging contemporary frameworks of dyslexia highlight the importance of neural oscillations to the execution of reading processes (Goswami, 2011), and suggest that disrupted oscillatory behaviour in auditory regions of the brain account for key deficits seen in dyslexia (De Vos et al., 2017; Doelling et al., 2014; Lehongre et al., 2011; Lehongre et al., 2013; Molinaro et al., 2016).

The oscillations recorded from the brain allow for analysis of the signal's various features, such as frequency, amplitude, and phase. The frequency of the signal refers to the number of times the signal oscillates per second (in Hertz, Hz); the amplitude is the strength of the signal; and the phase at any given moment is the particular point in the cycle of the oscillation. Just as with a pair of neurons, disparate brain regions with distinct response properties (e.g. visual and auditory) can communicate if the timing is right, and oscillations aid in ensuring that this timing is precise.

Several decades of EEG, magnetoencephalography (MEG), and local field potential (LFP) research have yielded useful insights as to how to interpret oscillatory

activity recorded from the brain. In practice, a broadband signal is broken into smaller canonical frequency bands: delta (1-4 Hz), theta (4-8 Hz), alpha (8-13 Hz), beta (13-30 Hz), and gamma (30+ Hz), each of which is associated with distinct forms of processing. In an effort to understand the various facets of cognition, researchers have looked to oscillations to investigate aspects of memory encoding and retrieval (Benchenane et al., 2011; Duzel et al., 2010; Jutras & Buffalo, 2010; Nyhus & Curran, 2010), language comprehension (Bastiaansen & Hagoort, 2006; Giraud & Poeppel, 2012; Pulvermuller et al., 2003), attention (Doesburg et al., 2008; Doesburg et al., 2012; Fries et al., 2001; Jensen et al., 2007), and reading (Bedo et al., 2014; Herdmann, 2011; Molinaro et al., 2013; Vidal et al., 2012). Armed with an understanding of neural oscillations, it becomes possible to leverage these principles to investigate the ways in which information is propagated in reading networks, and how that transmission of information may be interrupted.

In cognitive neuroscience, the current understanding of how information is transmitted between brain regions during reading is minimal and comes primarily from inferences made by examining patterns of activation of localized sources rather than from direct measures of connectivity between those sources. For example, using MEG, Marinkovic and colleagues have described a pattern of activation starting in early visual cortex in the occipital lobe, which rapidly sweeps across the left hemisphere through the temporal lobe and ultimately arrives at language centers in the inferior frontal lobe (Marinkovic et al., 2003). From results like these, it is clear that the reading signal is propagated from region to region. It remains unknown, however, just *how* these transitions occur across space, time, and oscillatory frequency, making interpretations of

sweeping neural activity difficult to characterize.

Some connectivity measures have been reported, however, offering a glimpse into the relations between some cortical sites during reading. Herdman (2011) has reported increased phase-locking of induced gamma-band (30+ Hz generally, 50-80 Hz reported here) oscillatory activity in posterior cortices during the perception of real letters compared with that during perception of pseudo-letters. This result suggests the existence of a preliminary orthographic evaluation network that determines whether or not visual symbol information is propagated to higher-level language centers. An intracranial EEG study has reported gamma amplitude correlations among reading-related sites, such as the left fusiform gyrus, IFG, MTG, STG, and SMG (Vidal et al., 2012). These correlations revealed potentially segregated semantic (ventral) and phonological (dorsal) networks, mirroring the dual-route model of word reading (Coltheart et al., 2001). With regard to reading performance, fronto-occipital theta-band (3-7 Hz) oscillatory phase-locking has been suggested to support the working memory aspects of sentence reading, aiding in the perception of expected words, while gamma-band phase-locking represents the evaluation of the orthographic symbols (Molinaro et al., 2013).

Studies of white matter pathways show structural long-distance connections between visual and language areas (Epelbaum et al., 2008; Wandell et al., 2012). Exploring the dynamics of the functional and effective implications of these tracts may prove crucial to understanding reading in the brain more completely. Under the premise that information integration is implemented by synchronized oscillatory neural dynamics (Fries, 2005; Varela et al., 2001), it is likely that the study of such dynamics will reveal new important aspects of the word reading process, and disruptions therein. Fortunately,

some such work has been approached in recent years. In my prior work (Bedo et al., 2014), I analyzed EEG activity to map out the fast connectivity dynamics of reading networks in typical adult readers. The premise of that study was to leverage principles of neural oscillations to gain insight into the processes within and between brain regions that give rise to reading ability, particularly with respect to theta (4-8 Hz) and gamma (30+ Hz, typically 30-50 Hz) activity. Findings have suggested that individuals with dyslexia have specific neural deficits in processing auditory information at theta and gamma rates (Lehongre et al., 2011; Lehongre et al., 2013). Therefore, these frequency bands are candidates for indicators of critical reading processes in the reading network. To that end, my prior work (Bedo et al., 2014) explored reading networks in these two frequency bands using a set of analysis techniques that will also serve as the primary analyses for each of the studies in this dissertation. In this experiment, adult participants were required to respond on a keyboard as to whether or not a word that appeared matched the word formed by the letter sequence that came before it. By examining the moments following the presentation of the complete word, I was able to map the moment-to-moment functional and effective connectivity as derived from the neural oscillations. Using EEG, I localized independent neural sources derived from that activity to a host of reading-related brain regions in the left hemisphere (Figure 1.4), including vOT, AG, SMG, and two distinct areas of the IFG.

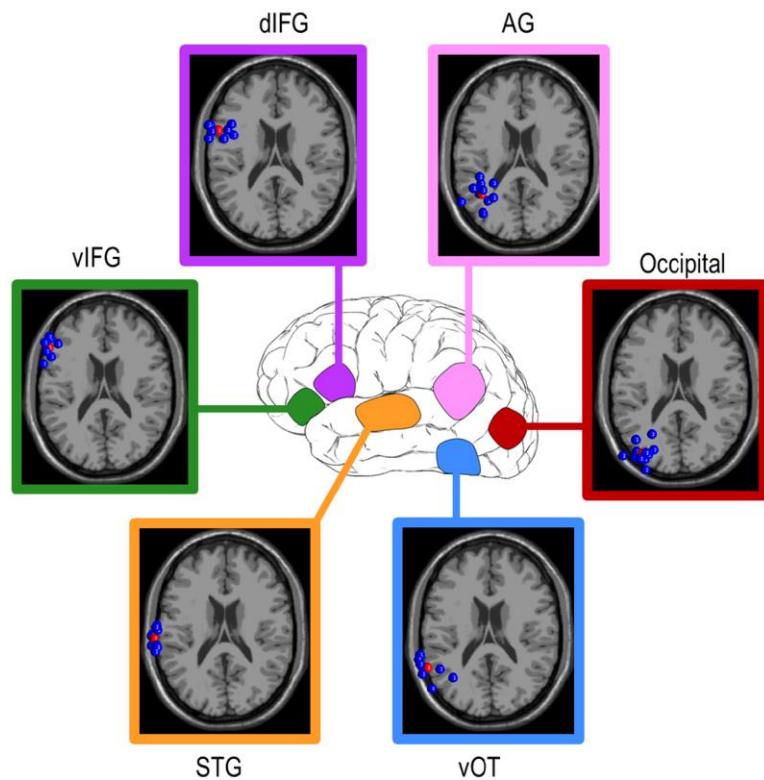


Figure 1.4. Reading network regions identified in the left hemisphere by independent component analysis and dipole fitting of EEG data. Blue dots are loci of individual dipolar neural sources, red dots are the centroids of the blue dots. The activity underlying these regions was then subjected to connectivity analyses. v = ventral; d = dorsal. (Bedo et al., 2014; figure reproduced with permission)

The evolution of functional connectivity (Figure 1.5) following the presentation of a word matches the general pattern of feed-forward activations (Marinkovic et al., 2003), beginning in posterior sensory areas and then rapidly engaging the high-level language regions.

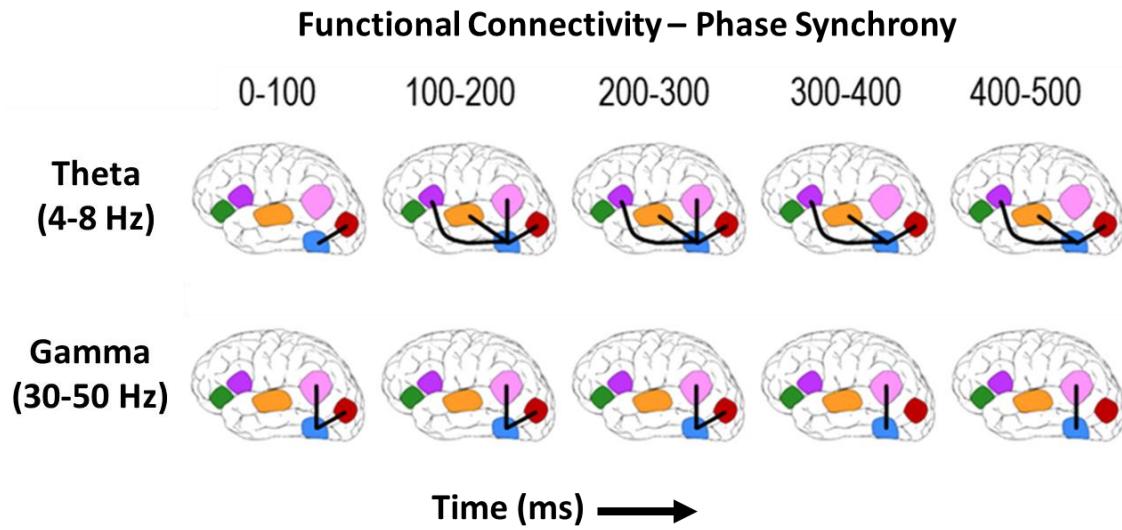


Figure 1.5. Oscillatory functional connectivity dynamics during word reading. Theta- and gamma-band phase synchrony (significant functional connectivity, black lines) relative to area vOT, evolving over the course of viewing a word. (Bedo et al., 2014; figure adapted with permission)

The effective (causal) connectivity patterns (Figure 1.6) show very similar results, in that the connectivity resembled traditional feed-forward patterns of brain activity. However, with this technique, we were able to capture an early (<100 ms) top-down signal from IFG to vOT, a result consistent with prior findings showing early engagement of left IFG in reading (Cornellisen et al., 2009). Using phase synchrony and transfer entropy measures (see later in this chapter for precise definitions), we showed how a widely distributed reading network in the left hemisphere propagates information over time to support reading capabilities.

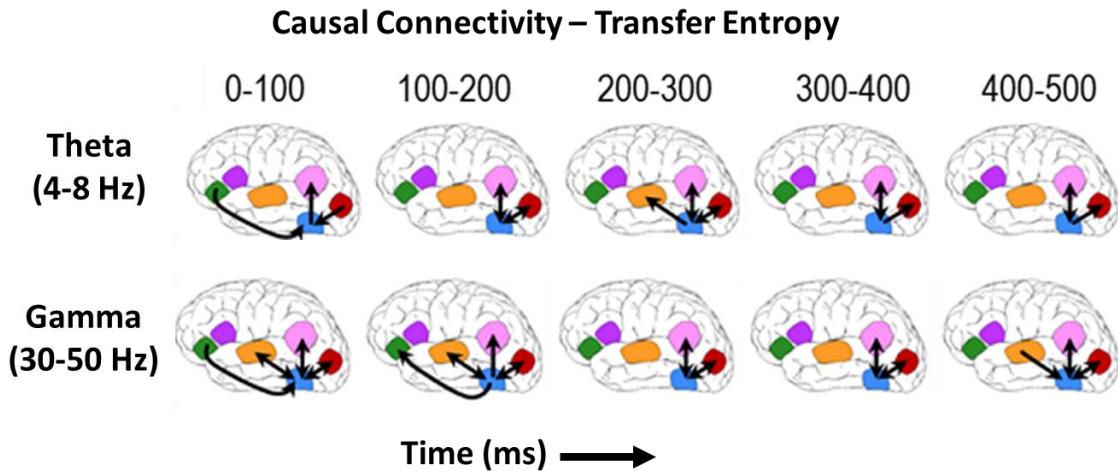


Figure 1.6. Oscillatory effective connectivity dynamics during word reading. Theta- and gamma-band transfer entropy (significant effective, or causal, connectivity, black arrows) relative to area vOT, evolving over the course of viewing a word. (Bedo et al., 2014; figure adapted with permission)

What Happens 220 Milliseconds After Word Presentation?

The temporal resolution of a technique like EEG affords the examination of brain activity at millisecond precision. Using such techniques, researchers have found specific moments in processing that reflect critical steps in the cognitive processing of words. Perhaps the most-commonly reproduced finding is the N170 ERP component in the left fusiform gyrus in adult readers, in which a prominent negative peak is observed 170 ms after word presentation (Dujardin et al., 2011; Mahe et al., 2012; McCandliss et al., 2003). This moment represents the orthographic processing step in word reading, where visual inputs are classified as orthography (written language) to then be passed along to higher level language areas for further evaluation (e.g. extracting phonological information; Price & Devlin, 2011). In young children, this same processes is delayed by a short time to ~220 ms, as they are still developing the skills necessary to decode orthographic information (Brem et al., 2010; Hasko et al., 2013; Hasko et al., 2014). So,

when studying the neural dynamics of reading in children, this moment becomes critical in pushing our understanding.

With the exception of chapter 2, all other experiments in this dissertation focus on a specific window of time, 200-250 ms after word presentation, to capture the brain connectivity dynamics of orthographic processing and the propagation of the reading information thereafter in the reading networks of dyslexic and typically-developing children. The lateralization of the connectivity, as well as the engagement of language areas at this time window may offer critical insights as to the neural underpinnings of dyslexia.

General Methodology

In this dissertation, three specific analyses were employed in the investigation of the network dynamics of reading: event-related spectral perturbation, phase synchrony analysis, and transfer entropy analysis. Each method contributed uniquely to understanding how reading networks propagate information.

Event-related Spectral Perturbation (ERSP)

It has been shown that individuals with dyslexia have key deficits in synchronizing their oscillations to certain types of incoming auditory stimuli, specifically at theta (4-8 Hz) and gamma (30-50 Hz) rates (Cutini et al., 2017; De Vos et al., 2017; Doelling et al., 2014; Lehongre et al., 2011; Lehongre et al., 2013; Molinaro et al., 2016), which may be the basis for the behavioral deficits in reading ability. Analyzing event-related spectral perturbations (ERSPs) affords the observation of the moment-to-moment fluctuations in oscillatory power in a given brain region, potentially offering insight into key reading processes in the brain. To measure the ERSP, a wavelet analysis is done on

the individual epochs of the EEG, yielding a time-frequency decomposition of the EEG time series. The ERSP is the log of the ratio of the oscillatory power at a particular frequency and time point to that of a standard baseline at the same frequency and a set of neutral time points. The resulting values can be tested statistically to determine whether oscillatory power changes caused by the presentation of relevant stimuli differ between conditions or participant samples, for example between typical and dyslexic readers.

Measures of Functional and Effective Connectivity

Phase Synchrony (PLVs) – Functional Connectivity

ERSPs are useful, but only account for the dynamics of individual regions. More recently, so-called phase-locking analyses have been developed that compute the degree to which two regions are sharing information based on their oscillatory activity. This technique capitalizes on the idea that two regions in a network will coordinate their oscillations to maximize the likelihood that a message is propagated from one region to the next (Fries, 2005; Varela et al., 2001). In other words, the oscillatory *phase* of one region should correspond to some phase of the other region in order to optimally communicate, and the assumption is that this relationship is roughly constant. For example, if region *B* optimally responds when it is near its oscillatory peak while region *A* is at its trough, this relationship should generally remain the same. After many trials in a task, researchers can examine to see if the oscillations from two regions show a constant phase relationship over the trials. If so, then they are phase-locked, possibly indicating some form of communication.

Phase synchrony analyses are conducted in order to assess inter-regional functional connectivity, or the degree to which two brain areas are sharing information at

a particular frequency. This is done by computing the phase-locking values (PLVs) between pairs of signals localized to specific brain regions. Just as with ERSPs, a wavelet analysis is performed on the data from the two sources whose relationship is being investigated. However, instead of measuring the spectral power of each source, the phase information from these wavelets is used to compute the degree of phase-locking between regions over time, at each frequency. The PLVs produced by these computations indicate the degree of constancy of the phase differences between signals at a specific oscillatory frequency across trials. PLVs range from 0 to 1, where 0 indicates the absence of any phase locking, and 1 indicates perfect phase locking, such that the phase difference between two ICs at a given time point remains constant across all trials. In a similar fashion to ERSPs, hypothesis testing for pairs of brain regions employ t-tests at each time point and each frequency between conditions.

Transfer Entropy – Effective (Causal) Connectivity

Whereas measures of functional connectivity show which brain areas are engaged and sharing information, these measures do not indicate the causal flow of the information. That is, a measure such as phase synchrony does not indicate which site is *sending* the information, and which site is *receiving* the information, or if a bi-directional relationship exists. In order to understand such relationships, effective (causal) connectivity analyses must be employed. One such analysis that is commonly used is Granger causality, or variants thereof. A disadvantage of Granger causality approaches, however, is that they assume, *a priori*, a linear model of the interaction between neural sources (Wibral et al., 2011). A linear model may become problematic when trying to determine causal relations in a highly non-linear system such as the brain. For this reason,

we adopted a recent technique called transfer entropy, as it can determine causal interactions, including especially non-linear ones, without needing to specify or fit a model. With regard to information transfer between neural sources, transfer entropy computes the additional information predicted by one region that is not already predicted by another region's prior activity. Typically, transfer entropy is computed on a broadband brain signal. However, the type of transfer entropy we used for our analyses is applied to specific frequency bands of interest; as such, it is termed narrow-band transfer entropy (NBTE). NBTE computes the information transfer within a specific frequency band rather than that of the broadband signal (Wibral et al., 2011).

Overview of Dissertation

The purpose of this research is to investigate the local and long-distance brain network dynamics underlying reading in the brain, and how these networks are altered or perturbed in dyslexia. As well, this research investigates how reading interventions affect the connectivity dynamics of reading in young children with dyslexia. By examining the fast connectivity dynamics of word reading, I aim to provide novel insights into the mechanisms of reading and dyslexia that are otherwise intractable using more traditional methods.

In Chapter 2, I compare the network dynamics of reading letter strings with linguistic content (i.e. words) and those lacking in linguistic content (i.e. consonant strings) in adult readers. Results show that in both theta- and gamma-bands, words produced more robust connectivity patterns than consonant strings, as revealed by phase synchrony and transfer entropy. This significant increase in connectivity occurred primarily at a later stage of processing (>400 ms), likely representing the access of

higher-level linguistic properties such as semantics and phonology.

Chapter 3 investigated the moment-to-moment connectivity in children with dyslexia and typical readers during a phonological-lexical decision task. By leveraging pseudowords (word-like stimuli that elicit phonological process, but have no semantic content), the impaired phonological systems in dyslexic children can be taxed and observed under load compared to typically developing readers. I examined specific moments in processing that have been shown to be crucial for reading, and found that dyslexic children actually showed distinct and greater connectivity compared to typical readers.

In Chapter 4, I examined the brain networks of a separate group of children, some of whom have specific challenges in reading. EEG was recorded from these challenged readers during a reading task at the start of a FastForWord reading training program. The brain activity of these children was compared to comparable classmates who were not in the training program. Challenged readers were more prone to increased engagement of higher-level language areas even for consonant strings, suggesting that they required more communication to resolve the same amount of information.

Chapter 5 revisits the children enrolled in the FastForWord reading program after six months of intervention. This group of children again performed the same reading task while EEG was recorded. Pre-Post comparisons of network behavior shows a significant reduction in the engagement of language processing areas after training seen in Chapter 4. This reduction of connectivity was also negatively correlated with gains in reading performance, such that children who showed the highest gains in reading performance also showed the most reduction in connectivity between these sites, suggesting an

increase in communication efficiency.

The experiments outlined above examined the connectivity dynamics in readers from several populations and reading abilities. Taken together, the findings from this dissertation fit within the frameworks of reading processing in the brain and extend our understanding of how neural oscillations and connectivity fit into these frameworks.

CHAPTER 2: Reading Network Dynamics in Adults

Introduction

Reading words requires the recruitment of brain regions responsible for orthographic, phonological, and semantic processing among others, generally along the left hemisphere. Deeper processing of content in written language (e.g. words) requires more engagement from these systems compared to shallower processing (e.g. meaningless consonant strings) as more information must be evaluated in order to resolve the letter string.

Neuroimaging studies have suggested that language processing above and beyond orthography alone activates several high-level language areas (Dehaene et al., 2001). In this study, Dehaene and colleagues used a form of stimulus masking to inhibit conscious access to words read on a screen. When participants could only detect that the stimuli were orthographic in nature, these cases only showed activations in left vOT cortex. In cases where linguistic content was accessed beyond simple orthography, a host of higher-level regions in frontal, temporal, and parietal lobes showed significantly increased activation.

Neurophysiological studies of neural oscillations have also investigated reading in the brain. The ability of cortical regions to generate synchronous oscillatory behaviour during reading, as well as the ability to entrain neural oscillations to auditory or linguistic stimuli, seems to be perturbed in dyslexia, further indicating the importance of such oscillatory behavior for reading. Given the importance of phonological processing for reading, theta-band (4-8 Hz) and gamma-band (30-50 Hz) oscillations have garnered some attention as those frequency bands capture the rough cadence of spoken syllables

and words, respectively (Doelling et al., 2014; Goswami 2011; Gross et al., 2013; Klimesch et al., 2001; Lehongre et al., 2011; Lehongre et al., 2013; Molinaro et al., 2013; Vidal et al., 2012).

Just as important as understanding which regions are active at various stages of reading, however, is understanding how information is propagated among these brain areas over time. Traditional methods have indicated a feed-forward sweep of activity (Marinkovic et al., 2003; Pammer et al., 2004), originating in the occipital lobe, progressing through the temporal and parietal lobes, and finally reaching the inferior frontal lobe, all primarily within the left hemisphere (Dehaene, 2009). However, even though these patterns of activation give us insight as to the general flow of information in the brain during reading, these visualizations do not actually measure the instances of connectivity that give rise to those activations. To that end, I sought to investigate the connectivity dynamics of reading as it relates to the access of these language systems in the brain.

If a stimulus with high linguistic content engages more diverse and distributed brain regions as part of their processing, then perhaps studying connectivity among these regions can offer insight as to the network behavior underlying word reading. Various research groups have pursued this connectivity approach in reading and general language processing studies (Bedo et al., 2014; Horwitz et al., 1998; Ligges et al., 2010; Molinaro et al., 2013; Pugh et al., 2000).

This dissertation is primarily concerned with the neural underpinnings of dyslexia, but before investigating the differences between neurotypical and dyslexic readers, it is important to understand how the reading networks function in expert or

well-experienced adult readers to use as a benchmark. This involves testing experimentally what models have already been suggesting – that reading requires the coordination of multiple sub-processes (each presumably controlled by regional brain networks), and that the perturbation of one region, or one sub-network, can impact the overall network processing, and thus cognition and ultimately behavior (i.e. reading performance). The present study aims to provide insights into “typical” reading network behavior.

Neural oscillations have been shown to be useful in investigating such network connectivity. The degree to which neural oscillations in different brain regions are in lock-step (i.e. phase-locked) at particular frequencies is one way to measure the functional connectivity between those regions, which in turn facilitates the propagation of neural signals (Fries, 2005; Sauseng & Klimesch, 2008). Moreover, effective (or causal) connectivity between the active brain regions can be measured by using techniques such as computing the transfer entropy between their oscillations (Wibral, et al., 2011, see Chapter 1).

The present experiment represents the next iteration of a previous study from our research group (Bedo et al., 2014, see Chapter 1). In that study, we examined the functional and effective neural connectivity of neurotypical adult readers during a reading task in which participants compared a presented word with a sequence of letters that came before it. Originally, the aim was to design an experiment that could be analyzed at an incremental letter level (building letter-by-letter) as well as at the string level (i.e. reading the complete word), similar to how sentence-reading experiments can investigate the impact of each word in a complete sentence. However, the analysis in this chapter

focuses only on the presentation of the completed letter strings, as the rest of the dissertation also emphasizes the reading of letter strings. The aim of the present experiment was to build on that previous study and now compare written stimuli at two levels of linguistic complexity – real words and consonant strings. In the original iteration, we found robust theta- and gamma-band networks that evolved over the span of reading a word. In the present study, I expect theta- and gamma-band connectivity to be significantly greater for words than for consonant strings after the point of initial orthographic processing (i.e. 200-250 ms). If access to higher-level linguistic content generates increased activations (Dehaene et al., 2000), then the connectivity that underlies that activity should increase, as well.

In this experiment, adult readers performed a reading task while their EEG was recorded. Functional and effective (causal) connectivity analyses were conducted on these EEG recordings. My hypothesis was that stimuli with substantial linguistic content, in this case words, would show more widespread connectivity, especially engaging more frontal, temporal, and parietal regions when compared to stimuli lacking linguistic content (i.e. consonant strings).

Methods

Participants

Fourteen adult volunteers (11 female, 2 left-handed) attending the University of British Columbia, age 18–36 years (mean=21.64, SD=5.03), were paid to participate. All participants indicated English as their first and primary language, and reported no histories of neurological, learning, or reading disorders or dysfunctions during a prescreening interview. All participants had normal or corrected-to-normal visual acuity.

Experimental Procedures

This task is a variant of one used in my previous research (Bedo et al., 2014). Participants were instructed to observe a sequence of three individual letters followed by a three-letter string, either a real word (e.g. ‘bed’) or a consonant string (e.g. ‘xjp’). The participants’ task was to respond on a keyboard as to whether or not the letter string that appeared matched the string formed by the letter sequence that came before it (Fig. 2.1). All letter sequences and words were three letters long, and were sourced from a pool of 456 possible strings. Consonant strings were randomly generated and composed of three distinct consonants (i.e. no duplicate letters within a string); each consonant string in the list was unique. Each trial had six possible stimulus combinations occurring at equal probabilities: (1) word-word match (c-a-t/cat), (2) word-word nonmatch (c-a-t/dog), (3) word-consonants nonmatch (c-a-t/xjp), (4) consonants-consonants match (x-j-p/xjp), (5) consonant-consonant nonmatch (x-j-p/qpb), and (6) consonant-word nonmatch (x-j-p/cat). Letters and words were presented with Presentation software (Version 14; Neurobehavioral Systems, USA) in 65-point Times New Roman (lower case) font on a high-resolution 60 Hz CRT monitor approximately 65 cm from participants’ eyes at a visual angle of approximately 1.7°, and the font color was white on a black background. The task was conducted using a Pentium 4 computer running Windows XP in a quiet, well-lit room. Participants completed a practice session of ten trials prior to the experimental task and were offered extra practice trials if needed (no one needed extra practice). Trials began with a fixation cross for 1000 ms, followed by each of three letters being presented for 100 ms, with a 900 ms inter-stimulus interval. Finally a three-letter word appeared, at which point the participant was required to respond. The word

remained on the screen for 1500 ms before automatically moving on to the next trial. Trials were separated by a 900 ms inter-trial interval, and a 30 s break was given after each 50-trial block. Each participant completed nine (approximately) 50-trial blocks, comprising a total of 228 each of match and non-match trials. Only “match” trials on which a correct response was made were selected for EEG analysis, so as to not include potentially misleading findings based on error-detection network dynamics as might be found in non-match trials (e.g. mismatch negativity and other such phenomena).

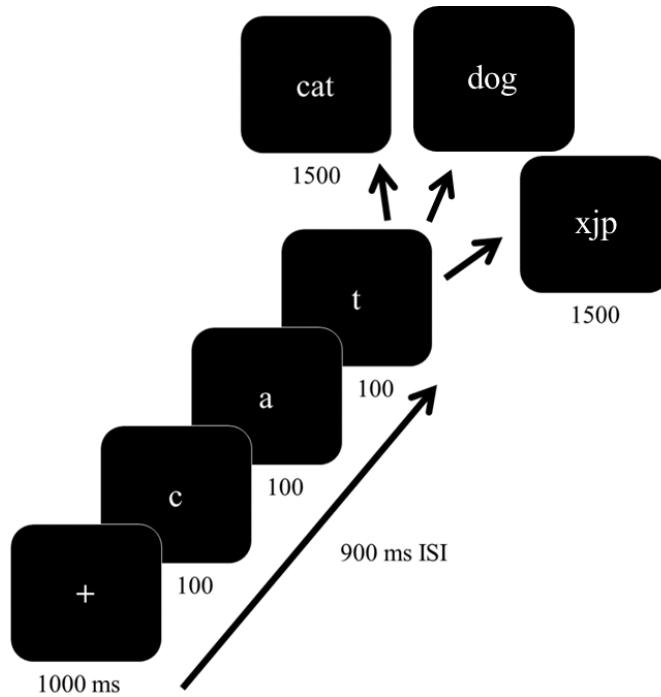


Figure 2.1. Schematic of reading task. Participants were presented with a three letter sequence (e.g. c-a-t) followed by a three-letter string (word or consonant string). The task required participants to respond as to whether or not the presented string matched the sequence that came before it. In this example, the initial sequence spelled out a word, but could have been a sequence of consonants.

EEG Acquisition

EEG was recorded from 60 passive electrodes in a standard electrode cap (Electro-cap, Inc., Eaton, OH, USA) at equidistant locations based on the International

10–10 System, referenced to the mastoids with the ground at AFz. EEG signals were amplified and sampled at 500 Hz through an analog passband of 0.01– 100 Hz (SA Instrumentation, San Diego, CA, USA). Eye muscle activity was recorded by electro-oculogram (EOG) from four periocular electrodes. All electrode impedances were below 30 k Ω (input impedance of the amplifier was 2 g Ω). Prior to analysis, all signals were re-referenced to an average reference, resampled to 250 Hz, and digitally filtered from 1– 50 Hz using EEGLAB software (Delorme & Makeig, 2004), an open source MATLAB toolkit (MathWorks, Natick, USA), and custom scripts. The continuous data were epoched into 3.5 s bins time-locked to the presentation of the word. The epochs captured 2 s before and 1.5 s after word presentation. Epochs were rejected if their eye movement (EOG) voltage levels surpassed $\pm 150 \mu\text{V}$ within the window of 100 ms pre-stimulus to 700 ms post-stimulus. Each participant contributed an average of 180.75 trials (SD=40.98), for a total of 2169 trials for the experiment.

Current Source Density

A common concern when analyzing EEG data is the occurrence of volume conduction—the diffusion of neural signals across tissue which linearly adds the signals acquired in one region with other signals produced elsewhere in the brain. The end result is a diffuse region of activity on the scalp that makes it difficult to pinpoint the underlying source of the signal, which is important for interpreting results. To reduce the impact of volume conduction on subsequent analyses, the EEG signals were first converted to current source density (CSD).

Essentially, CSD acts as a spatial filter, in that it is strongly affected by the distance from which an EEG signal travels away from a source. Thus, it “sharpens” the

distribution of EEG activity on the scalp, emphasizing shallow sources close to the recording electrode (Fig. 2.2). CSD thus aids in the localization of brain sources by reducing the impact of volume conduction, thereby increasing confidence that the channels being analyzed did in fact represent true activity of the brain regions over which the corresponding electrodes sat. Furthermore, CSD acts as a form of artifact rejection or attenuation, particularly of muscular artifacts that can heavily contaminate EEG signals (Fitzgibbon et al., 2015).

CSD Toolbox for MATLAB was used to compute the CSD values (Kayser, 2009; Kayser & Tenke, 2006a; Kayser & Tenke, 2006b). CSD is the second spatial derivative of the scalp potential recorded by EEG. Historically, the earliest iterations of CSD were simply estimated by subtracting the average of the nearest neighbour electrode recordings from the recording of the electrode of interest, at each time point (Hjorth, 1975; Hjorth, 1991). Because this assumes that the relevant electrodes sit on a flat plane, and this is incorrect for human heads, better estimates have been developed that correct for the curvature by first performing a spline interpolation of the scalp potential (e.g., Perrin, Pernier, Bertrand & Echallier, 1989). This latter method is implemented in the MATLAB toolbox and has been shown to be accurate for a variety of curved surfaces (e.g., Kayser & Tenke, 2006a; Kayser & Tenke, 2006b). This current study used the default CSD toolbox parameters for calculating the spline flexibility (spline interpolation constant $m = 4$) and smoothing (smoothing constant $\lambda = 0.00001$). CSD was computed from the continuous EEG data from each individual participant.

ROI Selection

Cortical regions of interest (ROI) for further analysis were selected based on reading-related brain areas as revealed in previous research (Table 1; Jobard et al., 2003). The cortical Talairach coordinates of these sites were then cross-referenced to anatomical locations of electrodes based on the 10-10 system (Koessler et al., 2009). The nearest electrodes to these sites, as measured by Euclidean distance, were then selected for further analysis. The subset of electrodes selected in this manner were C5, C6, CP5, CP6, F5, F6, F7, F8, FC5, FC6, O1, O2, P7, P8, T7, and T8. For ease of exposition, the ROIs will be referred to by their cortical locations from now on, but it must be remembered that in fact the data to be analysed are the CSD values computed for the electrode locations nearest those cortical locations and not the activation levels of dipoles or other types of cortical sources inferred by localization analysis.

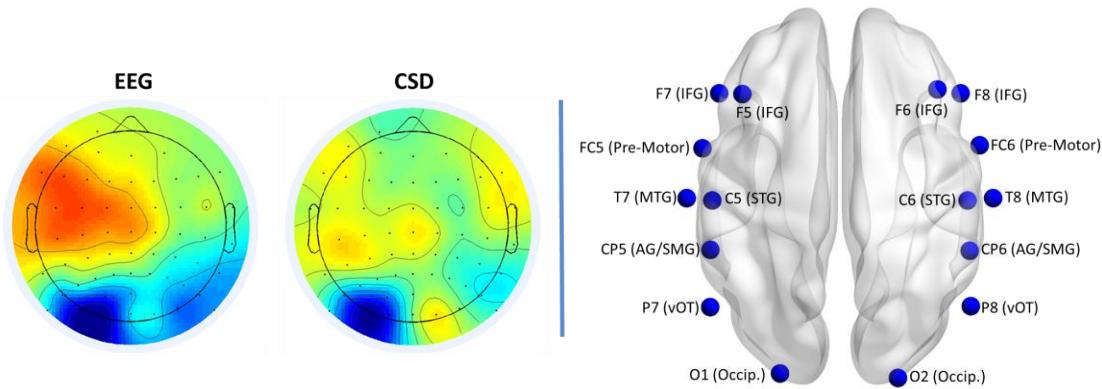


Figure 2.2. Current source density and selected electrodes. (Left) Example of a CSD conversion of EEG data. CSD spatially “sharpens” the topographic map, reducing the diffusion of brain signals across electrodes. (Right) Selected channels for connectivity analyses.

Table 2.1. Reading-related Brain Regions and Their Corresponding EEG Channels.

EEG channel	Talairach coordinates			Corresponding brain region
	x	y	z	
F5	-51	27	25	L. IFG
F6	51	27	25	R. IFG
F7	-52	28	4	L. IFG
F8	52	28	4	R. IFG
FC5	-59	3	26	L. PreMotor
FC6	59	3	26	R. PreMotor
C5	-64	-19	26	L. STG
C6	64	-19	26	R. STG
T7	-66	-18	-3	L. MTG
T8	66	-18	-3	R. MTG
CP5	-62	-46	23	L. AG/SMG
CP6	62	-46	23	R. AG/SMG
P7	-56	-65	0	L. Fusiform
P8	56	-65	0	R. Fusiform
O1	-26	-93	8	L. Occip
O2	26	-93	8	R. Occip

Table 2.1. EEG channels and their corresponding brain regions. EEG channels were selected for further analysis based on their proximity to previously established ROIs (Jobard et al., 2003) and their cross-hemispheric counterparts. Anatomic locations of EEG channels in Talairach space were derived from Koessler et al., 2009.

Event-Related Potentials (ERPs)

Each channel's event-related potentials (ERPs) were computed by averaging each participant's epoched EEG activity across trials. This was done separately for each condition. ERPs were baseline corrected relative to a 100 ms pre-stimulus window and low-pass filtered at 20 Hz. ERPs from each condition were then compared using pairwise *t*-tests at each time point. Instances of significant differences between conditions sustained across multiple time points then informed the subsequent connectivity analyses as to which moments might provide insights into important network differences.

Event-Related Spectral Perturbations (ERSPs)

Analyzing event-related spectral perturbations (ERSPs; $10 \log$ (power-at-a-time-point/average-baseline-power); dB units) affords the observation of the moment-to-moment fluctuations in oscillatory power in a given brain region, potentially offering insight into key reading processes in the brain. The powers at different frequencies were computed in 1.5 Hz increments from 3 Hz to 50 Hz using a sliding cosine wavelet (Hanning-windowed) with linearly increasing cycles from 1.8 cycles at 3 Hz to 30 cycles at 50 Hz. The total duration covered by the complete wavelet at each frequency was thus always 600 ms, but because of the shape of the wavelet, the central 200 ms of the wavelet, where the weighting was above 0.75, comprised approximately one cycle (200 ms) at 5 Hz and 10 cycles at 50 Hz. ERSPs were computed across trials for each subject separately. This technique produced an output 400 time points in length, capturing ERSPs from -1440 to 940 ms of the original epoch (baseline-corrected using the 100 ms prior to string presentation), as per EEGLab's *newtimesf()* function.

Each ERSP output was then collapsed across each selected frequency band (i.e. theta and gamma) at each time point, such that the maximum absolute value of ERSP at any individual frequency in the band was used (Fig. 2.3). This produced a time series for each channel that reflected its most prominent level of activation in a region at each time point. ERSPs from each condition were then compared using pairwise *t*-tests at each time point. Sustained instances of significant differences between groups then informed the eventual connectivity analyses as to which moments might provide insights into important network differences.

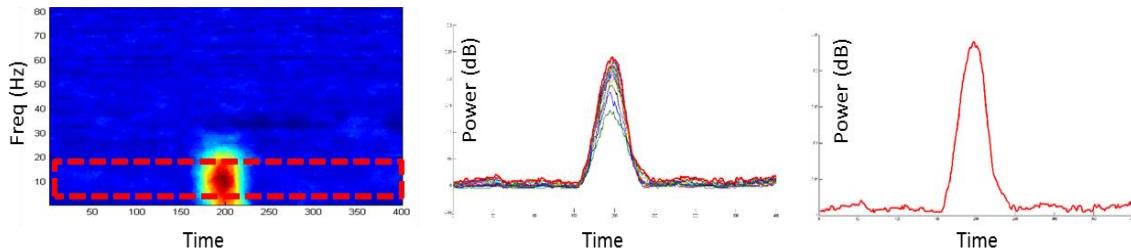


Figure 2.3. Extracting time-frequency measures for ERSP analysis. This figure depicts the processing procedure for a single EEG channel from a single subject (e.g. channel P5 from subject 12). This approach distills activity across a frequency range down to a single line to then be analyzed in group comparisons. (Left) A time-frequency plot shows an increased response (red coloring) within the designated frequency band. (Middle) The time-frequency response within the dotted line represented as a line graph. Each line represents the activity from a different individual frequency in the range highlighted within the dotted line. Signal power corresponds to the red coloring on the left. (Right) The maximum absolute value at each time point was selected as the most representative response within the frequency band. This time series was then used for further analysis. This approach was applied to phase synchrony measures, as well.

Phase Synchrony

Phase synchrony analyses were conducted in order to assess inter-regional functional connectivity, or the degree to which two brain areas are sharing information. This was done by computing the phase-locking values (PLVs) between pairs of electrodes located over reading-related brain regions. PLVs were computed using the following formula (Delorme & Makeig, 2004):

$$PLV_{1,2}(f,t) = \frac{1}{N} \sum_{k=1}^N \frac{W_{1,k}(f,t)W_{2,k}^*(f,t)}{|W_{1,k}(f,t)W_{2,k}(f,t)|}$$

where $W_{i,k}(f,t)$ are the wavelet coefficients for each time point, t , and frequency, f , for each EEG channel, i , and $k=1$ to N is the index of epochs. The PLVs produced by these computations indicate the degree of constancy of the phase differences between signals at a specific oscillatory frequency across trials (Fig. 2.4). PLVs range from 0 to 1, where 0

indicates the absence of any phase locking, and 1 indicates perfect phase locking, such that the phase difference between two channels at a given time point remains constant across all trials. Only stochastic phase locking, with $0 < \text{PLV} < 1$, is expected from any time series of brain activity because of neural noise (McDonnell & Ward, 2011).

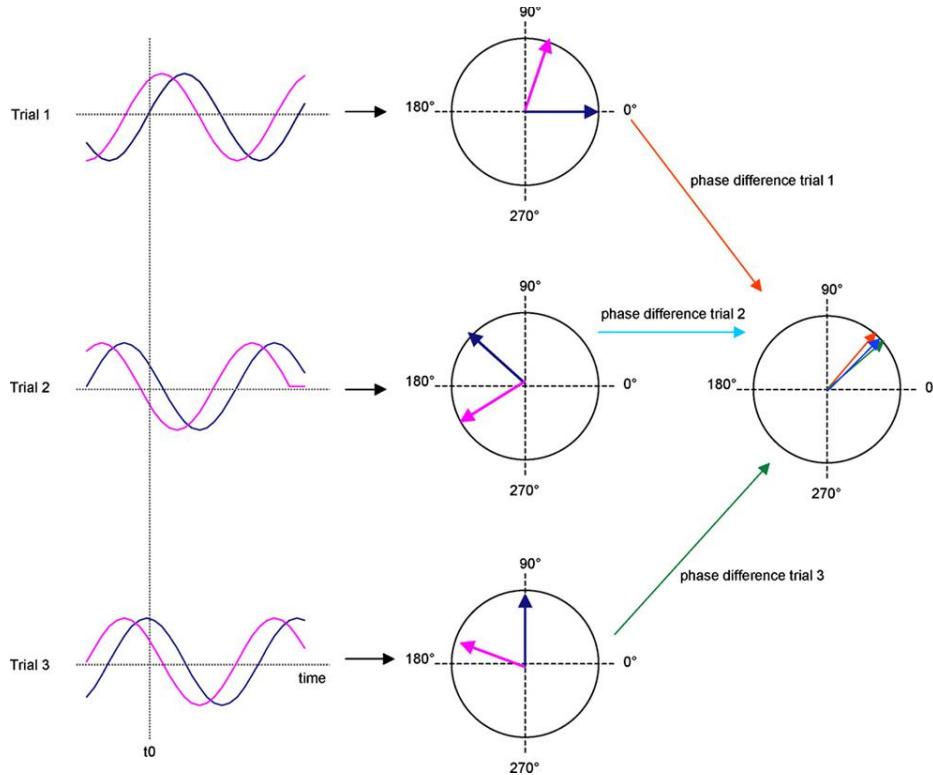


Figure 2.4. Constancy of phase difference and phase-locking values (PLVs). The phase difference between the two signals (e.g., from two distinct EEG channels) in this time window remains essentially the same across all trials. When averaged across trials, this produces a large phase locking value, which indicates a functional relationship between the two signals. Adapted from Sauseng and Klimesch, 2008.

PLVs were computed across subjects separately and for each time point for all channel pairs. This technique produced an output 400 time points in length, capturing ERSPs from -940 to 1440 ms of the original epoch, as per EEGLab's *newcrossf()* function. The phase lags of the significant PLVs were always significantly different from

zero (as determined by circular t-tests, $p < 0.001$), indicating that volume conduction, which can cause spurious zero-phase-lag synchronization, could not have been responsible for the significant PLVs.

PLVs were baseline corrected by subtracting the mean of PLVs in the 100 ms window immediately preceding stimulus presentation from the dataset. Each output was then collapsed across each frequency band at that time point (theta and gamma bands), such that the maximum absolute value of PLV at any individual frequency in the band was used, identical to the process used for ERSPs (Fig. 2.3). This consolidated the time series for each channel pair so that it reflected their degree of functional connectivity in this pair of regions at each time point. In order to differentiate PLV connectivity patterns between groups, two-tailed independent t -tests ($\alpha = 0.01$) were used.

To assess the statistical reliability of these t -tests, time points from 0 to 900 ms following the stimulus onset were divided into non-overlapping 50 ms time bins (i.e., 18 such bins). To control for multiple comparisons, and to exclude meaningless interactions, we adopted a conservative criterion and considered a 50 ms bin to contain meaningful evidence of greater functional connectivity for one condition than for the other if at least half (5 or more of 9) of the time points in that bin reached the statistical threshold described earlier for either words over consonants, or vice versa, and none did for the opposite comparison (Fig. 2.5). To assess the experiment-wise error of this procedure, we used $p = 0.01$ ($q = 1 - p = 0.99$) as the probability of a success in a single binomial trial to compute the binomial probability of getting 5 or more significant time points by chance out of the total of 19 time points in each 50-ms bin (Onton et al., 2005). This probability is 1.21×10^{-8} if all of the time points in a bin represented independent tests. This

assumption is probably not precisely correct as using consecutive time points lack complete independence, although it is not too unreasonable because the tests were made across subjects, who were independent of each other. Since we made 120 (inter-regional) comparisons (each possible pairing of 16 different channel ROIs) for 18 time bins, there were 2160 such tests. At most ($p = 0.01$, with the minimum 5 of 9 significant data points per bin), the experiment-wise error probability for each set of t-tests, assuming independence, was $2160 \times 1.21 \times 10^{-8} = 0.0000261$.

Once time bins were evaluated for their statistical significance, instances of significantly different functional connectivity between the two groups were then visualized (Figure 2.5) using the BrainNet Viewer toolbox for MATLAB (Xia et al., 2013).

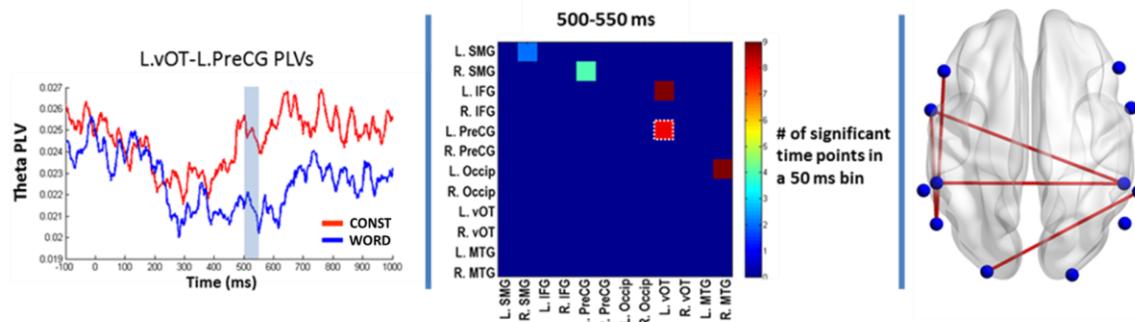


Figure 2.5. The process of mapping connectivity from time series. (Left) Group PLV means are compared with *t*-tests. Significant statistical differences are then evaluated in 50 ms bins, which are considered to be significant if at least half of the time points in the bin showed significant *t*-values. This is done for every pair of electrodes. (Middle) For each bin, a connectivity matrix is assembled, which tracks the number of significant time points in that bin. (Right) Channel pairs that achieved significance in at least half of the time points in a given bin are then visualized. This is done for each bin, allowing for the visualization of connectivity patterns over time.

Transfer Entropy

Whereas measures of functional connectivity show which brain areas are engaged

and sharing information (i.e. functionally connected), these measures do not indicate the causal flow of the information. That is, a measure such as phase synchrony does not indicate which site is *sending* the information, and which site is *receiving* the information, or if a bi-directional relationship exists. In order to understand such relationships, effective (causal) connectivity analyses must be employed. To address this, we employed transfer entropy, a recently developed technique for revealing Granger-causal interactions, particularly non-linear ones, without needing to specify or fit a model (Schreiber, 2000). Transfer entropy from time series J to time series I is defined (Schreiber, 2000) as the (asymmetric) Kullback-Liebler entropy between two time series at a specified, non-zero, lag ($k-l$):

$$T_{J \rightarrow I} = \sum p(i_{n+1}, i_n^{(k)}, j_n^{(l)}) \log \frac{p(i_{n+1} | i_n^{(k)}, j_n^{(l)})}{p(i_{n+1} | i_n^{(k)})}.$$

Transfer entropy measures the extent to which the transition probabilities (dynamics) between states within one time series (say J) are *not* independent of the past states of another time series (say I). It is larger the greater the influence of the state of I on the transition probabilities of J . Both the influence of J on I and that of I on J can be computed in this way. With regard to information transfer between neural sources, transfer entropy computes the additional information predicted by one region that is not already predicted by another region's prior activity. Narrow-band transfer entropy (NBTE) is a variant of this, whereby transfer entropy is computed *within a specific frequency band* rather than over the broadband signal (Wibral et al., 2011). TIM toolbox, developed by German Gomez-Herrero and Kalle Rutanen, for MATLAB (<http://www.cs.tut.fi/~timhome/tim/tim.htm>) was employed to compute theta- and

gamma-band NBTE.

Theta-band (3–8 Hz) oscillatory time series were obtained by filtering the CSD activations in the epochs using EEGLab’s digital FIR filter. NBTE was then computed across trials for each subject at 30 ms and 50 ms lags. The lags used here span the range of lags found to contain significant NBTE in previous similar investigations (Bedo, et al., 2014; Doesburg et al., 2016; Wibral et al., 2011). In order to avoid spurious NBTE because of correlations between successive samples in time series, the lags used should be longer than the autocorrelation time of the time series. That is, they should be longer than the time interval over which the correlation between successive samples decays to zero, typically around 8 – 10 ms for EEG/MEG data (Wibral, et al., 2011). The lags used here are longer than this, but not so long that effective connectivity would be expected to be zero; at lags greater than 100 ms, for example, we would expect information transfer between brain regions to fall off sharply for cognitive operations such as word reading which occur on the scale of a couple of hundred ms. Each output was then collapsed across lags, such that the maximum NBTE, whether at 30 ms or 50 ms lag was used (Wibral et al., 2011). This produced a time series for each source pair that reflected the amount of information flowing in a given direction in the brain at each time point. Importantly, the requirement of a lag for two sources to be considered to be interacting provides protection against spurious connectivity due to volume conduction, as such effects would be observed across sources with no time lag (i.e. a lag of 0 ms).

Once NBTE was computed and baseline corrected, it was further analyzed almost identically to the methods used for PLVs.

In order to differentiate NBTE connectivity patterns between groups, two-tailed

independent *t*-tests ($\alpha = 0.01$) were used, comparing word and consonant conditions at each time point.

To assess the statistical reliability of these *t*-tests, time points from 0 to 900 ms following the stimulus onset were divided into non-overlapping 50 ms time bins (i.e., 18 such bins). To control for multiple comparisons, and to exclude meaningless interactions, we adopted a conservative criterion and considered a 50 ms bin to contain meaningful evidence of functional connectivity for one group over the other if at least half (7 or more of 13) of the time points in that bin reached statistical threshold for either words over consonants, or vice versa, and none did for the opposite comparison (Figure 2.5 again). To assess the experiment-wise error of this procedure, we used $p = 0.01$ ($q = 1 - p = 0.99$) as the probability of a success in a single binomial trial to compute the binomial probability of getting 7 or more significant time points by chance out of the total of 13 time points in each 50-ms bin (Onton et al., 2005). This probability is 1.62×10^{-11} if all of the time points in a bin represented independent tests. This assumption is probably not precisely correct, as using consecutive time points lack complete independence, although it is not too unreasonable because the tests were made across subjects, who were independent of each other. Since we made 240 (inter-regional) comparisons (each possible pairing of 16 different brain ROIs in both directions) for 18 time bins, there were 3840 such tests. At most ($p = 0.01$, with the minimum 7 of 13 significant data points per bin), the experiment-wise error probability for each set of *t*-tests, assuming independence, was $3840 \times 1.62 \times 10^{-11} = 0.0000000622$.

Just as with PLVs, instances of significant effective connectivity by NBTE were then visualized using the BrainNet Viewer toolbox for MATLAB (Xia et al., 2013). This

process was performed for analysis of gamma (30-50 Hz) NBTE, as well.

Results

Accuracy

Across all conditions, participants scored above 94% correct. Trials were classified into four conditions based on the presentation of the complete string: Word-Match (i.e. the presented string was a word, and matched the sequence of letters that came before it; $M=94.79$, $SD=6.75$), Word-Nonmatch ($M=97.47$, $SD=3.75$), Consonant-Match ($M=94.79$, $SD=7.56$), Consonant-Nonmatch ($M=97.28$, $SD=4.38$). Only Match trials were selected for further analysis.

Reaction Time

Participants were significantly faster during word trials ($M=526$ ms, $SD=111$) compared to consonant trials ($M= 598$ ms, $SD=112$) as indicated by pairwise t -test, $t(13) = -6.39$, $p<0.001$ (Fig. 2.6).

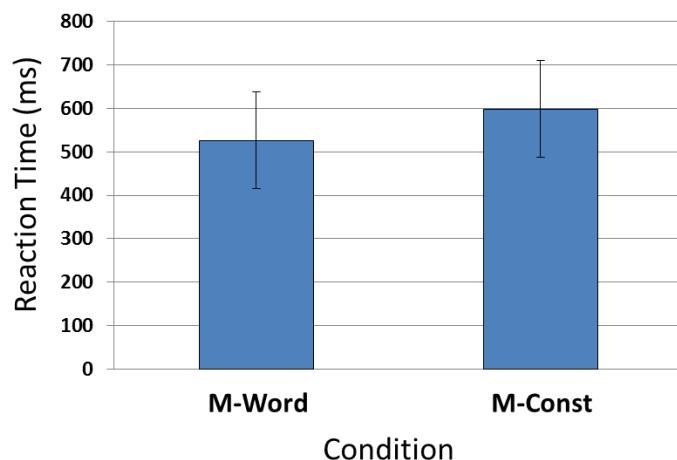


Figure 2.6. Reaction times relative to the onset of the complete letter string. Participants were faster in identifying matching words compared to matching consonant strings ($p<0.001$). Error bars represent one standard deviation.

ERP Results

ERPs from reading-relevant brain regions (Figure 2.7) showed no differences over time between conditions. Both vOT locations produced N170 components, representing the processing of orthographic information.

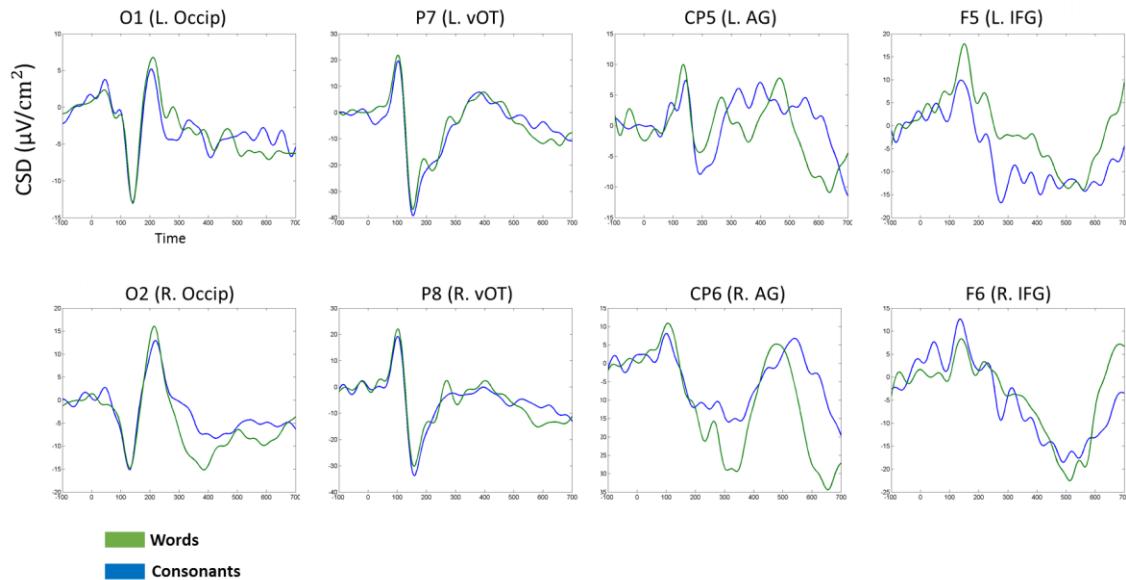


Figure 2.7. ERPs of reading-related brain areas. No significant differences were found between conditions at any major reading-related brain area; both conditions showed nearly identical ERP responses across all critical regions. Importantly, vOT areas exhibited the hallmark N170 ERP component commonly found in studies of orthographic processing.

ERSP Results

Six locations were selected for examination of ERSPs: left and right vOT, AG, and IFG areas. Theta-band ERSPs showed a significantly greater early (<300 ms) response to consonants at left vOT and IFG sites (Figure 2.8). However, words produced greater theta ERSP responses in the later processing stages (>400 ms) in the left AG, as well as the right vOT, AG, and IFG regions ($p < .05$, uncorrected).

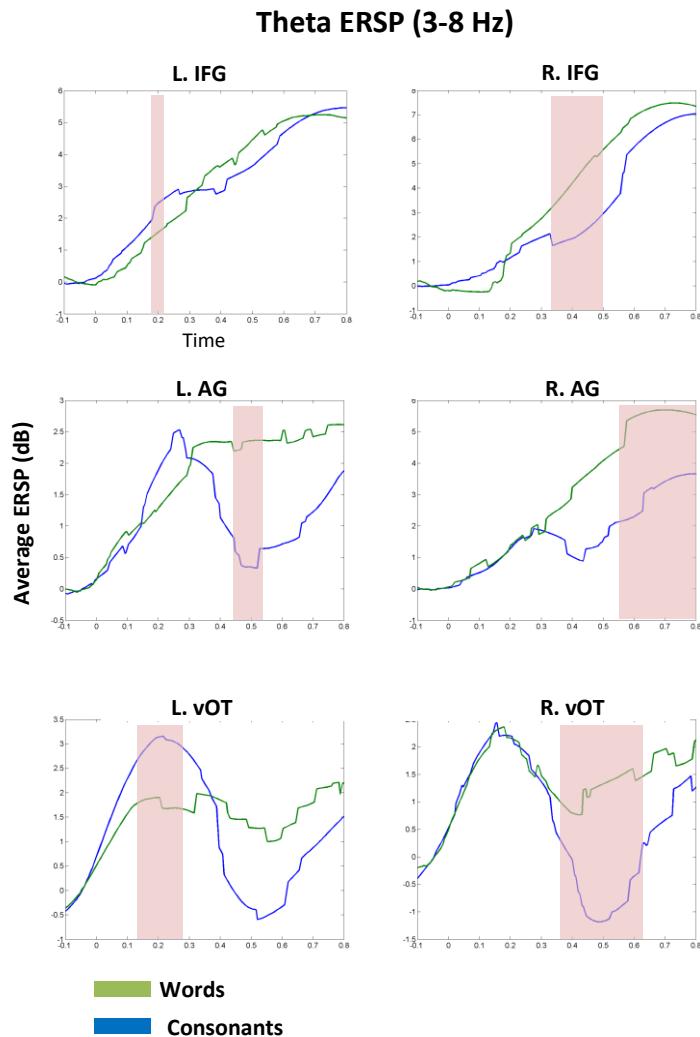


Figure 2.8. Theta ERSPs of reading-related brain areas. Consonants produced significantly greater early theta responses (<300 ms) in left vOT and IFG regions. However, words produced greater late theta responses (>400 ms) in the left AG, as well as vOT, AG, and IFG regions in the right hemisphere. Sections highlighted in pink represent significant differences ($p < 0.05$, uncorrected).

Gamma-band ERSPs showed a significantly greater responses for words in the later processing stages (>400 ms) in the left vOT and IFG areas, as well as the right vOT, AG, and IFG regions (Figure 2.9).

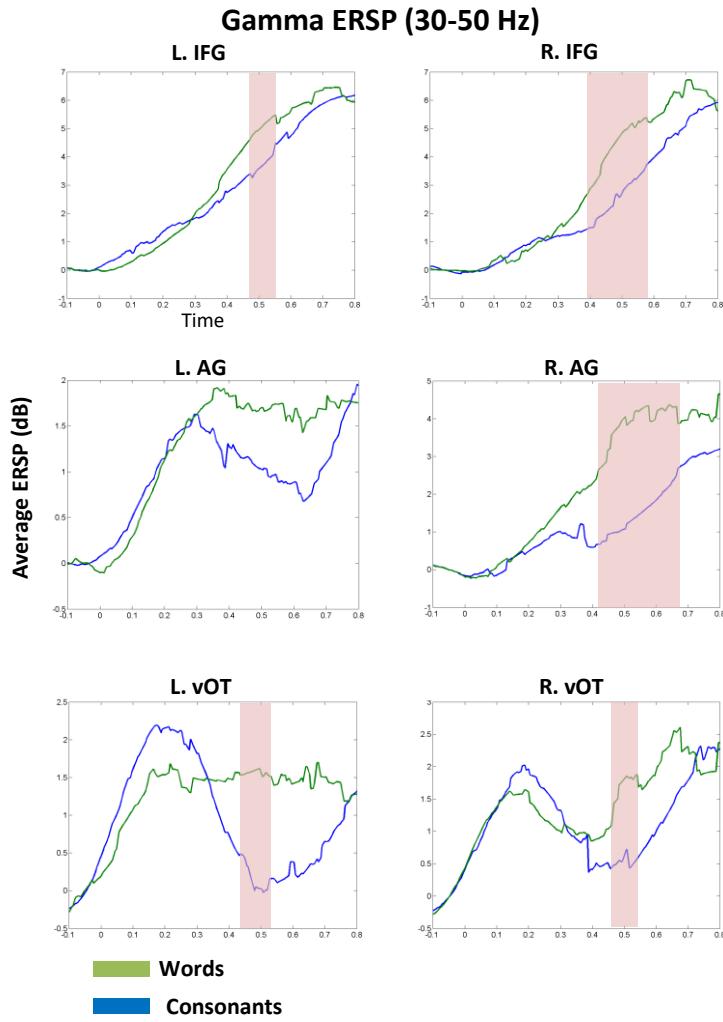


Figure 2.9. Gamma ERSPs of reading-related brain areas. Words produced greater late gamma responses (>400 ms) in the left vOT and IFG areas, as well as vOT, AG, and IFG regions in the right hemisphere. Sections highlighted in pink represent significant differences ($p < 0.05$, uncorrected).

Phase Synchrony Results

Phase synchrony was used to measure the degree of functional connectivity between pairs of regions. Differences between conditions were evaluated in 50 ms non-overlapping intervals. A time bin was considered to show a significant difference if at least half of the data in the bin showed a significant difference by pairwise t -tests ($p < .01$).

Compared to consonant strings, words produced more robust and widespread

theta- and gamma-band functional connectivity among brain areas relevant to reading, over time.

Theta PLVs

Words, when compared to consonant strings, elicited higher theta PLVs between left vOT and right STG at approximately 100-150 ms (Figure 2.10). Beginning at ~250 ms, word processing showed larger occipito-temporal PLVs compared to consonant strings, eventually showing larger occipito-frontal and fronto-temporal PLVs as well. There were no instances of significantly greater connectivity in response to consonant strings.

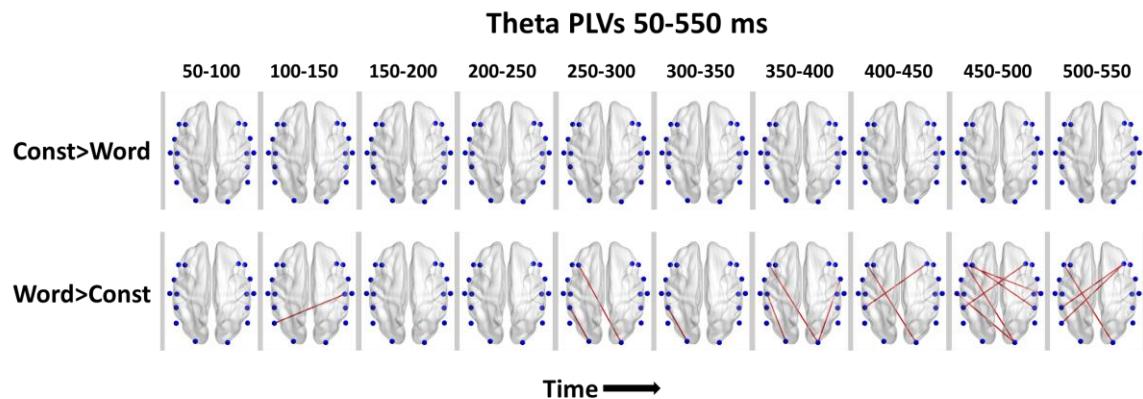


Figure 2.10. Time course of theta-band phase synchrony (functional connectivity) between reading-related brain areas. For each bin, at least half of the data points had to reach significance by *t*-test ($p<0.01$) in order for the bin to be considered significant.

Gamma PLVs

Words elicited higher gamma PLVs among frontal and temporal regions starting at ~400 ms, including left and right IFG, left and right AG, left vOT, right MTG, and right STG regions (Figure 2.11). There were no instances of significantly greater gamma connectivity in response to consonant strings.

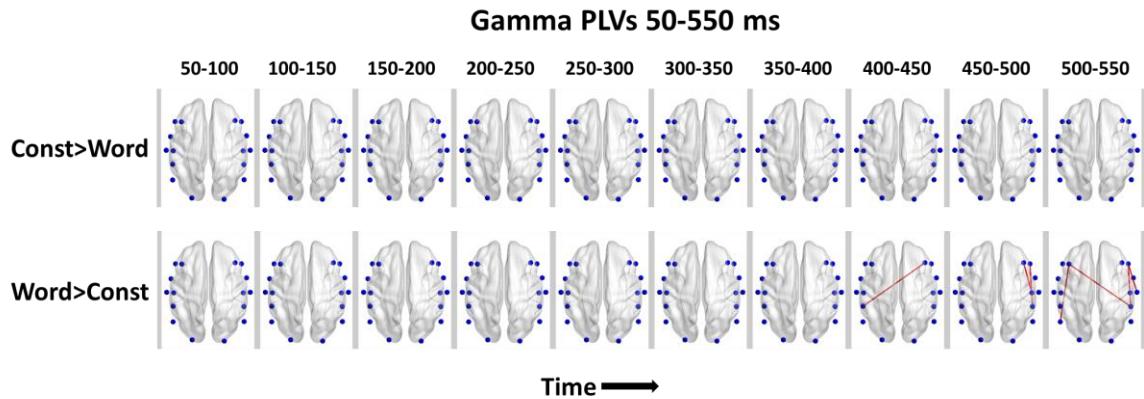


Figure 2.11. Time course of gamma-band phase synchrony (functional connectivity) between reading-related brain areas. For each bin, at least half of the data points had to reach significance by t -test ($p<0.01$) in order for the bin to be considered significant.

Transfer Entropy Results

Transfer entropy was used to measure the degree of effective connectivity between cortical sites. Differences between conditions were evaluated in 50 ms non-overlapping intervals. A time bin was considered to show a significant difference if at least half of the data in the showed a significant difference by pairwise t -tests ($p<.01$).

Compared to consonant strings, words produced more robust and widespread theta- and gamma-band effective connectivity among brain areas relevant to reading, over time (Figure 2.12).

Theta NBTE

Words elicited higher theta NBTE from left vOT to right vOT at approximately 150-200 ms, and then from right vOT to left MTG at ~200 ms. At ~250 ms post-stimulus, words showed greater NBTE from left vOT to left MTG and from right AG to right MTG. After ~400 ms, words elicited significantly greater theta NBTE from posterior

occipital and occipito-temporal sites to frontal regions, as well as from left temporal areas to temporal regions in the right hemisphere.

One bin showed greater NBTE in the consonant string condition (200-250 ms), from left AG to right AG, and from right AG to left Pre-Motor cortex.

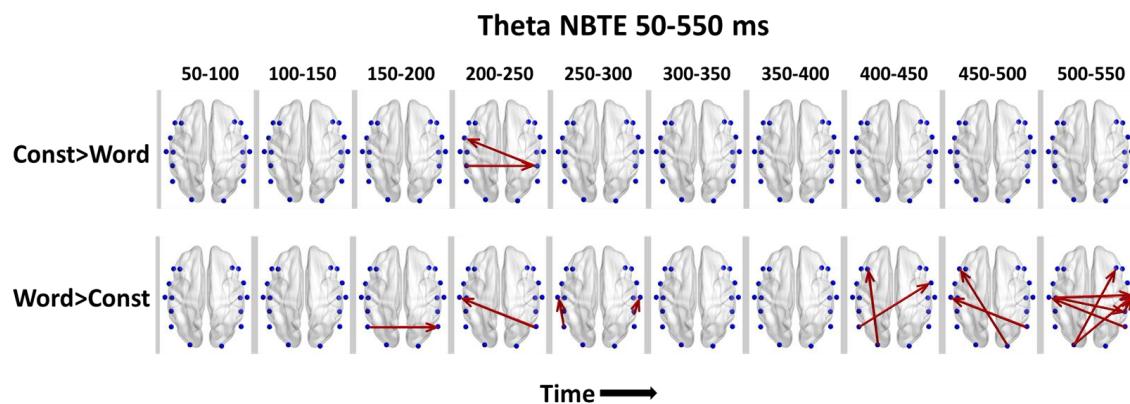


Figure 2.12. Time course of theta-band NBTE (effective connectivity) between reading-related brain areas. For each bin, at least half of the data points had to reach significance by *t*-test ($p<0.01$) in order for the bin to be considered significant.

Gamma NBTE

Words elicited higher early (<100 ms) gamma NBTE from right occipital cortex to right MTG, and from left IFG to right IFG, followed by increased NBTE from right occipital cortex to left STG 200-300 ms post-stimulus (Figure 2.13). From 400 ms onward, words show greater NBTE to and from frontal sites (i.e. IFG and Pre-Motor cortex); in particular, left IFG regions show increased information exchange with superior temporal regions of the right hemisphere (i.e. STG and AG), several of which were top-down signals (i.e. not bi-directional).

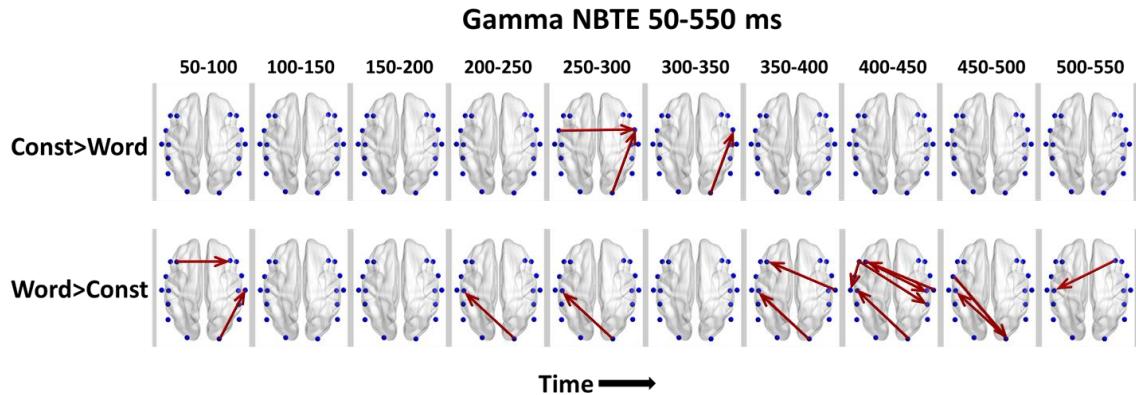


Figure 2.13. Time course of gamma-band NBTE (effective connectivity) between reading-related brain areas. For each bin, at least half of the data points had to reach significance by t -test ($p<0.01$) in order for the bin to be considered significant.

Discussion

In this study, the neural responses to reading words and consonant strings were compared. Specifically of interest were the network connectivity dynamics subserving the cognitive functions involved in reading. By comparing stimuli high in linguistic content (i.e. words) and stimuli lacking in linguistic content (i.e. consonant strings), I sought to examine the network processes involved in reading above and beyond simple orthographic processing. Phase synchrony and transfer entropy were used to measure functional and effective connectivity, respectively. Connectivity measures were then compared between conditions and results were visualized to examine differences in connectivity patterns. Results confirmed the hypothesis that engagement of linguistic content beyond orthography would generate increased connectivity involving language processing centers in the brain, including frontal and temporal sites.

Here I showed that linguistically-rich letter strings generate higher levels of functional and effective connectivity over time, compared to letter strings that lack such

linguistic content (i.e. consonant strings), particularly at durations longer than 250 ms post-onset, where word processing would be expected to engage linguistic processing that would not occur for letter strings that did not form words. The late (>400 ms) connectivity differences between conditions suggests that these differences represent later stages of reading such as semantics and phonology, indicated by N400 ERP components (Moisescu-Yiflach & Pratt, 2005; Russeler et al., 2007). Our results also show theta connectivity prior to the critical 400 ms mark, which may be the instance of communication that transmits orthographic information to then extract phonological information.

The progression of brain activations shown by Marinkovic and colleagues (2003) is reflected in our connectivity results in that we see a posterior-to-anterior progression along the left hemisphere. Interestingly, the present results show that the right hemisphere was recruited rather extensively in the processing of words—a somewhat unexpected result given the emphasis on left-hemisphere dominance in reading research (Dehaene, 2009). Widespread right hemispheric sites were engaged in reading processes, both in terms of local oscillatory power (ERSP) as well as communicating with regions in the left hemisphere, as shown with both PLVs and NBTE.

These results aid in interpreting the local dynamics seen in ERP and fMRI research, showing not only which regions exhibit increased activation, but also how these regions communicate over time in the propagation of brain signals.

Local Neural Activity

Prior to investigating connectivity, local measures of neural activation were examined to see if they were in accordance with previous research. Although the ERPs

showed nearly identical cortical responses from reading-related areas between conditions, the frequency-specific ERSP results suggested a divergence between conditions at approximately 350-400 ms after stimulus presentation. Specifically, words generated greater late (>300 ms) theta- and gamma-band responses at sites critical for higher language processes, including left and right AG and IFG regions, reflecting the access of additional information elicited by words, as they contain semantic and phonological content not present in consonant strings (Dehaene et al., 2006). Notably, the right hemisphere was significantly involved in this processing, a result that is not often emphasized (Dehaene, 2009).

Connectivity Dynamics During Reading

As expected, compared to consonant strings, reading words resulted in considerably more robust and widespread functional connectivity over time, as measured by phase synchrony. Since words tended to show greater local theta and gamma ERSPs at reading-relevant areas at later points of processing, it makes sense that those areas would also show greater connectivity with one another in those same frequency bands.

Theta-band phase synchrony showed increased functional connectivity for words as early as 100-150 ms after stimulus presentation. Theta-band PLVs also showed increased engagement of various regions over time; in particular, occipito-temporal and temporo-parietal connectivity seemed to dominate shortly after stimulus presentation, with anterior sites being recruited later on. Gamma-band PLVs began showing differentiation between conditions at approximately 400-450 ms, particularly with fronto-temporal and fronto-parietal connections. The timing of these connectivity results falls in

line with the general posterior-to-anterior sweep of activations demonstrated in previous studies (Marinkovic et al., 2003; Pammer et al., 2004).

Considering the normal time-course of reading processes in the brain, we would expect orthographic decoding to occur around 170 ms after stimulus presentation (Dujardin et al., 2011; Jucla et al., 2010). At this point, this orthographic information is made accessible to the rest of the reading network. As such, the connectivity seen immediately after 170 ms may reflect this transmission of orthographic information. Given that the cognitive demands of the two conditions diverge following the basic orthographic processing, it follows that we would see differences in regional activity and inter-regional connectivity exhibited around 200-250 ms.

Somewhat surprising was the greater connectivity response for Words between occipital and frontal sites during later stages of processing. Prior studies (Marinkovic et al., 2003) depict a wave of activity originating in the occipital lobe and roving across the left hemisphere toward inferior frontal cortex; our results may represent top-down signals that aid in sustaining perceptual processing (Di Lollo et al., 2000).

We did expect gamma connectivity to match the theta network to some extent. Vidal and colleagues (2012) have found that correlations in gamma power between disparate reading-related regions in the left hemisphere are related to linguistic processing. In that regard, they posit that gamma might be a mechanism for large scale neural integration, which in our case might contribute to the smooth processing of written language.

Top-Down Signals

The contribution that NBTE offers is directionality of the connectivity. As reading

is a multi-stage process that engages several regions, orthographic and linguistic information must be routed in this network. Price and Devlin (2011) have noted the importance of top-down processing in word identification. Our results showed very few instances of top-down information flow, primarily shown in gamma NBTE 400-450 ms following stimulus presentation from left IFG to left and right temporal sites.

However, top-down signals are not only useful in the later processes – they are also important in the early orthographic processing (Price & Devlin, 2011). From this perspective, top-down predictions are evaluated against bottom-up signals; if these are incongruent, the prediction is updated and this evaluation is done again. This pattern is similar to Di Lollo's re-entrant processing framework (Di Lollo et al., 2000), which posits that perceptual representations are maintained in consciousness by re-entrant loops by which bottom-up information is propagated to higher-level regions, which in turn refine and update the lower-level representations through top-down signaling. It is this constant iteration that supports conscious perception. As it relates to the present study, this framework suggests that top-down signaling should be quite widespread, including among lower-level language areas, and yet we only found it from frontal to temporal sites. One potential explanation is the ease of the task; the words were only three letters long and our participants were extremely experienced readers. Considering Price and Devlin's framework, it may be the case that the top-down predictions were usually correct, thus requiring little to no updating in response to the bottom-up information, thus resulting in no top-down NBTE. Additionally, our conservative statistical approach could have omitted any short-lived or inconsistent top-down signaling that was, in actuality, present.

Limitations

In this study, we included two left-handed individuals in our pool of participants. It is possible that handedness may have played a distinct role in shaping the language networks that emerged from our analysis. However, the extent to which this is the case, if at all, is unclear. The literature concerning the impact of handedness on reading and language networks lacks consensus. Some findings suggest that left-handedness is related to the reversal of language lateralization in the brain to the right hemisphere, whereas other findings indicate a reduction of lateralization altogether. One such neuroimaging study found that out of 100 participants (50 left-handed), 10% of the left-handed group showed right-hemispheric dominance during a silent reading task, although the authors admit that the dominance was weak in these cases (Pujol et al., 1999). Another fMRI study looking at 50 non-right-handed individuals found that 8% showed right-hemispheric dominance during an auditory language task (Szaflarski et al., 2001); unfortunately, exclusively right-handed individuals were not included in this study. Others have proposed right-hemispheric dominance for up to 27% for strong left-handers (Knecht et al., 2000), although this study used somewhat unconventional neuroimaging techniques (fTCD, based on the same principles as fMRI). More recently, such investigations in children and adolescents comparing 27 left-handers and 54 age- and gender-matched right-handed controls reported just 1 (4%) left-hander and 1 (2%) right-hander with right-hemispheric dominance during a verb generation task (Szaflarski et al., 2012).

If left-handed participants did have reduced hemispheric asymmetry, or were right-hemisphere-dominant, that underlying brain activity would add variability to the

rest of the presumably left-hemisphere-dominant activity. This additional variability would negate some of the results that would otherwise reach statistical significance. With our conservative approach, we already omit many inconsistent results, so adding more variability might further omit some less consistent results. However, that same logic increased our confidence in the connectivity that we do see, as that would indicate a level of consistency that was resistant to increased variability.

In this study, we did not formally assess the reading ability of our participants. It may be argued that without clearly establishing normal reading ability, we may unknowingly be evaluating brain activity from a population with reading difficulties (e.g. dyslexia). However, even though no formal reading assessments were conducted, we have reason to believe that our sample did not have deficits in reading ability. First, all participants scored at least 94% accuracy in a fast-moving reading task. Furthermore, all participants were enrolled at a university with reading-intensive coursework, and were alerted of the study's focus on reading prior to contacting us; and, when specifically asked on multiple occasions, reported no known history of such reading difficulties. Taken together, we believe these to be sufficient criteria for inclusion in this particular analysis.

CHAPTER 3: Functional and Effective Connectivity Differences in Dyslexic and Non-impaired Children

Introduction

Developmental dyslexia is a learning disability characterized by impaired reading speed and accuracy, poor spelling, and poor decoding abilities despite having normal intelligence. Dyslexia affects 3-7% of schoolchildren (Lindgren et al., 1985; Goswami, 2008), and their challenges with reading remain with them into adulthood.

Neuroimaging studies have provided useful insights into identifying the brain regions of interest that relate to dyslexia (Eden et al., 2004; Hoeft et al., 2006; Jobard et al., 2003), yet few studies have examined just how these regions dynamically communicate while processing written language.

One major recurring finding is that dyslexic readers utilize their right hemisphere in reading tasks to an extent not found in typical readers; often, these sites are right-hemispheric analogues of left-hemispheric regions used by typical readers. This pattern is not necessarily a complete migration of activity to the right hemisphere, but rather a lack of asymmetry such that the activations are more evenly distributed between hemispheres rather than being predominantly found in the left hemisphere (Eden et al., 2004; Hoeft et al., 2006). Some have speculated that this is the result of genetic aberrations of neural migration in the left hemisphere during fetal development, leading to impaired neural coordination and ultimately the recruitment of comparable regions in the right hemisphere to compensate for these maladaptations (Galaburda et al., 1985; Galaburda, 2004; Giraud et al., 2013; Hancock et al., 2017).

Some have posited that neural oscillations – particularly theta- and gamma-bands

– play a critical role in the processing of written language (Bedo et al., 2014; Giraud et al., 2013; Goswami, 2011; Lehongre et al., 2011; Lehongre et al., 2013); and in particular, that these neural oscillations are perturbed in dyslexic readers.

Despite various studies examining regional activity in dyslexic readers, few studies have investigated the underlying connectivity patterns that characterize dyslexia (Horwitz et al., 1998; Pugh et al., 2000). Still lacking are measures of connectivity that are derived from the aforementioned neural oscillations, particularly in theta and gamma bands. Our research shown in Chapter 2 corroborated the notion that oscillatory activity among reading-related sites increased in response to written language in typical adults. This chapter aims to examine similar phenomena in dyslexic children.

To that end, I conducted a secondary analysis of an existing dataset of EEG activity from 87 German children during a reading task (Hasko et al., 2013). Using a lexical decision task, the researchers of the original study compared ERP responses of dyslexic and typical readers. They did not, however, perform any brain network analyses on the data. The task employed in this study was specifically designed to tax the phonological systems that are supposedly impaired in dyslexia, and thus is ideal for examining the underlying network interactions subserving these functions. Particularly of interest was the interval 200-250 ms following stimulus presentation, as this marks a critical moment when orthographic information is processed and distributed to other brain regions for further evaluation in young readers.

A well-practiced and efficient reading network in controls should require fewer neural resources for reading compared to the dyslexic group. Therefore we hypothesized that, in this interval, dyslexic readers would show increased oscillatory power and

connectivity involving the right hemisphere compared to typical readers.

Methods

Participants

Through broad and thorough recruitment of German grade 2 students, 29 typical (TYP) readers and 58 readers with developmental dyslexia (DYS) participated in this study (87 total).

Participants in this experiment were selected after multiple stages of recruitment designed to identify dyslexic readers in the community. This process began with large city-wide survey, eventually identifying children who did not otherwise have severe psychiatric or attentional disorders, and finally identifying children who specifically had challenges with reading.

Initial inquiries were sent to 10,000 randomly selected families throughout Munich, Germany. From this broad sample, only native German speakers were selected to continue in the recruitment process.

Potential participants were excluded from the next stage of recruitment if one of the parents indicated that his or her child had a history of specific language disorders, had been treated for any neurological or psychiatric disorder or was currently under medication. Parents were also asked to estimate their child's symptoms of Attention-Deficit Hyperactivity Disorder (ADHD) using the “Attention Problems” sub-test of the Child-Behavior-Checklist (CBCL 1-4; Achenbach, 1991) in order to prevent the inclusion of children with heightened risk of ADHD in the study. Children who scored above average in the parent questionnaire (CBCL-score >7 for girls and CBCL-score >8 for boys) were considered high-risk for ADHD, and were therefore excluded.

After narrowing the participant pool into the next stage of recruitment, 250 second graders were screened for common word and pseudoword reading fluency using a German standardized one-minute reading test (German: Ein-Minuten-Leseflüssigkeitstest [SLRT-II]; Moll & Landerl, 2010). In this test, children are presented with a list of common words and pseudowords and are given one minute to read as many items as possible. Spelling was assessed with a German standardized basic vocabulary spelling test for grades 2–3 (German: Weingartener Grundwortschatz Rechtschreib-Test für zweite und dritte Klassen [WRT2+]; Birkel, 1994). A German standardized reading comprehension test for grades 1–6 (German: Ein Leseverständnistest für Erst- bis Sechstklässler [ELFE 1–6]; Lenhard & Schneider, 2006) was used to assess comprehension abilities (Table 3.1).

In order to ensure differentiation between the dyslexic and typical readers, children were selected for the TYP group if they showed average (or above average) assessment scores. Children belonging to the TYP group were required to be within 0.70 standard deviations of the lower end of the norm scale calculated in *T*-values (mean = 50; $SD = 10$; cutoff criterion was therefore set to a *T*-value of 43). Participants who fulfilled the developmental dyslexia diagnosis requirements according to the International Classification of Diseases (ICD-10: F 81.0; Dilling, 2006) were admitted to the DYS group; their reading and spelling scores had to diverge from the mean *T*-value for at least one standard deviation; therefore, children scoring below 40 were placed in the DYS group.

Both groups were approximately the same age, on average (TYP: $M = 8.15$, $SD = 0.27$; DYS: $M = 8.30$, $SD = 0.37$), and had an IQ-score within the normal range (≥ 85

points). The control group IQ score average was 111.79 ($SD = 10.42$), the dyslexic group average was 105.35 ($SD = 8.20$), $p = 0.003$. These differences in IQ scores may be due to the types of tasks included in the assessments. In measuring IQ, both verbal and non-verbal scores are combined to calculate a composite IQ score. Whether or not they are poor readers because of lower IQ, or if their verbal score is negatively impacted by poor reading ability is difficult to know. However, given that the groups differ by less than a standard deviation, and both groups have slightly above average IQ scores in aggregate, we are inclined to believe that general intelligence likely plays a minimal role in this particular experiment.

Both groups showed similar gender distributions (control group: 13 females, 16 males; dyslexia group: 21 females, 37 males). All participants were right-handed, except for one child from the TYP group and one child from the DYS group. All participants had normal hearing and normal or corrected-to-normal visual acuity.

Table 3.1 Descriptive statistics of Typical and Dyslexic readers.

	TYP (n = 29)	DYS (n = 52)	p-value
	M (SD)	M (SD)	
Word reading ^a	56.21 (6.76)	32.36 (3.96)	<0.001
Pseudoword reading ^a	54.62 (7.82)	36.33 (4.41)	<0.001
Reading comprehension ^b	56.96 (8.03)	36.09 (4.15)	<0.001
Spelling ^c	52.04 (5.38)	34.75 (3.94)	<0.001

Table 3.1. Descriptive statistics of assessments for dyslexic (DYS) and typical (TYP) readers. Average reading and spelling scores are delineated by T-values; T-values have a mean of 50 ($SD \pm 10$). Adapted from Hasko et al. (2013). a, SLRT-II; b, ELFE 1-6; c, WRT 2+. Six participants were excluded due to artifacts in their EEG recordings.

Experimental Procedures

Children performed a phonological lexical decision task (Hasko et al., 2013; Kronbichler et al., 2007; Bergmann & Wimmer, 2008; van der Mark et al., 2009, 2011), in which participants had to decide whether or not a visually presented stimulus sounded like a real word (“Does _____ sound like a real word?”, see Figure 3.1). Stimuli presented to the children consisted of four possible types: real words (orthographically and phonologically familiar forms of German nouns; e.g., ‘brain’), pseudohomophones (phonologically correct but orthographically unfamiliar forms derived from the real words; e.g., ‘brane’), pseudowords (phonologically and orthographically unfamiliar forms; e.g., ‘croll’) and false fonts (e.g., €øψќđ). Real words and pseudohomophones required a “yes” response, as they did produce phonologically familiar forms that “sound like words.” Pseudowords and false fonts required a “no” response. For each of the four conditions, 60 stimuli were presented once, for a total of 240 trials. Pseudowords were derived from the pool of real word stimuli by taking a word and changing a single letter (e.g. *bread* to *brean*).

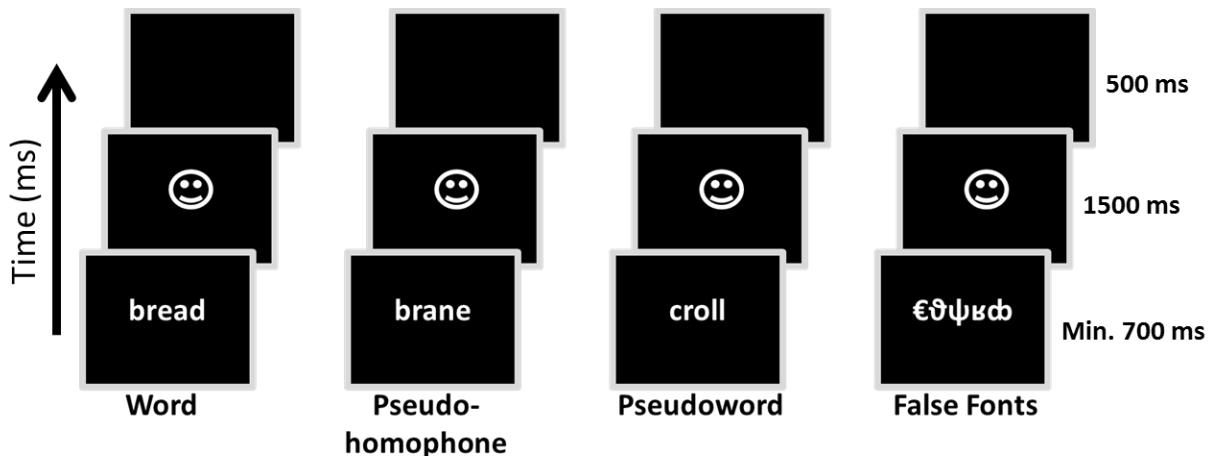


Figure 3.1. Schematic of Hasko et al. (2013) phonological lexical decision task. Participants were required to judge whether or not a letter string sounded like a real word. Figure adapted with permission.

E-Prime 2.0 software (Psychology Software Tools, Inc.) was used to present stimuli in white font on a black background. All stimuli were centered on a 17-inch computer monitor placed 70cm in front of the participants, resulting in a vertical visual angle of 1.23° and an average horizontal angle of 3.44° . The set of 240 stimuli were ordered into two possible pseudorandomized arrangements; each participant was presented with one such arrangement. This was done to counterbalance the order of word and pseudohomophone appearances to minimize systematic priming, since the pseudohomophone stimuli were derived from the real words. In one list, the presentation of the real words preceded their pseudohomophone counterparts appearing later in the list (e.g. “brain” before “brane”), whereas this pattern was reversed in the other list. Sessions were divided into four blocks of 60 stimuli with short breaks after each block. A 24-trial practice block preceded the experiment, however none of those trials were repeated in the experiment.

Stimuli were presented for a minimum of 700 ms and then remained on the screen until the participant responded as to whether or not the stimulus sounded like a word. Half of the participants used their right hand for “yes” while the other half use their left hand for “yes.” After each response, the children were presented with visual feedback in the form of a happy face or a sad face (1500 ms), corresponding to a correct or incorrect response, respectively. A black screen (500 ms) was then shown before automatically initiating the next trial.

EEG Acquisition

Continuous EEG was recorded using an Electrical Geodesic Inc. 128-channel system during the task using EGI Net Station (version 5) recording software. Impedances were kept below 50 kΩ. EEG signals were sampled at 500 Hz and referenced to electrode Cz. All further processing and analysis was performed using MATLAB software (Mathworks, Natick, USA). Six participants were excluded due to artifacts in their EEG recordings.

Prior to analysis, EEG channels were pruned down to 64 channels that conformed to the 10-10 international system of electrode placement. All signals were then re-referenced to an average reference, resampled to 250 Hz, and digitally filtered from 1-100 Hz using EEGLAB software (Delorme & Makeig, 2004), an open source MATLAB toolkit, and custom scripts. A digital notch filter between 45 Hz to 55 Hz was applied to reduce line noise. The continuous data were epoched into 3500 ms bins time-locked to the presentation of the letter strings, capturing 1500 ms before and 2000 ms after word presentation. Each participant contributed an average of 191 trials (SD=30.29), for a total of 16622 trials for the experiment.

Current Source Density

The methods for deriving CSD were identical to those used in Chapter 2, with some minor differences based on the EEG system used to collect data. CSD Toolbox for MATLAB was used to compute the CSD values (Kayser, 2009; Kayser & Tenke, 2006a; Kayser & Tenke, 2006b). Cortical regions of interest for further analysis were selected based on reading-related brain areas as revealed in previous research (Table 3.2; Jobard et al, 2003). The cortical Talairach coordinates of these sites were then cross-referenced to

anatomical locations of electrodes based on the 10-10 system (Figure 3.3; Koessler et al, 2009). The nearest electrodes to these sites, as measured by Euclidean distance, were then selected for further analysis. The subset of electrodes selected in this manner were CP5, CP6, F5, F6, FT7, FT8, O2, P7, P8, TP7, and TP8. For ease of exposition the ROIs will be referred to by their cortical locations from now on, but it must be remembered that in fact the data to be analysed are the CSD values computed for the electrode locations nearest those cortical locations and not the activation levels of dipoles or other types of cortical sources inferred by localization analysis.

Table 3.1. Reading-related Brain Regions and Their Corresponding EEG Channels.

EEG channel	Talairach coordinates			Corresponding Brain Region
	x	y	z	
F5	-51	27	25	L. IFG
F6	51	27	25	R. IFG
FT7	-59	3	-2	L. PreCG
FT8	59	3	-2	R. PreCG
TP7	-64	-45	-4	L. MTG/STG
TP8	64	-45	-4	R. MTG/STG
CP5	-62	-46	23	L. AG/SMG

CP6	62	-46	23	R. AG/SMG
P7	-56	-65	0	L. Fusiform
P8	56	-65	0	R. Fusiform
O2	26	-93	8	R. Occip

Table 3.2. EEG channels and their corresponding brain regions. EEG channels were selected for further analysis based on their proximity to previously established ROIs (Jobard et al., 2003) and their cross-hemispheric counterparts. Anatomic locations of EEG channels in Talairach space were derived from Koessler et al. (2009).

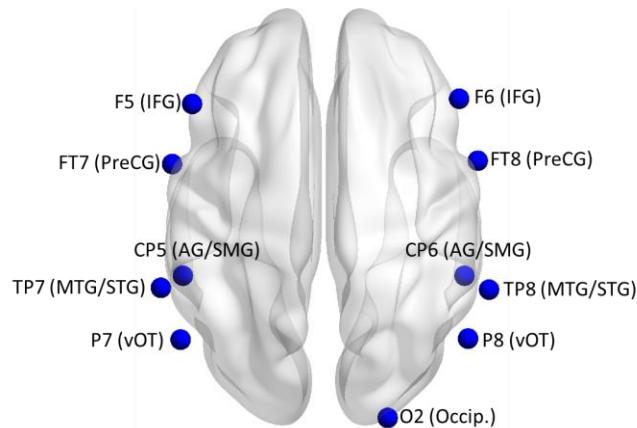


Figure 3.2. Selected electrodes that overlap with reading-related brain areas. Visual representation of anatomical locations of channels described in Table 3.2.

Event-Related Potentials (ERPs)

ERP parameters and rejection criteria were identical to those used in Chapter 2. ERPs were computed by averaging each participant's epoched EEG activity across trials. This was done separately for each condition. ERPs were baseline corrected relative to a 100 ms pre-stimulus window and low-pass filtered at 20 Hz. ERPs from each group were then compared using (uncorrected) pairwise *t*-tests at each time point. Instances of significant differences between conditions sustained across multiple time points then

informed the subsequent connectivity analyses as to which moments might provide insights into important network differences.

Event-Related Spectral Perturbations (ERSPs)

The ERSP processing and analysis procedures for this experiment were identical to those explained in Chapter 2. ERSPs allow us to observe the moment-to-moment fluctuations in oscillatory power at various oscillatory frequencies (i.e 3-100 Hz) relative to a 100 ms pre-stimulus baseline. ERSPs were computed across trials for each subject separately. This technique takes the input of 750 data points (one epoch) and compresses the outgoing spectral data, producing an output 400 data points in length, capturing ERSPs from -940 to 1440 ms of the original epoch, as per EEGLab's *newtimef()* function.

Phase Synchrony

The phase synchrony processing and analysis procedures for this experiment were nearly identical to those explained in Chapter 2. Phase synchrony analyses were conducted in order to assess inter-regional functional connectivity, or the degree to which two brain areas are sharing information, in particular, theta- (3-8 Hz) and gamma- (30-50 Hz) bands. PLVs range from 0 to 1, where 0 indicates the absence of any phase locking, and 1 indicates perfect phase locking, such that the phase difference between two channels at a given time point remains constant across all trials. This technique takes the input of 750 data points (one epoch) and compresses the outgoing spectral data, producing an output 400 time points in length, capturing ERSPs from -940 to 1440 ms of the original epoch, as per EEGLab's *newcrossf()* function. Issues of spurious PLVs or the entrainment of oscillations by volume conduction were again minimized by computing the wavelet transforms of the CSD time series rather than those of the scalp potentials.

Moreover, the phase lags of the significant PLVs were always significantly different from zero (as determined by circular t-tests, $p < 0.001$), indicating that volume conduction, which can cause zero-phase-lag synchronization, could not have been responsible for the significant PLVs.

In order to assess the connectivity patterns with each group, two-tailed one-sample t -tests ($\alpha = 0.001$) were employed to determine the statistical significance of these PLVs relative to zero at each time point. As a means to differentiate PLV connectivity patterns between groups, two-tailed independent t -tests ($\alpha = 0.01$) were used, comparing FFW and TYP groups at each time point.

To assess the statistical reliability of these t -tests, time points from 0 to 900 ms following the stimulus onset were divided into non-overlapping 50 ms time bins (i.e., 18 such bins). To control for multiple comparisons, and to exclude meaningless interactions, we adopted a conservative criterion and considered a 50 ms bin to contain meaningful evidence of greater functional connectivity for one group than for the other if at least half (5 or more of 9) of the time points in that bin reached the statistical threshold described earlier for either TYP > FFW, or vice versa, and none did for the opposite comparison. To assess the experiment-wise error of this procedure, we used $p = 0.01$ ($q = 1 - p = 0.99$) as the probability of a success in a single binomial trial to compute the binomial probability of getting 5 or more significant time points by chance out of the total of 9 time points in each 50-ms bin (Onton, et al., 2005). This probability is 1.21×10^{-8} if all of the time points in a bin represented independent tests. This assumption of independence is probably not precisely correct as using consecutive time points will lack complete independence, although it is not too unreasonable because the tests were made across

subjects, who were independent of each other. Since we made 55 (inter-regional) comparisons (each possible pairing of 11 different brain ROIs) for 18 time bins, there were 990 such tests. At most ($p = 0.01$, with the minimum 5 of 9 significant data points per bin), the experiment-wise error probability for each set of t-tests, assuming independence, was $990 \times 1.21 \times 10^{-8} = .0000111$.

Transfer Entropy

The NBTE processing and analysis procedures for this experiment were nearly identical to those explained in Chapter 2.

Theta-band (3-8 Hz) oscillatory time series were obtained by filtering the CSD activations in the epochs using EEGLab's digital FIR filter. NBTE was then computed across trials for each subject at 30 ms and 50 ms lags. The lags used here span the range of lags found to contain significant NBTE in previous similar investigations (Bedo, et al., 2014; Wibral et al., 2011).

In order to assess the connectivity patterns with each group, two-tailed one-sample t -tests ($\alpha = 0.01$) were employed to determine the statistical significance of these NBTE values relative to zero at each time point. As a means to differentiate NBTE connectivity patterns between groups, two-tailed independent t -tests ($\alpha = 0.01$) were used, comparing FFW and TYP groups at each time point.

To assess the experiment-wise error of this procedure, we used $p = 0.05$ ($q = 1 - p = 0.95$) as the probability of a success in a single binomial trial to compute the binomial probability of getting 7 or more significant time points by chance out of the total of 13 time points in each 50-ms bin (Onton, et al., 2005). This probability is 9.85×10^{-7} if all of the time points in a bin represented independent tests. This assumption of independence

is probably not precisely correct as using consecutive time points will lack complete independence, although it is not too unreasonable because the tests were made across subjects, who were independent of each other. Since we made 110 (inter-regional) comparisons (each possible pairing of 11 different brain ROIs in both directions) for 18 time bins, there were 1980 such tests. At most ($p = 0.05$, with the minimum 7 of 13 significant data points per bin), the experiment-wise error probability for each set of t-tests, assuming independence, was $1980 \times 9.85 \times 10^{-7} = .00195$.

Just as with PLVs, instances of significant effective connectivity by NBTE were then visualized using the BrainNet Viewer toolbox for MATLAB (Xia et al., 2013). This process was performed for analysis of gamma (30-50 Hz) NBTE, as well.

Results

Behavioral Results

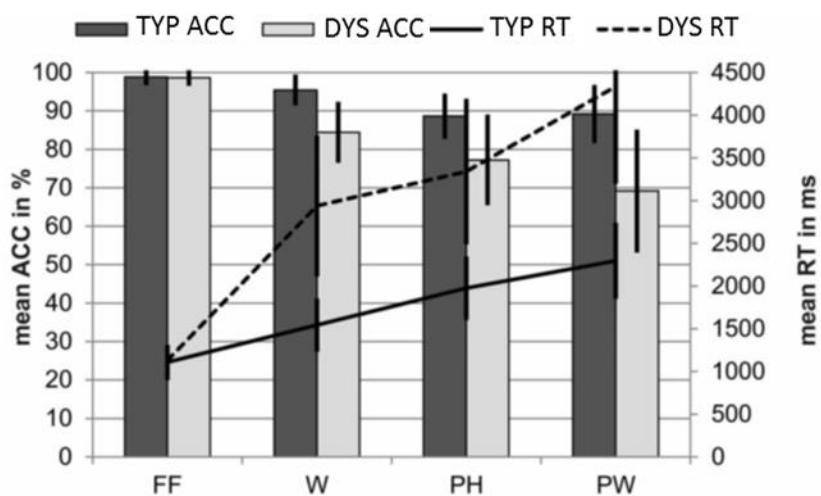
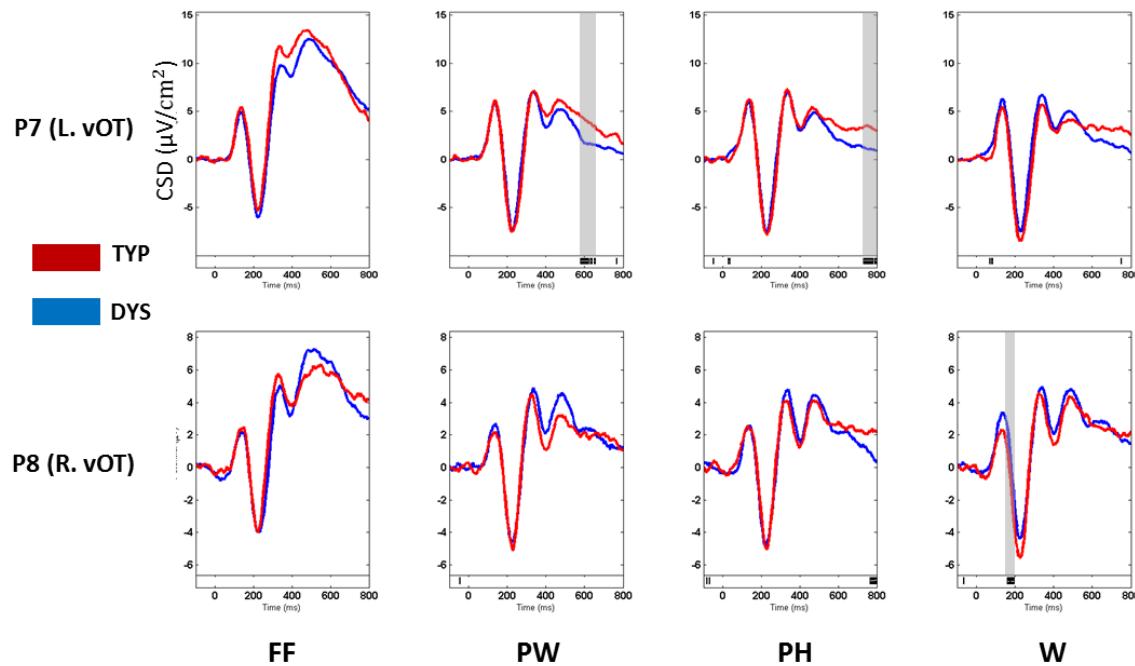


Figure 3.3. Behavioral results for typical (TYP) and dyslexic (DYS) readers the lexical decision task. ACC = accuracy; RT = reaction time; FF = false fonts; W = words; PH = pseudohomophones; PW = pseudowords. Error bars represent the standard deviation. Figure adapted with permission.

ERP Results

ERPs at P7, P8, CP5, and CP6 were compared between groups at each condition (Fig. 3.4). The TYP group showed greater L.vOT activations from 580-680 ms in the Pseudoword condition ($p<0.05$, uncorrected), while the DYS group showed greater activation in the same region from 175-200 ms in the Word condition.

The TYP group showed greater activation in L.AG 50-130 ms and 590-720 ms in the Pseudoword condition, and R.AG from 80-130 ms, 170-240 ms, and 450-600 ms. TYP showed greater activation form 470-570 ms in L.AG in the Word condition.



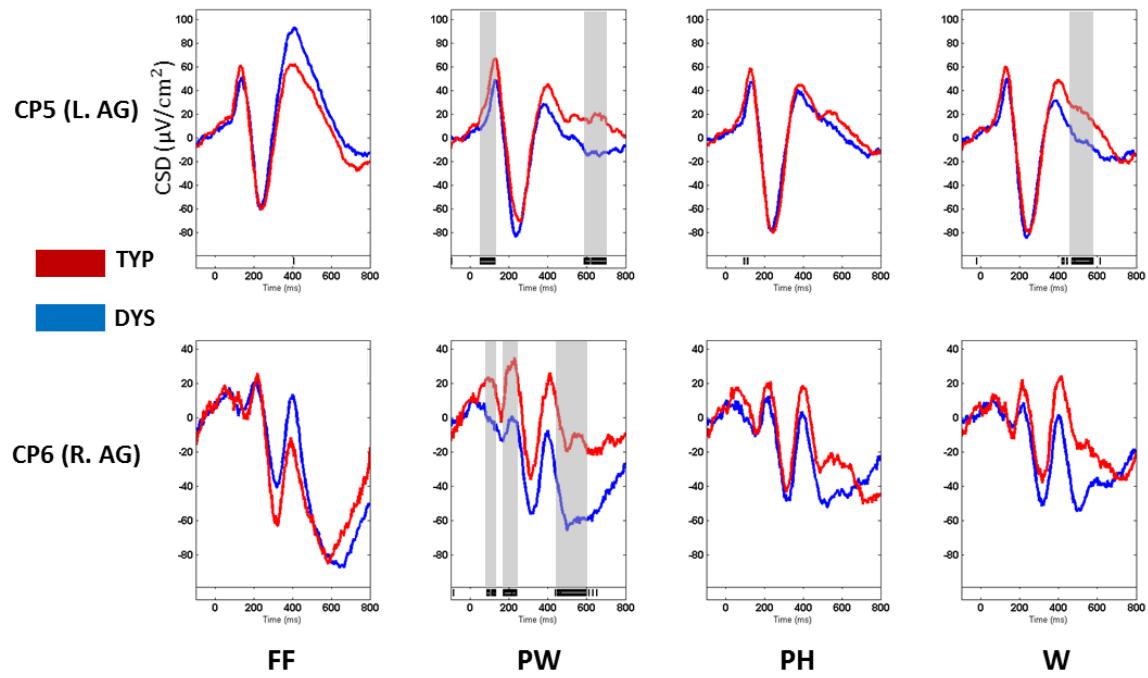


Figure 3.4. Event-related potentials (ERPs) during word reading. Areas vOT and AG were selected here due to their importance to reading processes. Sections highlighted in grey indicate significant differences between groups ($p < .05$, uncorrected). FF = False Font; PW = Pseudoword; PH = Pseudohomophone; W = Word; vOT = ventral Occipito-Temporal cortex; AG = Angular Gyrus.

ERSP Results

Spectral power dynamics were monitored at reading-related sites at theta (3-8 Hz) and gamma (30-50 Hz) frequency bands.

Theta

Between-subjects t -tests (Fig. 3.5) revealed greater theta power for the DYS group in the Pseudohomophone condition at L.IFG from 450-600 ms, R.IFG at 200-550 ms, L.AG at 270-700 ms, L.vOT at 400-620 ms, and R.vOT at 300-750 ms ($p < 0.05$, uncorrected).

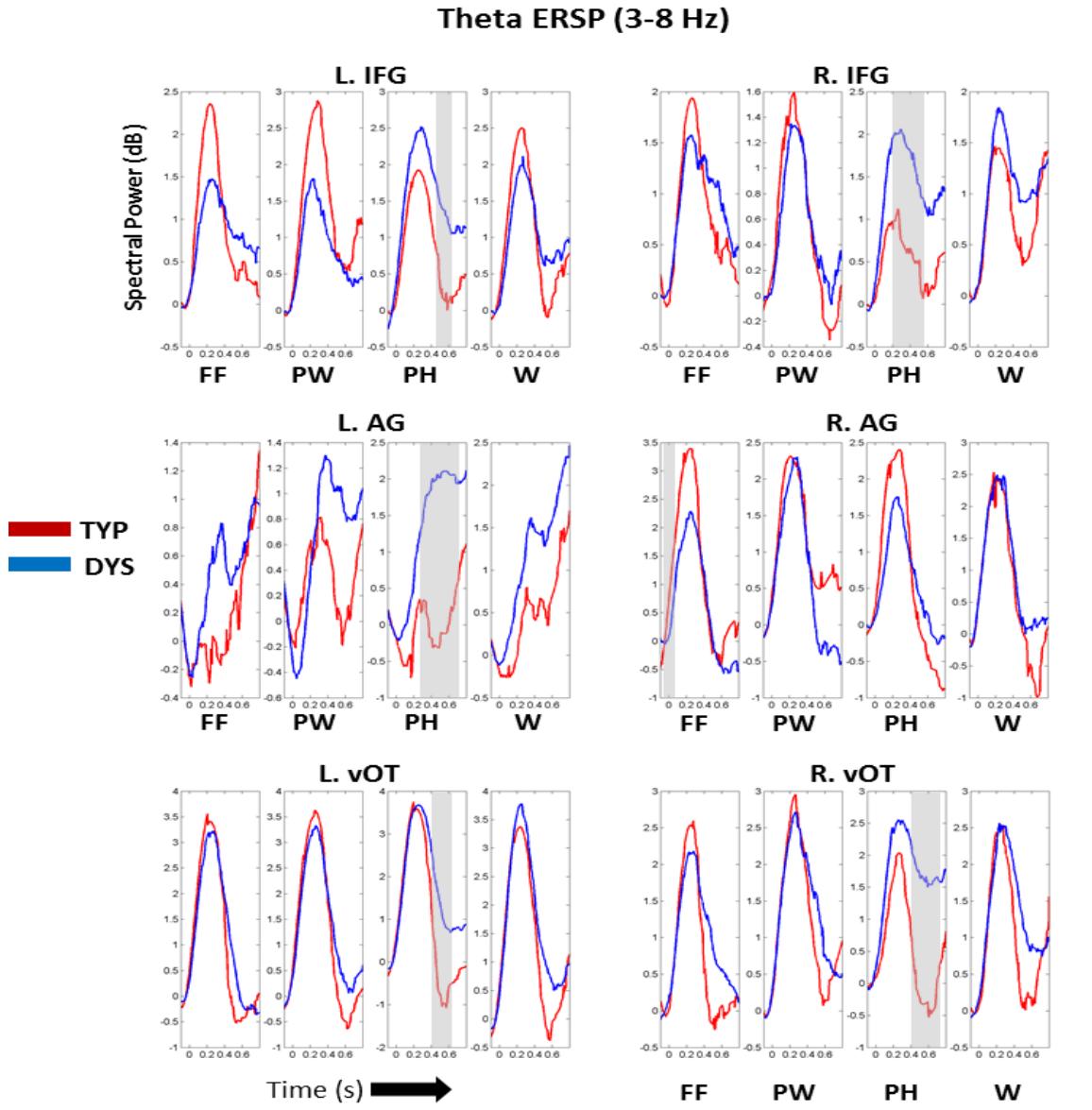


Figure 3.5. Theta (3-8 Hz) event-related spectral perturbations (ERSPs) during word reading. Sections highlighted in grey indicate significant differences between groups ($p < 0.05$, uncorrected). The DYS group (blue lines) showed significantly greater levels of theta-band power compared to the TYP group (red lines) across several regions in the Pseudohomophone condition. FF = False Font; PW = Pseudoword; PH = Pseudohomophone; W = Word; vOT = ventral Occipito-Temporal cortex; AG = Angular Gyrus; IFG = Inferior Frontal Gyrus.

Gamma

Between-subjects *t*-tests revealed greater widespread gamma-band power for the DYS group (Fig. 3.6), particularly in the in the PH condition ($p<0.05$, uncorrected). In the PH condition, the DYS group showed greater gamma power at R.IFG at 280-550 ms, L.AG at 350-650 ms, L.vOT at 400-600 ms, and R.vOT at 350-600 ms. The TYP group showed greater gamma power at L.IFG at 150-420 ms in the Word condition.

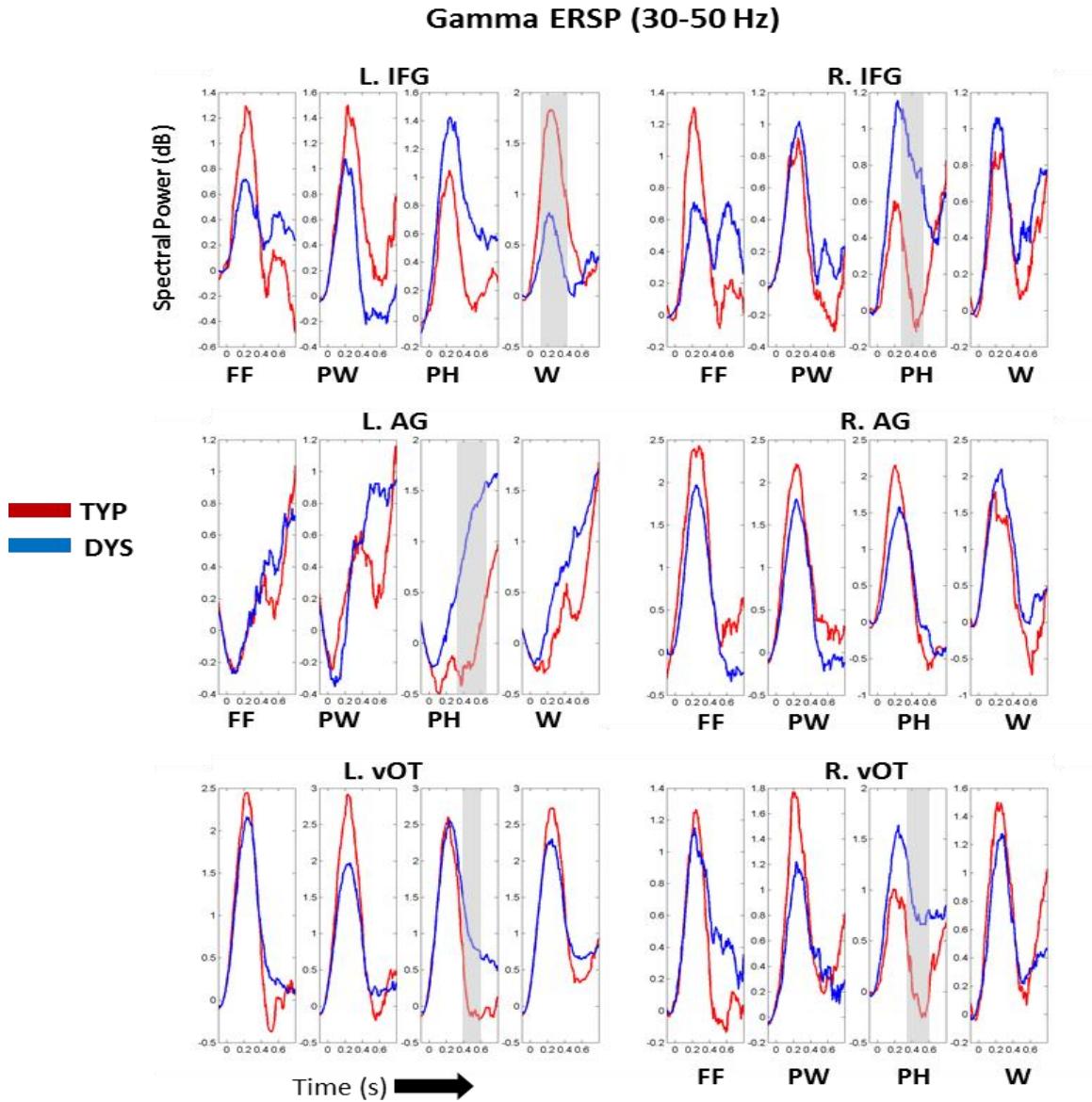


Figure 3.6. Gamma (30-50 Hz) event-related spectral perturbations (ERSPs) during word reading. Sections highlighted in grey indicate significant differences between groups ($p<0.05$, uncorrected). In several regions, the DYS group (blue lines) showed significantly greater levels of theta-band power compared to the TYP group (red lines). FF = False Font; PW = Pseudoword; PH = Pseudohomophone; W = Word; vOT = ventral Occipito-Temporal cortex; AG = Angular Gyrus; IFG = Inferior Frontal Gyrus.

Phase Synchrony

The emphasis of the theta-band phase synchrony (phase-locking values, PLVs)

analysis was placed on the 200-250 ms window, as that coincides with the timing of the N170 ERP component (which generally occurs at ~220 ms in children).

Theta

Both groups showed distributed theta-band network functional connectivity relative to baseline across all conditions in the 200-250 ms window ($p<0.001$; Fig. 3.7). The DYS group showed significantly greater connectivity, particularly with respect to right temporal, R.IFG, R.PreCG, R.AG, and R.vOT regions, both intra- and inter-hemispherically ($p<0.01$). The TYP group showed greater PLVs between R.Occip and R.IFG, and between R.AG and L.IFG in the Word condition.

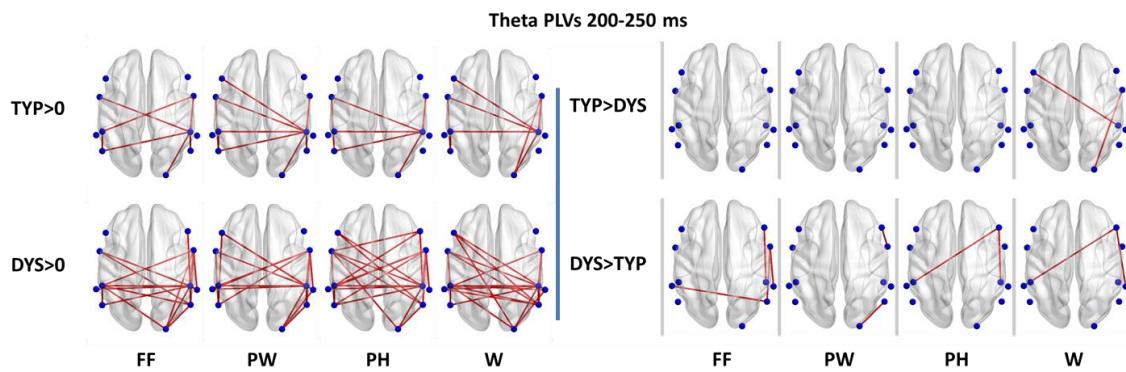


Figure 3.7. Theta (3-8 Hz) phase synchrony from 200-250 ms. (Left) Theta PLVs, when compared to baseline, show distributed connectivity among reading-related brain areas in both TYP and DYS groups. (Right) Theta PLVs, when comparing groups, showed significantly greater intra-hemispheric (right hemisphere) and cross-hemispheric connectivity in the DYS group in all conditions except Word, in which both groups show distinct connectivity increases among different regions. FF = False Font; PW = Pseudoword; PH = Pseudohomophone; W = Word.

Gamma

In the 200-250 ms window, both groups showed distributed gamma-band network connectivity relative to baseline across all conditions ($p<0.001$), particularly including

L.PreCG, R.AG, R.vOT, and R.PreCG sites (Fig. 3.8). Groups showed no difference in gamma PLVs in the False Font condition. In the Pseudoword condition, the TYP group yielded greater gamma PLVs between L.IFG and L.PreCG sites, whereas the DYS showed greater right-hemispheric engagement. In the Pseudohomophone condition, the TYP group showed greater theta PLVs between L.PreCG and R.AG, L.vOT and R.STG, and R.AG and R.STG, while the DYS group showed greater theta synchrony between L.IFG and R.Occipital cortex, L.AG and R.PreCG, and R.IFG and R.AG. In the Word condition, the TYP group showed greater PLVs between L.vOT and L.PreCG, L.PreCG and R.PreCG, L.IFG and R.AG, and R.PreCG and R.AG.

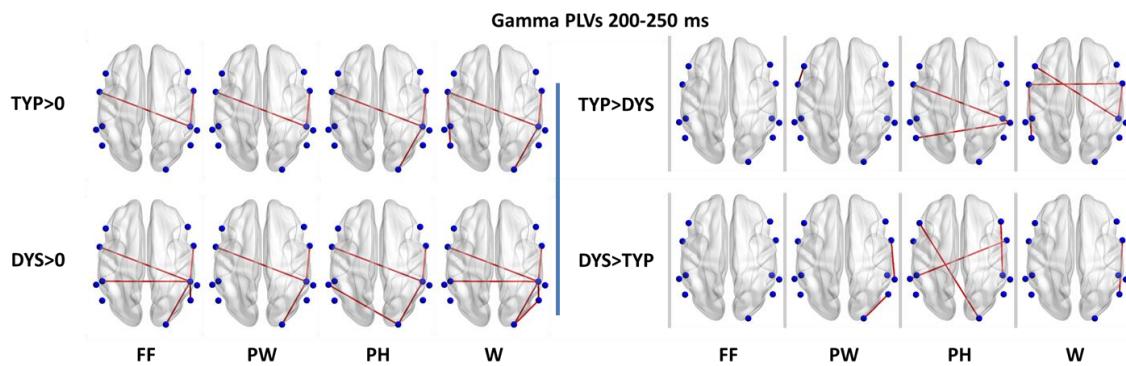


Figure 3.8. Gamma (30-50 Hz) phase synchrony (PLVs) from 200-250 ms. (Left) Gamma PLVs, when compared to baseline ($p<0.001$), show distributed connectivity among reading-related brain areas in both TYP and DYS groups. (Right) Gamma PLVs, when comparing groups ($p<0.01$) indicate significantly greater intra-hemispheric (right hemisphere) and cross-hemispheric connectivity in the DYS group in the PW condition, while both groups showed distinct increases among different regions in the PH and W conditions. FF = False Font; PW = Pseudoword; PH = Pseudohomophone; W = Word.

Narrow-Band Transfer Entropy (NBTE)

For the same reasons described in the phase synchrony section above, the 200-250 ms window was selected for closer scrutiny of NBTE network connectivity.

Theta

In the 200-250 ms window, the TYP group showed significant theta NBTE from L.PreCG to R.PreCG relative to baseline in the Pseudoword condition ($p<0.01$; Fig. 3.9). The DYS group showed significant theta NBTE from R.vOT to R.STG relative to baseline in the Word condition.

In between-group comparisons, the TYP group showed significantly greater NBTE from R.IFG to L.IFG and R.vOT regions in the Pseudoword condition ($p<0.05$). The DYS group showed greater theta NBTE from L.PreCG to R.vOT in the Pseudohomophone condition.

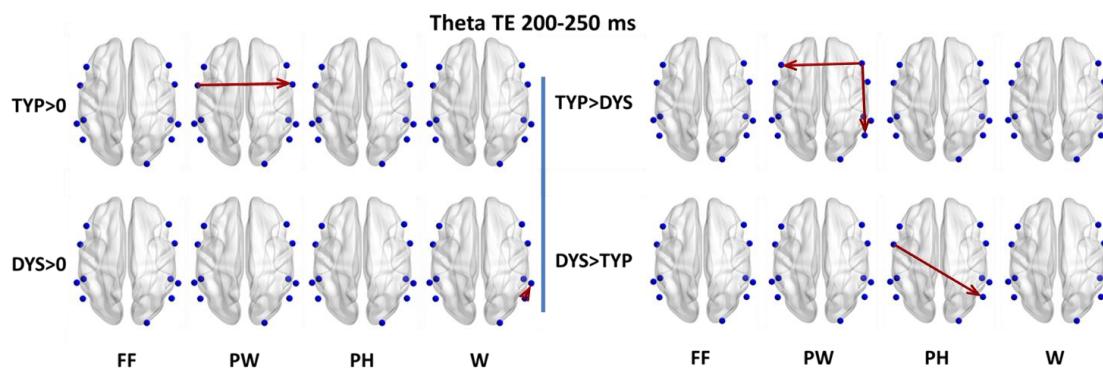


Figure 3.9. Theta (3-8 Hz) NBTE from 200-250 ms. Arrows indicate effective (i.e. causal) connectivity between brain regions. (Left) Theta NBTE, when compared to baseline ($p<0.01$) and (Right) when comparing groups ($p<0.05$). FF = False Font; PW = Pseudoword; PH = Pseudohomophone; W = Word.

Gamma

In the 200-250 ms window, the TYP group showed significant gamma NBTE from R.IFG to R.vOT relative to baseline in the False Font condition ($p<0.01$, Fig. 3.10). In the Pseudoword condition, the TYP group showed NBTE from L.vOT to L.STG. The

TYP group also showed gamma NBTE from L.vOT to L.STG, L.IFG to L.vOT, L.STG to R.STG, and L.IFG to R.STG in the Pseudohomophone condition. No significant gamma NBTE was observed in the Word condition for the TYP group.

The DYS group showed significant gamma NBTE from R.Occipital cortex to R.vOT relative to baseline in the False Font condition. In the Pseudoword condition, the DYS group showed NBTE from L.STG to L.IFG and R.STG to R.PreCG. The DYS group showed gamma NBTE from L.PreCG to L.vOT and L.STG to R.vOT in the Pseudohomophone condition and from L.AG to L.IFG in the Word condition.

In between-group comparisons, the TYP group showed significantly greater gamma NBTE in the Pseudohomophone condition only, from L.IFG to R.STG and R.vOT sites ($p<0.05$). The DYS group showed greater gamma NBTE from R.Occipital cortex to R.vOT in the False Font condition. The DYS group showed greater gamma NBTE from R.STG to R.PreCG in the Pseudoword condition. The DYS group showed greater gamma NBTE from L.PreCG to L.vOT and from L.AG to R.AG in the Pseudohomophone condition.

No significant differences in gamma NBTE were observed between groups in the Word condition.

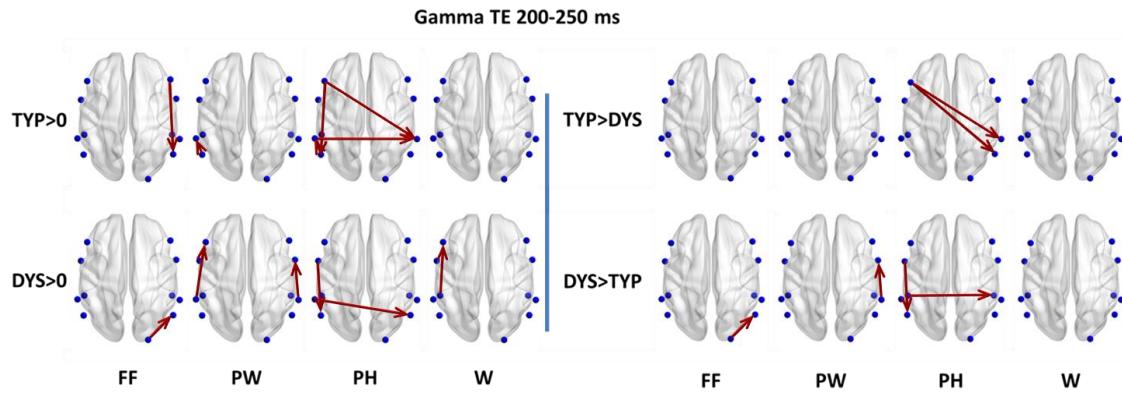


Figure 3.10. Gamma (30-50 Hz) NBTE from 200-250 ms. Arrows indicate effective (i.e. causal) connectivity between brain regions. (Left) Gamma NBTE, when compared to baseline ($p<0.01$) and (Right) when comparing groups ($p<0.05$). FF = False Font; PW = Pseudoword; PH = Pseudohomophone; W = Word.

Discussion

The present study examined differences in brain network activity, comparing typical and dyslexic readers in grade 2. Brain activity was recorded using EEG during a lexical decision task designed specifically to tax the phonological processing of participants. We initially hypothesized that dyslexic readers would generate more functional (phase synchrony) and effective (NBTE) connectivity in response to orthographic stimuli. Results did not overwhelmingly support the premise of substantially more widespread or distributed connectivity, but they did corroborate existing frameworks of the neurocognitive basic of dyslexia.

ERPs

In adult expert readers, orthographic information is identified ~170 ms after word presentation, as indexed by a negative trough in the ERP of the left fusiform gyrus and its immediate vicinity. In inexperienced readers, such as in the present study (ages 8-9), this process occurs at ~220 ms following word presentation (Hasko et al., 2013; Maurer et al.,

2005; Maurer et al., 2007). Both groups in this experiment showed pronounced negative troughs in ERP activations over reading critical sites. However, TYP and DYS groups showed no significant differences in N170 components at any condition in the vOT areas during this critical interval. These ERP results essentially replicate those found in the original study from which these data were collected (i.e. Hasko et al., 2013), in which both groups showed large negative ERP components at ~220 ms in left and right occipito-temporal regions following word presentation, and that these ERP components did not differ in size between groups. One caveat is that the activity in the Word condition immediately prior to the N170 component was significantly different between groups. However, given the pattern, it seems that it was due to TYP readers' processing being minimally faster, but this shift was enough to generate statistical significance.

Differences were seen in left and right angular gyrus (AG) sites in Pseudoword and Word conditions. The left AG response in TYP readers is more pronounced and is significantly greater prior to the N170 response, potentially reflecting a preparedness of the reading network to process incoming stimuli. The Pseudoword condition seemed to have a suppressed response in DYS readers, particularly during later processing stages (>400 ms). A difference here is in line with the premise that after orthographic decoding, dyslexic readers struggle with semantic and phonological processing, in which AG has been shown to contribute (Jobard et al., 2003; Vigneau et al., 2006).

ERSPs

When the EEG oscillations were examined at the level of frequency bands, notable differences were observed. In particular, the DYS group showed significantly greater theta- and gamma-band responses at a later stage of processing (>350 ms). These

differences were observed in both left and right hemispheres. The TYP group showed greater gamma-band power in the L.IFG region solely in the Word condition during this same late stage of processing. This result may suggest that this region is being underutilized by individuals with dyslexia. This notion is corroborated by neuroimaging evidence showing the involvement of L.IFG in linguistic processes, particularly language production and phonological processing (Jobard, 2003; Vigneau et al., 2006).

Brain Connectivity in Reading

Prior research has shown that connectivity differences exist between typical and dyslexic readers (Horwitz et al., 1998; Pugh et al., 2000). What is less understood is how connectivity dynamics (over the span of reading a word) coincide with other, more familiar, measures of brain activity. To that end, specific time windows were chosen. As hypothesized, the DYS group showed increased functional connectivity compared to the TYP group; and in many cases, the TYP group did not show *any* greater connectivity (see Fig. 3.7, Fig. 3.8, Fig. 3.9, and Fig. 3.10). This suggests that dyslexic readers were leveraging the same “typical” networks, but were also either demanding more out of those connections, or were making use of some entirely different connections.

This result is in line with so-called interactive frameworks of reading networks, which describe how, in dyslexic readers, area vOT (although other areas arguably fit this framework) actually requires more communication with other brain regions to propagate the same information throughout the network compared to that required by the same region in neurotypical readers. As the dyslexic brain attempts to process orthographic information, evaluation of these signals essentially requires more frequent “passes” to resolve, reducing efficiency and increasing processing time, overall.

With respect to phase synchrony, it appears that the DYS group leverages more networks in the right hemisphere than does the TYP group. This is in line with the idea that the reading networks of dyslexic readers are more bilateral than those of the TYP readers (or at least not as lateralized as TYP readers). This is seen particularly in the theta-band phase synchrony (Fig. 3.7).

Causal connectivity measured by NBTE offers insight into the differences in IFG engagement. So-called re-entrant processing (Di Lollo et al., 2000) suggests that a complete visual perceptual event not only includes bottom-up activations, but reverberatory top-down activity to complete perceptual loops to fully process stimuli and retain that information in consciousness. Local measures of activity such as ERPs or ERSPs unfortunately cannot adequately capture these directed signals from recorded activity. Nor can PLVs, as they measure functional connectivity, an association between regions. However, with the directed connectivity measure of NBTE, we can begin to test these theories. Therefore, it is very interesting to see that in the cases where the TYP group showed greater connectivity, it was top-down signaling *from* IFG sites to lower-level language centers. In no case did the DYS group exhibit greater connectivity *to* or *from* either IFG location. Our interpretation of this result is that TYP readers are faster to process written language, and therefore gain access to higher level language areas more quickly than that DYS readers. However, a top-down signal in this time interval does not fit the post-sweep narrative, as it is occurring far too early compared to the accepted timeline in which IFG and other sites are accessed (usually > 400 ms). However, this early signaling may reflect a pre-emptive top-down signal more akin to Price and Devlin's (2011) framework in which predictive signals can facilitate the bottom up

signals carrying visual and orthographic content. In that regard, the TYP readers are at a more advanced stage in the word reading process at 200-250 ms than their DYS counterparts.

In summary, these results indicate that while at this age, dyslexic and neurotypical readers may still engage with similar brain areas, the underlying communication and organization of those networks remains distinct. These connectivity measuring techniques may offer a fruitful avenue for identifying dyslexic brain networks at an earlier stage of development, where activation-focused approaches may not capture underlying differences when compared to neurotypical populations.

CHAPTER 4: Pre-intervention Connectivity Dynamics in Dyslexic and Typically-developing Children

Introduction

Given the prevalence of phonological deficits in people with dyslexia, it follows that training in phonological processing (and the underlying auditory processing therein) should improve reading ability. Indeed, there is abundant evidence supporting this idea. Training and remediation programs that emphasize the practice of phonics and phonemic awareness have been shown to improve fluency and comprehension (Byrne et al., 2000; Hatcher et al., 1994; Temple et al., 2003). Neuroimaging results reflect these findings, showing increases of cortical activity in reading-related areas including left fusiform, IFG, and temporo-parietal cortex, as well as right STG and IFG areas following training (Eden et al., 2004; Temple et al., 2003).

Therefore, this study sought to investigate the connectivity dynamics of reading before and after a reading training program. Of particular interest is the relationship between the improvement in reading performance and the changes in connectivity. Understanding this relationship may offer insights into reading disabilities as well as how to further optimize reading training programs to elicit the highest performance gains. In this chapter I will describe an experiment that compared the connectivity dynamics of a typical-reading group of children with that of a group of same-aged children who are significantly reading-impaired, before a reading training program in which they had been enrolled commenced. In Chapter 5 I will compare the connectivity dynamics of the impaired-reading group before and after the reading intervention.

The purpose of this experiment is two-fold – to compare against our findings from

the secondary analysis in Chapter 3, and to establish a “baseline” of brain network behavior prior to a reading intervention program. While readers in Chapter 3 were in grade 2, the readers in the present experiment were in grades 4 and 5. In grade 2, most children have only been reading in earnest for a short while. With this in mind, an additional two to three years of brain development – and particularly years of reading training – can produce very different reading network patterns. Therefore, while we might expect some overlap between these two populations of dyslexic readers, it is possible that additional years of development (potentially without reading improvement or intervention) would produce network behaviors in older children that did not overlap completely with the younger readers.

Prior to intervention, we hypothesize that children with reading difficulties will show increased functional and effective connectivity in the theta and gamma bands among reading-related sites.

Methods

Participants

Twenty-eight students attending various elementary schools in the greater Vancouver (Canada) area participated. In partnership with the school district, students in grades 4 and 5 were targeted to be a part of this study, making up a total pool of approximately 135 students. Parents of these students received information about the study and consent forms through the schools. Prior to our study, a subset of all grade 4 and grade 5 students had already been assessed by the schools as having specific reading difficulties and were placed in an intervention program using Fast ForWord software (FFW; Scientific Learning, USA) to practice core language skills such as phonemic

awareness, auditory discrimination, and spelling. Selection into the intervention program was determined over time, using a multi-tiered approach developed by the school teachers and administrators prior to the start of our study. Selection criteria for the FFW program included apparent auditory processing deficits, difficulty in associating letters with sound, and reading 1.5-2 years below their grade level—observations often further assessed by Woodcock-Johnson standardized achievement tests (Word Attack, Letter-Word Identification, and Passage Comprehension sub-tests), the Wechsler Intelligence Scale for Children – Fourth Edition (WISC-IV; Digit Span and Symbol Search sub-tests), and the Test of Auditory Processing Skills – Third Edition (TAPS-III; Word Discrimination, Phonological Blending, and Phonological Segmentation sub-tests). Guided by the district's selection criteria, Language Support Services (LSS; e.g. speech and language pathologists) were also involved as part of the process and aided in the admission into the FFW program, which was never used as the initial point of intervention; rather, students were only admitted into the targeted reading training if no other intensive strategies had worked (or if students were showing very small gains with other methods). These LSS professionals eventually conducted the training during school hours. Ultimately, through this vetting process, approximately 15 FFW-eligible students were given consent forms.

A set of typically developing readers (TYP, control sample) not enrolled in the reading training were selected at random from FFW students' classrooms to control for effects of teacher and general curriculum received. Woodcock-Johnson tests (Word Attack and Letter-Word Identification) were conducted on a subset of these children (9 FFW, 11 TYP) by experimenters to validate the differentiation of groups with regard to

reading difficulties initially appraised by the schools (Figure 4.1). The FFW group showed significantly lower scores compared to the TYP group in both the Word Attack subtest, $t(18) = 6.64$, $p < 0.0001$, and the Letter-Word Identification subtest, $t(18) = 5.14$, $p < 0.0001$.

All participants had English as their first and primary language, and had normal or corrected-to-normal visual acuity. FFW students had been in the program for less than one month at the time of the initial experimental session. This effort was made to record a baseline measure before any targeted reading intervention occurred. In total, 11 FFW readers and 17 TYP readers were recruited for this experiment.

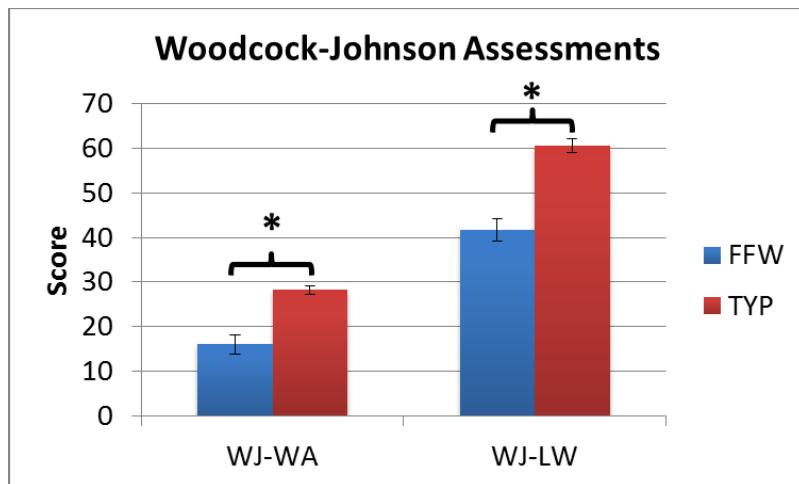


Figure 4.1. Reading assessments of typical readers (TYP) and those in the Fast Forward training program (FFW). In both the Word Attack and Letter-Word Identification tests, readers in the FFW group scored significantly lower than the TYP group. (* = $p < 0.0001$).

Experimental Procedures

The experiment was conducted on-site at elementary schools in the greater Vancouver area. A quiet room at each school was set aside for the session. First, children

were asked to simply sit in a relaxed position for five minutes while their brainwaves were recorded using EEG. Participants then performed a lexical decision task (similar to, but distinct from the design in Chapter 3), in which participants were asked to decide whether a letter string was a real word or not (i.e., “Is this a real word?”). Stimuli were classified into three conditions: real words (e.g., ‘bread’), pseudowords (e.g., ‘croll’), and consonant strings (e.g., ‘rplcg’). A fixation cross was presented for 500 ms followed by a jittered inter-stimulus interval lasting between 800-1200 ms (Figure 4.2). Then a letter string was presented for 1500 ms or until the participant pressed a response, whichever occurred first. After a 1000 ms inter-trial interval, the next trial began. For the Word condition, single-syllable words were aggregated from lists found at

<https://www.ontrackreading.com>. These lists have been assembled to be accessible to children and to represent a wide range of vowel sounds. Pseudowords were derived from the pool of real word stimuli by taking a word and changing a single letter (e.g. *bread* to *bream*).

Stimuli from each condition consisted of 4- and 5-letter strings (60 trials each), each presented randomly for a total of 360 trials. Blocks of 40 trials were separated by self-timed rest breaks. Participants had the option to continue to the next block immediately upon reaching a break or they could rest as long as necessary before continuing. The task was performed on a laptop while sitting at a desk. A height-adjustable chin rest was used to reduce the possibility of head movements.

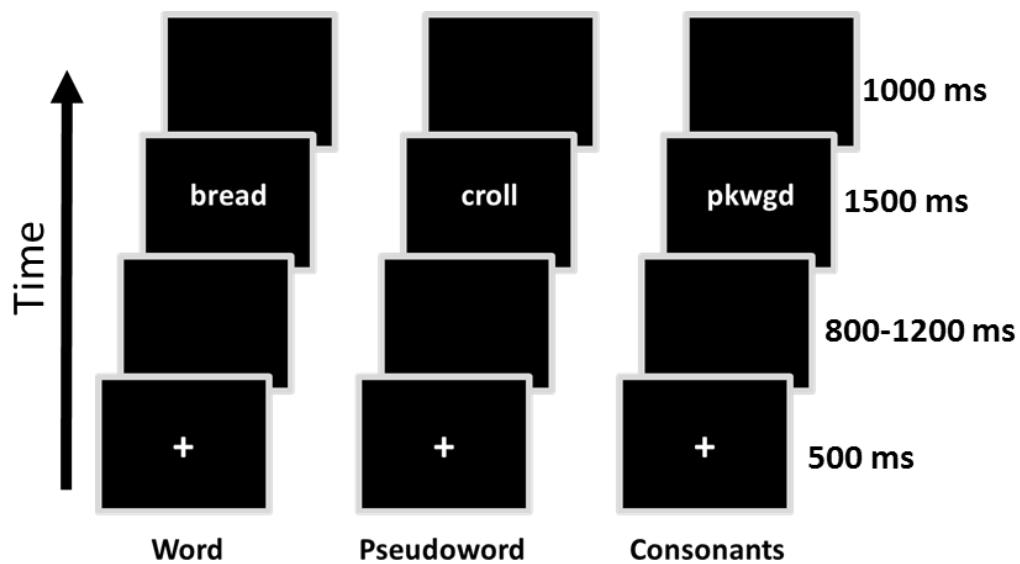


Figure 4.2. Schematic of phonological lexical decision task. Participants were required to judge whether or not a letter string was a real word.

Presentation software (Neurobehavioral Systems, USA) was used to present stimuli in white font on a black background. All stimuli were centered on a 17-inch computer monitor placed 45 cm in front of the participants. All participants used their right hand to respond on the keyboard; however, the response buttons used for “Yes” and “No” were counterbalanced across subjects.

EEG Acquisition

A portable BioSemi system was used to record continuous EEG from 64 active electrodes at equidistant locations based on the International 10–10 system of electrode placement, referenced to the average of all scalp signals (except Iz). EEG signals were amplified and sampled at 512 Hz through an analog passband of 0.16–100 Hz. Eye muscle activity was recorded by electro-oculogram (EOG) from two periocular electrodes. All electrode impedances were below 20 kΩ.

All further offline processing and analysis was performed using MATLAB software (Mathworks, Natick, USA). All signals were re-referenced to an average reference, resampled to 256 Hz, and digitally filtered from 1-100 Hz using EEGLAB software (Delorme & Makeig, 2004), an open source MATLAB toolkit, and custom scripts. A digital notch filter between 55 Hz to 65 Hz was applied to reduce line noise. The continuous data were epoched into 3500 ms bins time-locked to the presentation of the letter strings, capturing 1500 ms before and 2000 ms after word presentation. Each participant contributed an average of 256.12 trials (SD=73.41), for a total of 6659 trials for the experiment. All further processing and analysis was performed using MATLAB software (Mathworks, Natick, USA).

Current Source Density

The methods for deriving CSD were identical to those used in Chapter 2, with some minor differences based on the EEG system used to collect data. CSD Toolbox for MATLAB was used to compute the CSD values (Kayser, 2009; Kayser & Tenke, 2006a; Kayser & Tenke, 2006b). Cortical regions of interest for further analysis were selected based on reading-related brain areas as revealed in previous research (Table 4.1; Jobard et al, 2003). The cortical Talairach coordinates of these sites were then cross-referenced to anatomical locations of electrodes based on the 10-10 system (Koessler et al, 2009). The nearest electrodes to these sites, as measured by Euclidean distance, were then selected for further analysis. The subset of electrodes selected in this manner were CP5, CP6, F5, F6, FT7, FT8, O1, O2, P7, P8, TP7, and TP8 (Figure 4.3). For ease of exposition the ROIs will be referred to by their cortical locations from now on, but it must be remembered that in fact the data to be analysed are the CSD values computed for the

electrode locations nearest those cortical locations and not the activation levels of dipoles or other types of cortical sources inferred by localization analysis.

Table 4.1. Reading-related Brain Regions and Their Corresponding EEG Channels.

EEG channel	Talairach coordinates			Corresponding Brain Region
	x	y	z	
F5	-51	27	25	L. IFG
F6	51	27	25	R. IFG
FT7	-59	3	-2	L. PreCG
FT8	59	3	-2	R. PreCG
CP5	-62	-46	23	L. AG/SMG
CP6	62	-46	23	R. AG/SMG
TP7	-64	-45	-4	L. MTG/STG
TP8	64	-45	-4	R. MTG/STG
P7	-56	-65	0	L. Fusiform
P8	56	-65	0	R. Fusiform
O1	-26	-93	8	L. Occip
O2	26	-93	8	R. Occip

Table 4.1. EEG channels and their corresponding brain regions. EEG channels were selected for further analysis based on their proximity to previously established ROIs (Jobard et al., 2003) and their cross-hemispheric counterparts. Anatomic locations of EEG channels in Talairach space were derived from Koessler et al. (2009).

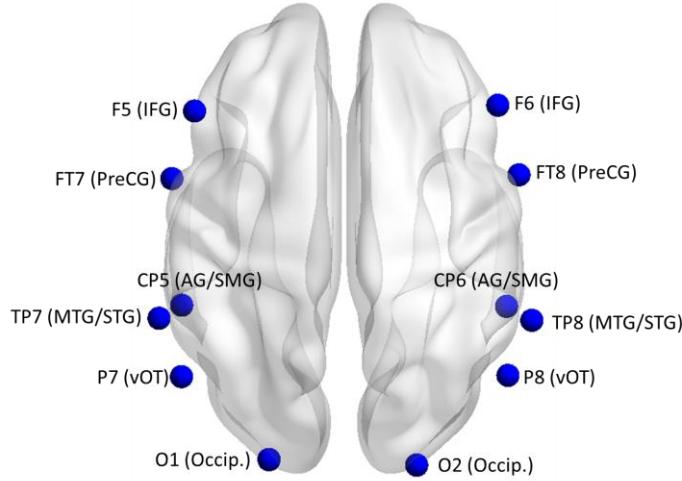


Figure 4.3. Selected electrodes that overlap with reading-related brain areas. Visual representation of anatomical locations of channels described in Table 4.1.

Event-Related Potentials (ERPs)

ERP parameters and rejection criteria were identical to those used in Chapter 2. ERPs were computed by averaging each participant's epoched EEG activity across trials. This was done separately for each condition. ERPs were baseline corrected relative to a 100 ms pre-stimulus window and low-pass filtered at 20 Hz. ERPs from each group were then compared using independent samples *t*-tests at each time point. Instances of significant differences between conditions sustained across multiple time points then informed the subsequent connectivity analyses as to which moments might provide insights into important network differences.

Event-Related Spectral Perturbations (ERSPs)

The ERSP processing and analysis procedures for this experiment were identical to those explained in Chapter 2. ERSPs allow us to observe the moment-to-moment fluctuations in oscillatory power at various oscillatory frequencies (i.e 3-100 Hz) relative to a 100 ms pre-stimulus baseline. ERSPs were computed across trials for each subject

separately. This technique produced an output 400 time points in length, capturing ERSPs from -940 to 1440 ms of the original epoch, as per EEGLab's *newtimef()* function.

Phase Synchrony

The phase synchrony processing and analysis procedures for this experiment were nearly identical to those explained in Chapter 2. Phase synchrony analyses were conducted in order to assess inter-regional functional connectivity, or the degree to which two brain areas are sharing information, in particular, theta- (3-8 Hz) and gamma- (30-50 Hz) bands.

In order to assess the connectivity patterns with each group, two-tailed one-sample *t*-tests ($\alpha = 0.001$) were employed to determine the statistical significance of these PLVs relative to zero at each time point. As a means to differentiate PLV connectivity patterns between groups, two-tailed independent *t*-tests ($\alpha = 0.01$) were used, comparing FFW and TYP groups at each time point.

To assess the statistical reliability of these *t*-tests, time points from 0 to 900 ms following the stimulus onset were divided into non-overlapping 50 ms time bins (i.e., 18 such bins). To control for multiple comparisons, and to exclude meaningless interactions, we adopted a conservative criterion and considered a 50 ms bin to contain meaningful evidence of greater functional connectivity for one group than for the other if at least half (5 or more of 9) of the time points in that bin reached the statistical threshold described earlier for either TYP > FFW, or vice versa, and none did for the opposite comparison. To assess the experiment-wise error of this procedure, we used $p = 0.01$ ($q = 1 - p = 0.99$) as the probability of a success in a single binomial trial to compute the binomial probability of getting 5 or more significant time points by chance out of the total of 9 time points in

each 50-ms bin (Onton, et al., 2005). This probability is 1.21×10^{-8} if all of the time points in a bin represented independent tests. This assumption of independence is probably not precisely correct as using consecutive time points will lack complete independence, although it is not too unreasonable because the tests were made across subjects, who were independent of each other. Since we made 66 (inter-regional) comparisons (each possible pairing of 12 different brain ROIs) for 18 time bins, there were 1188 such tests. At most ($p = 0.01$, with the minimum 5 of 9 significant data points per bin), the experiment-wise error probability for each set of t-tests, assuming independence, was $1188 \times 1.21 \times 10^{-8} = .0000144$.

Transfer Entropy

The NBTE processing and analysis procedures for this experiment were nearly identical to those explained in Chapter 2. Theta-band (3-8 Hz) oscillatory time series were obtained by filtering the CSD activations in the epochs using EEGLab's digital FIR filter. NBTE was then computed across trials for each subject at 30 ms and 50 ms lags. The lags used here span the range of lags found to contain significant NBTE in previous similar investigations (Bedo, et al., 2014; Wibral et al., 2011).

In order to assess the connectivity patterns with each group, two-tailed one-sample t -tests ($\alpha = 0.05$) were employed to determine the statistical significance of these NBTE values relative to zero at each time point. As a means to differentiate NBTE connectivity patterns between groups, two-tailed independent t -tests ($\alpha = 0.01$) were used, comparing FFW and TYP groups at each time point.

To assess the experiment-wise error of this procedure, we used $p = 0.05$ ($q = 1 - p = 0.95$) as the probability of a success in a single binomial trial to compute the binomial

probability of getting 7 or more significant time points by chance out of the total of 13 time points in each 50-ms bin (Onton, et al., 2005). This probability is 9.85×10^{-7} if all of the time points in a bin represented independent tests. This assumption of independence is probably not precisely correct as using consecutive time points will lack complete independence, although it is not too unreasonable because the tests were made across subjects, who were independent of each other. Since we made 132 (inter-regional) comparisons (each possible pairing of 12 different brain ROIs in both directions) for 18 time bins, there were 2376 such tests. At most ($p = 0.05$, with the minimum 7 of 13 significant data points per bin), the experiment-wise error probability for each set of t-tests, assuming independence, was $2376 \times 9.85 \times 10^{-7} = 0.00234$.

Just as with PLVs, instances of significant effective connectivity by NBTE were then visualized using the BrainNet Viewer toolbox for MATLAB (Xia et al., 2013). This process was performed for analysis of gamma (30-50 Hz) NBTE, as well.

Results

Accuracy

Accuracy in each task condition was measured as percentage of correct trials. The FFW group was significantly less accurate than the TYP group in the Consonant condition, $t(23) = 2.15, p = 0.04$ (Figure 4.4). The FFW was also significantly less accurate than in the TYP group in the Pseudoword condition, as well, $t(23) = 5.37, p < 0.0001$. The accuracy difference between groups in the Word condition was not statistically significant ($t(23) = 1.83, p = 0.08$), although the 11% difference was in the direction of TYP > FFW as for the other conditions. .

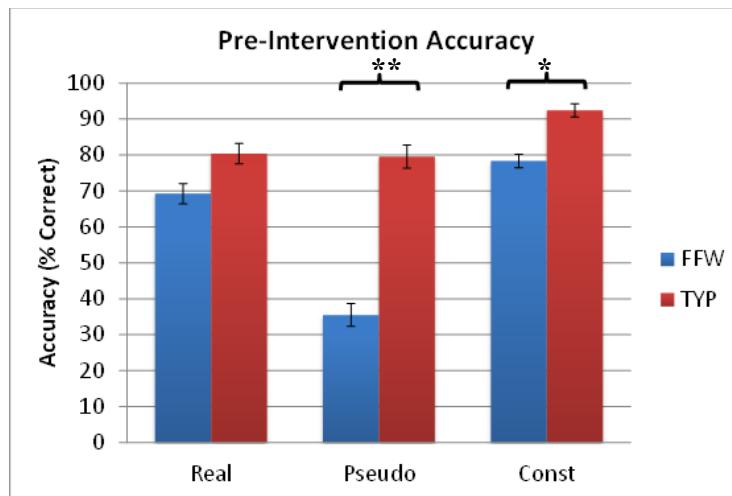


Figure 4.4. Lexical decision task accuracy. Dyslexic readers were significantly less accurate in the Pseudoword and Consonant conditions. There were no differences between groups in the Real condition. Real = Real Word, Pseudo = Pseudoword, Const = Consonant Strings. * $p<0.05$, ** $p<0.0001$

Reaction Time

With respect to reaction time, the FFW group was significantly slower than the TYP group in the Consonant condition, $t(23) = 2.54, p = 0.02$ (Figure 4.5). There was no significant difference in reaction time between groups in the Pseudoword condition, $t(23) = 1.11, p = 0.28$, or the Word condition, $t(23) = 1.49, p = 0.15$, although the TYP group was faster than the FFW group in all conditions.

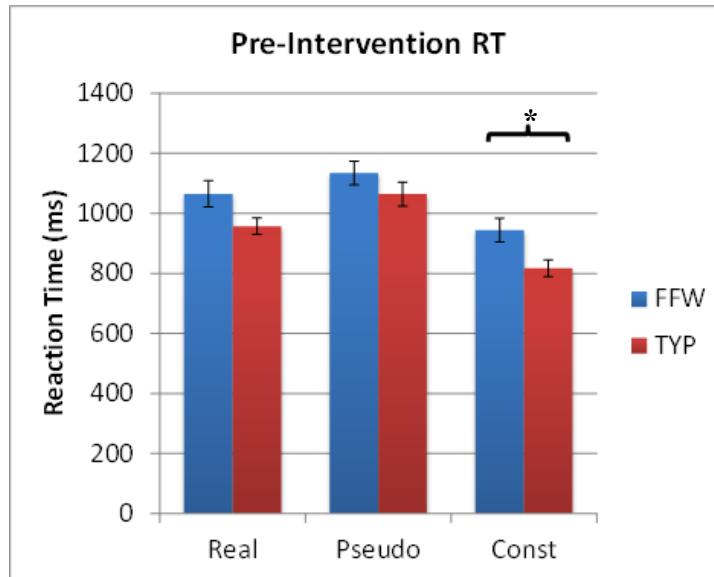


Figure 4.5. Lexical decision task reactions times. Dyslexic readers showed no significant differences in reaction time in the Real and Pseudoword conditions; however they were significantly slower to respond in the Consonant condition. Real = Real Word, Pseudo = Pseudoword, Const = Consonant Strings. * $p<0.05$.

ERPs

ERPs from TYP and FFW groups were compared at each condition using two-sample *t*-tests (Fig. 4.6). The FFW group showed a more pronounced N170 component (early negative peak) at R.vOT and R.AG sites in all three conditions 200-250 ms following stimulus presentation ($p<0.05$, uncorrected) as well as from L.AG in the Pseudoword condition. In the Pseudoword and Word conditions, the FFW group also yielded a greater P1 component at R.vOT 100-150 ms after stimulus presentation, as well as greater activation in L.vOT at 475-540 ms.

At area L.AG, the FFW group produced a significantly greater response immediately following stimulus presentation, as well as a more pronounced peak from 260-310 ms. The FFW group produced late ERP components (>500 ms) in both L.AG and R.AG sites in the Consonants condition, while R.AG showed this effect in the Word

condition, as well.

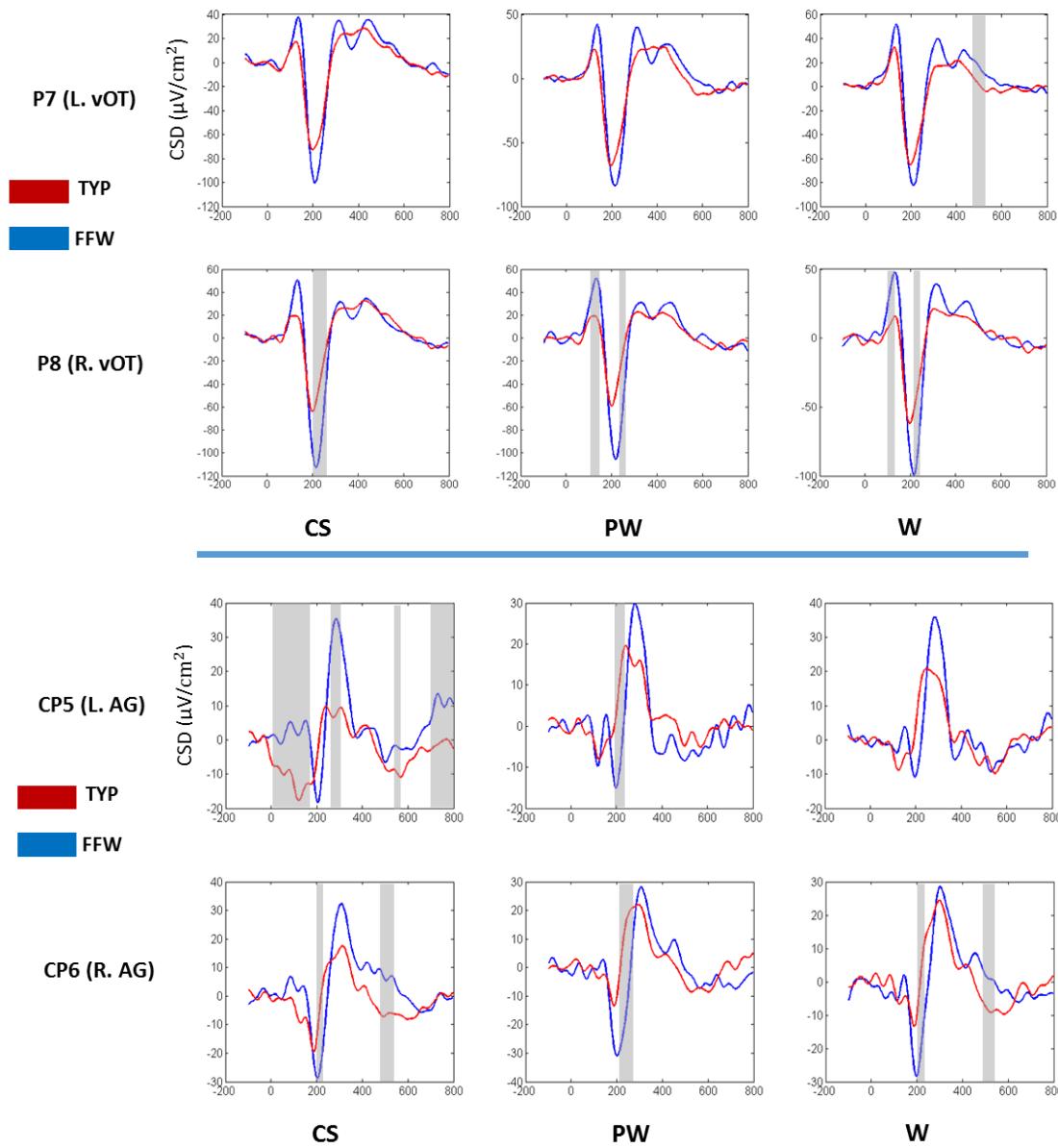


Figure 4.6. Event-related potentials (ERPs) during word reading. Areas vOT and AG were selected here due to their importance to reading processes. Sections highlighted in grey indicate significant differences between groups ($p < .05$, uncorrected). Both regions in the right hemisphere showed more pronounced N170 components for the FFW group. CS = Consonant String; PW = Pseudoword; W = Word; vOT = ventral Occipito-Temporal cortex; AG = Angular Gyrus.

ERSPs

Spectral power dynamics were investigated at reading-related sites at theta (3-8 Hz) and gamma (30-50 Hz) frequency bands.

Theta

Between-subjects *t*-tests (Fig. 4.7) revealed greater theta power for the FFW group in the Consonants condition at L.AG from 210-280 ms, R.AG from 650-800 ms, and R.AG from 100-260 ms and 360-410 ms ($p<0.05$, uncorrected). The FFW group showed greater theta power at R.vOT in the Pseudoword condition from 180-240 ms. In the Word condition, the FFW group showed greater theta power at R.AG from 195-300 ms and at R.vOT from 175-290 ms.

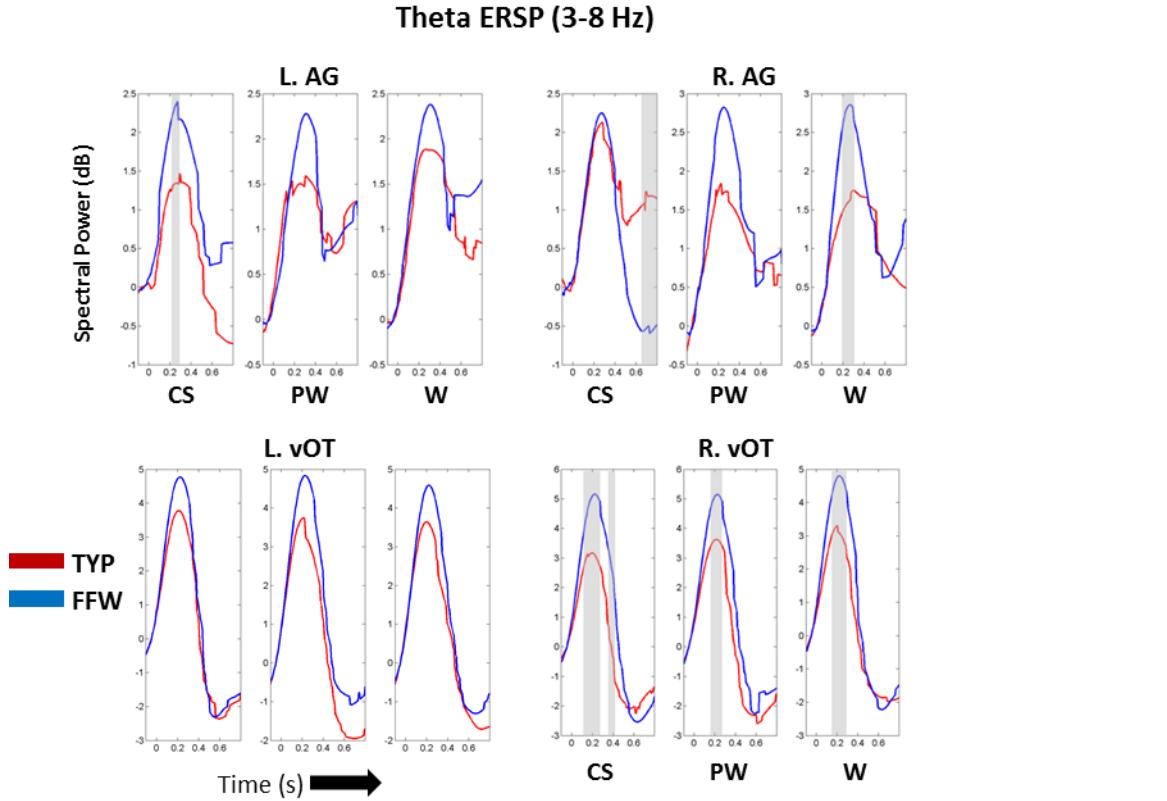


Figure 4.7. Theta-band ERSPs. The FFW group displayed greater theta power in the R.vOT region at ~220 ms across all conditions. They showed a similar result in the R.AG region in the Word condition. These results highlight not only the greater amount of resources engaged by the FFW group for written language, but also the bilateral nature of this processing, such that they utilize regions of the right hemisphere to an extent that TYP readers do not. Sections highlighted in grey indicate significant differences between groups ($p < .05$, uncorrected). CS = Consonant String; PW = Pseudoword; W = Word; vOT = ventral Occipito-Temporal cortex; AG = Angular Gyrus.

Gamma

Between-subjects t -tests (Fig. 4.8) revealed greater gamma power for the FFW group in the Consonants condition at R.vOT from 110-385 ms and 595-780 ms ($p < 0.05$, uncorrected). The FFW group showed greater gamma power in the Pseudoword condition at R.AG from 270-305 ms, and at R.vOT from 300-405 ms.

The TYP group showed greater gamma power in the Consonant condition at R.AG from 585-630 ms, in the Pseudoword condition at L.AG from 440-510 ms, and in

the Word condition at R.vOT from 475-580 ms.

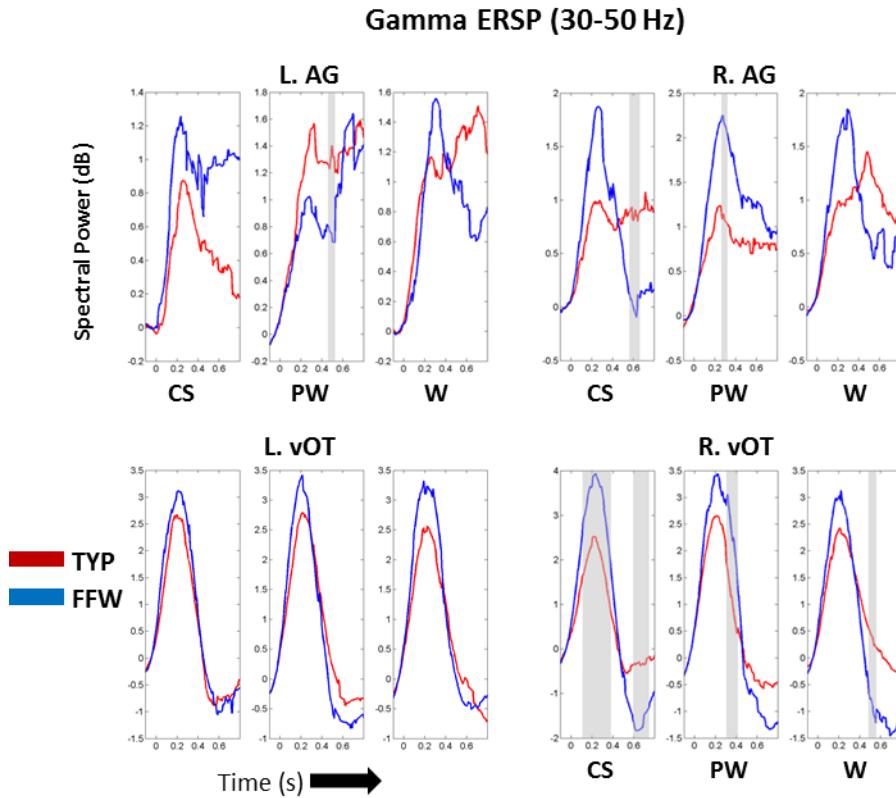


Figure 4.8. Gamma-band ERSPs. The FFW group showed significantly greater early (<400 ms) gamma power in right-hemispheric analogs of orthographic and phonological processing regions (v.OT and AG). The TYP group showed more gamma power later in the trial (>400 ms) in the right-hemispheric regions during Consonant and Word trials, as well as in L.AG during Pseudoword trials. Sections highlighted in grey indicate significant differences between groups ($p < .05$, uncorrected). CS = Consonant String; PW = Pseudoword; W = Word; vOT = ventral Occipito-Temporal cortex; AG = Angular Gyrus.

Phase Synchrony

Theta

Both groups showed distributed theta-band network functional connectivity relative to baseline across all conditions in the 200-250 ms window ($p < 0.001$; Fig. 4.9). Supplementary Figures 1 and 2 depict the broader time course of theta-band synchrony.

Comparing groups, the TYP group show no instances of greater theta synchrony ($p<0.01$) in any condition. The FFW group showed greater theta PLVs between R.PreCG, L.STG, L.vOT, and R.vOT in the Consonant condition, and between R.IFG and R.vOT in the Pseudoword condition. The FFW group showed greater theta PLVs between L.STG and R.vOT, L.vOT and R.PreCG, and R.vOT and R.AG in the Word condition.

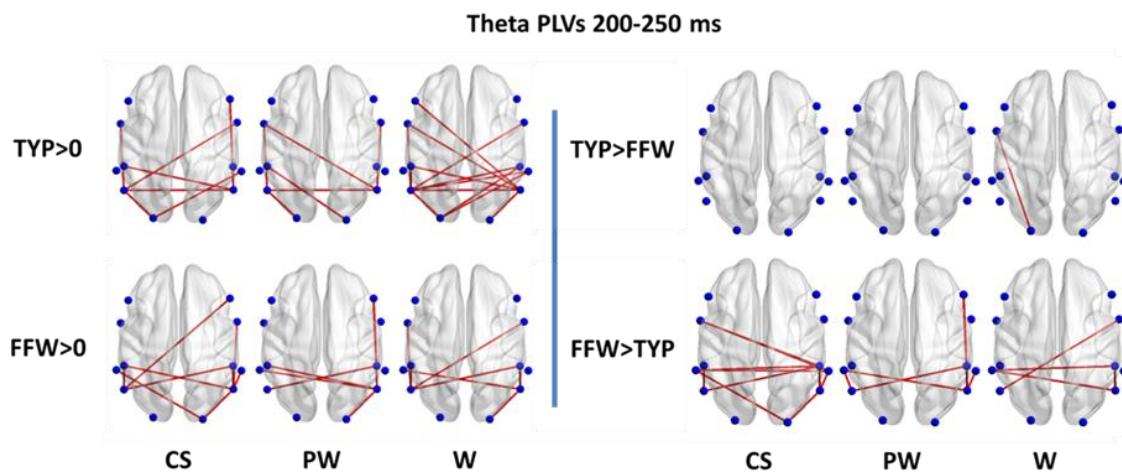


Figure 4.9. Theta (3-8 Hz) phase synchrony from 200-250 ms. (Left) Theta PLVs, when compared to baseline ($p<0.001$), show distributed connectivity among reading-related brain areas in both TYP and FFW groups. (Right) Theta PLVs, when comparing groups ($p<0.01$) indicate significantly greater connectivity in the FFW group in all three conditions, with no instances of greater connectivity in the TYP group. Especially notable is the engagement of the vOT and AG regions in the right hemisphere across all conditions in the FFW group. CS = Consonant String; PW = Pseudoword; W = Word.

Gamma

Both groups showed distributed gamma-band network functional connectivity relative to baseline across all conditions in the 200-250 ms window ($p<0.001$; Fig. 4.10).

Comparing groups, the TYP group did not yield any instances of greater gamma-band synchrony in any condition ($p<0.01$). The FFW group showed greater gamma PLVs

between R.vOT and R.AG in the Consonant condition, and between R.vOT and L.STG in the Pseudoword and Word conditions from.

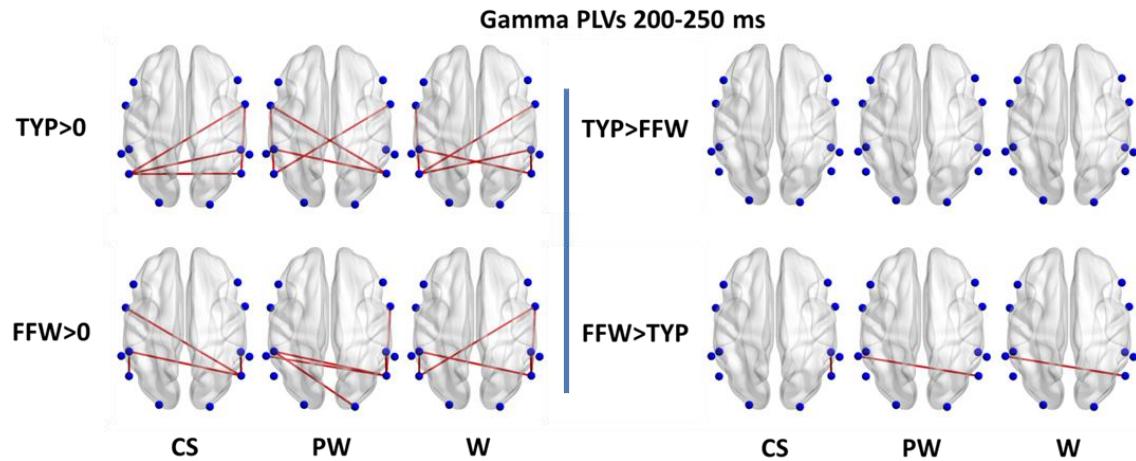


Figure 4.10. Gamma (30-50 Hz) phase synchrony from 200-250 ms. (Left) Compared to baseline ($p<0.001$), both TYP and FFW groups show distributed gamma-band connectivity among reading-related brain areas. (Right) Gamma PLVs, when comparing groups ($p<0.01$) indicate significantly greater connectivity in the FFW group in all three conditions. Especially notable is the engagement of the vOT region in the right hemisphere across all conditions. CS = Consonant String; PW = Pseudoword; W = Word.

Transfer Entropy

Theta

In the 200-250 ms window, the TYP group showed significant theta NBTE from L.STG to R.STG in the Consonant condition, as well as from L.vOT to R.vOT in the Word condition ($p<0.05$; Fig. 4.11). The FFW group showed significant NBTE from R.STG to L.STG and L.AG sites, in addition to a bi-directional relationship between L.vOT and R.vOT in the Consonant condition. The bi-directional relationship was present in the Pseudoword condition, accompanied by theta NBTE from L.PreCG to R.PreCG. In

the Word condition, the FFW group showed NBTE from L.IFG to L.STG and R.IFG, as well as from R.vOT to L.vOT.

Comparing groups, the TYP group showed no instances of greater theta NBTE ($p<0.01$) in the Consonant condition, although this group showed greater connectivity from R.STG to L.PreCG in the Pseudoword condition, and from R.IFG to L.PreCG in the Word condition. The FFW group showed no instances of greater theta NBTE in the Word condition, but showed greater connectivity from R.vOT to L.vOT and from L.vOT to L.AG in the Consonant condition, and from R.vOT to L.vOT and from R.vOT to R.AG in the Pseudoword condition.

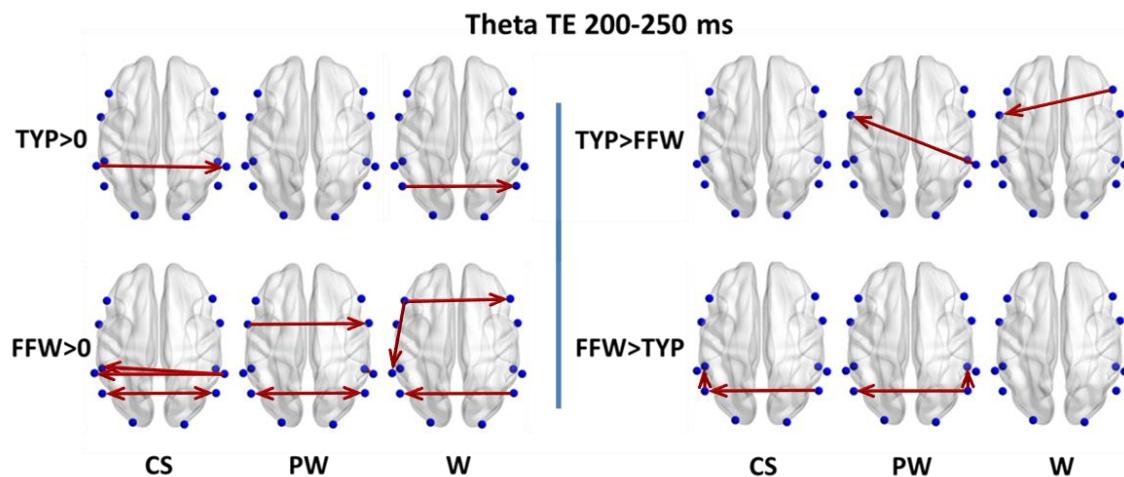


Figure 4.11. Theta (3-8 Hz) NBTE from 200-250 ms. CS = Consonant String; PW = Pseudoword; W = Word.

Gamma

In the 200-250 ms window, the TYP group showed significant gamma NBTE (relative to baseline) from L.PreCG to R.PreCG in the Consonant condition, from

L.PreCG to R.Occipital cortex in the Pseudoword condition, and from L.STG to R.PreCG in the Word condition ($p<0.05$, Fig. 4.12). The FFW group showed significant gamma NBTE from L.AG to R.PreCG, from L.STG to R.STG, and from R.Occipital cortex to L.vOT in the Consonant condition, from L.vOT to R.vOT in the Word condition, and no gamma NBTE in the Pseudoword condition.

Comparing groups, the TYP group showed greater gamma NBTE from L.PreCG to R.Occipital cortex in the Pseudoword condition ($p<0.01$), from L.STG to R.PreCG and from L.vOT to R.Occipital cortex in the Word condition. The FFW group showed greater gamma NBTE from L.AG to R.PreCG in the Consonant condition and from R.Occipital cortex to R.PreCG in the Pseudoword condition.

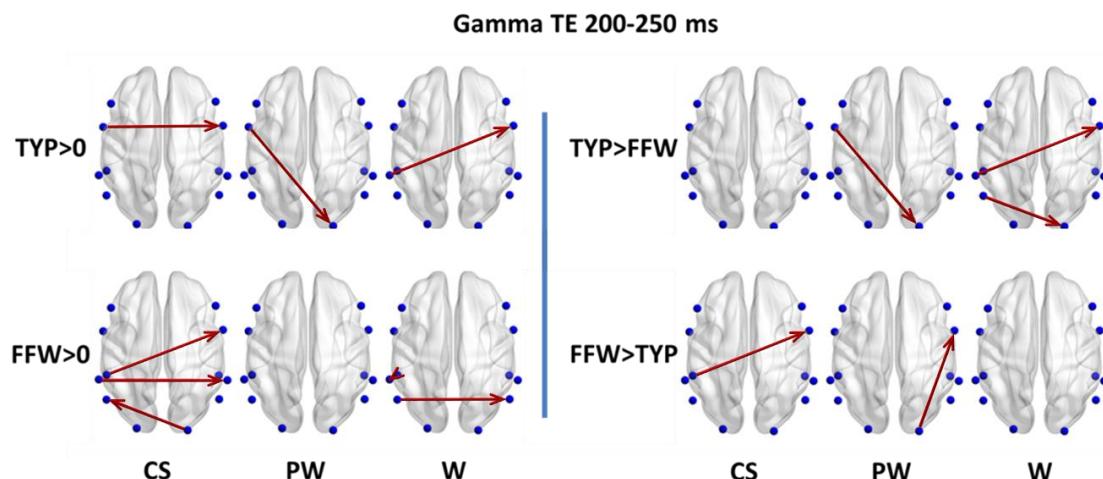


Figure 4.12. Gamma (30-50 Hz) NBTE from 200-250 ms. CS = Consonant String; PW = Pseudoword; W = Word.

Discussion

The present study examined the differences in neural processing dynamics

between typically developing readers (TYP) and challenged readers who have been enrolled in a reading training program (Fast ForWord, FFW), prior to training. Our initial hypothesis of dyslexic readers generating more functional connectivity (phase synchrony) in response to words was supported. With regard to causal connectivity (NBTE), the results were supported by theta-band NBTE, although somewhat ambiguous in the gamma band.

ERPs

Both groups in this experiment showed pronounced N170 components at reading-critical sites in response to orthographic stimuli. However, the FFW group showed more pronounced negative peaks across all conditions in the R.vOT region – a right-hemispheric analog to the so-called visual word-form area (VWFA), which is thought to be critical to the processing of sub-lexical orthographic information (Cohen et al., 2000; Dehaene, 2009). These results may reflect a similar specialization for orthographic processing that is leveraged by dyslexic readers to compensate for under-developed regions in the left hemisphere. Or it could reflect a less efficient (more effortful) bilateral form-processing response to orthographic stimuli, as the original function of these areas is visual form processing.

ERSPs

Observing oscillatory activity at specific frequency bands allows for more nuanced examinations of brainwaves that help to further characterize patterns observed in ERPs. To that end, I investigated the fluctuations in theta- and gamma-band power following the presentation of written words. Similar to the ERP results, the FFW group showed significantly larger bursts of theta-band power from R.vOT at the same time as

the N170 component, a relationship that has been documented in prior studies of the oscillatory dynamics of reading in the brain (Bedo et al., 2014).

Theta-band Connectivity in Dyslexia

The connectivity results further corroborate this assertion of a right-hemispheric network at play in dyslexic children during reading. Neuroimaging studies have repeatedly identified regions in the right hemisphere producing stronger activations in dyslexic individuals in response to reading tasks (Eden et al., 2004; Hoeft et al., 2006; Hoeft et al., 2011; Temple et al., 2000; Temple et al., 2002). Here we showed that, at the moment that orthographic information is first being processed, each group leverages distinct neurocognitive networks to carry out this process – such that dyslexic children display more inter-hemispheric connectivity, as well as right-sided intra-hemispheric connectivity in response to written language.

FFW readers showed a robust increase in posterior (occipito-temporal) connectivity across all three conditions. Notably, this includes the Consonants condition, in which the stimuli lacked any linguistic content to be evaluated by the central question “Is this a real word?” Presumably, if dyslexia targets processing beyond simple orthographic decoding, then the two groups should be identical until such processing is required. Our interpretation of the overactive connectivity in the Consonant condition is that there is a bottleneck in the processing of dyslexic networks. Note that regardless of the actual linguistic content in the stimuli, the string still must be evaluated as though it *may* have linguistic content, which is enough to engage various aspects of the reading network to evaluate the content (Price & Devlin, 2011). This window 200-250 ms after

stimulus onset captures the moment in which orthographic decoding occurs and information is relayed to other sites to be further evaluated for content. For FFW readers, a set of alternative processes and pathways are engaged to handle the consonants. First, as we saw with ERPs and ERSPs in this chapter, as well as the results in Chapter 3, the right hemisphere plays a large role for dyslexic readers, particularly in posterior sites. In the decoding and transmission of orthographic information, the lack of expertise in dyslexic kids means that they must evaluate the stimuli longer in order to make their judgement.

Theta-band NBTE results (Fig. 4.11) continue this framing with dyslexic readers showing greater effective connectivity from R.vOT to L.vOT, then from vOT sites to AG regions. While dyslexic connectivity was contained to occipito-temporal sites in posterior cortex, the neurotypical group was showing greater engagement of frontal sites.

Chapter 5: Post-intervention Connectivity Dynamics in Dyslexic and Typically-developing Children

Introduction

Despite a growing literature on the development of reading-related brain regions in dyslexia (Hoeft et al., 2011; Temple et al., 2003), it is much less understood just how the communication between these regions also changes as a function of time. In what ways does the reading network become more or less efficient throughout development, and which connections are being utilized more or less effectively? To that end, this study sought to investigate the development of connectivity in dyslexic children by comparing functional and effective connectivity measures prior to intervention (chapter 4) and after 5-6 months of schooling supplemented by a reading training program. The relationship between gains in connectivity and gains in reading performance was also examined.

Despite the evidence as to how specific brain sites develop in response to this training, it remains unclear how the overarching reading networks develop as a function of this training. With regard to laterality of reading functions in the brain, it is unclear as to whether connectivity in dyslexic children shifts to include more traditional left-hemispheric engagement, or if their reading networks instead continue to emphasize right-hemisphere networks.

Methods

Participants

Nine of the dyslexic students from Chapter 4 that were enrolled in the Fast ForWord (FFW; Scientific Learning, USA) program were tested again after 5-6 months.

FFW is a suite of educational games that have been designed to train users in various aspects of word reading, especially those abilities that seem to be deficient in dyslexia, including the sequencing of sounds, listening accuracy, image and sound mapping, syntax and morphology, sustained and focused attention, and working memory. The games use animations and scoring feedback to keep the children active and motivated in the tasks. Students participated in the FFW intervention program in addition to their usual classroom instruction.

Woodcock-Johnson tests (Word Attack and Letter-Word Identification) were conducted after the training period by experimenters. Data from this group's pre-intervention (PRE) session were used for Pre-Post comparisons. Additionally, data from typically developing classmates from Chapter 4 (TYP, control sample) were used for group comparisons.

All participants had English as their first and primary language, and had normal or corrected-to-normal visual acuity.

Experimental Procedures

The procedures and stimuli were identical to those used in Chapter 4. The primary focus was to compare the first session (pre-intervention, PRE) to the second session (post-intervention, POST) for all analyses. Some additional analyses compared the POST session data to original TYP data from Chapter 4.

The experiment was conducted on-site at elementary schools in the greater Vancouver area. A quiet room at each school was set aside for the session. First, children were asked to simply sit in a relaxed position for five minutes while their brainwaves were recorded using EEG. Participants then performed a lexical decision task (identical

to Chapter 4), in which participants were asked to decide whether a letter string was a real word or not (i.e., “Is this a real word?”). Stimuli were classified into three conditions: real words (e.g., ‘bread’), pseudowords (e.g., ‘croll’), and consonant strings (e.g., ‘rplcg’). A fixation cross was presented for 500 ms followed by a jittered inter-stimulus interval lasting between 800-1200 ms (Figure 5.1). Then a letter string was presented for 1500 ms or until the participant pressed a response, whichever occurred first. After a 1000 ms inter-trial interval, the next trial began. For the Word condition, single-syllable words were aggregated from lists found at <https://www.ontrackreading.com>. These lists have been assembled to be accessible to children and to represent a wide range of vowel sounds. Pseudowords were derived from the pool of real word stimuli by taking a word and changing a single letter (e.g. *bread* to *bream*).

Stimuli from each condition consisted of 4- and 5-letter strings (60 trials each), each presented randomly for a total of 360 trials. Blocks of 40 trials were separated by self-timed rest breaks. Participants had the option to continue to the next block immediately upon reaching a break or they could rest as long as necessary before continuing. The task was performed on a laptop while sitting at a desk. A height-adjustable chin rest was used to reduce the possibility of head movements.

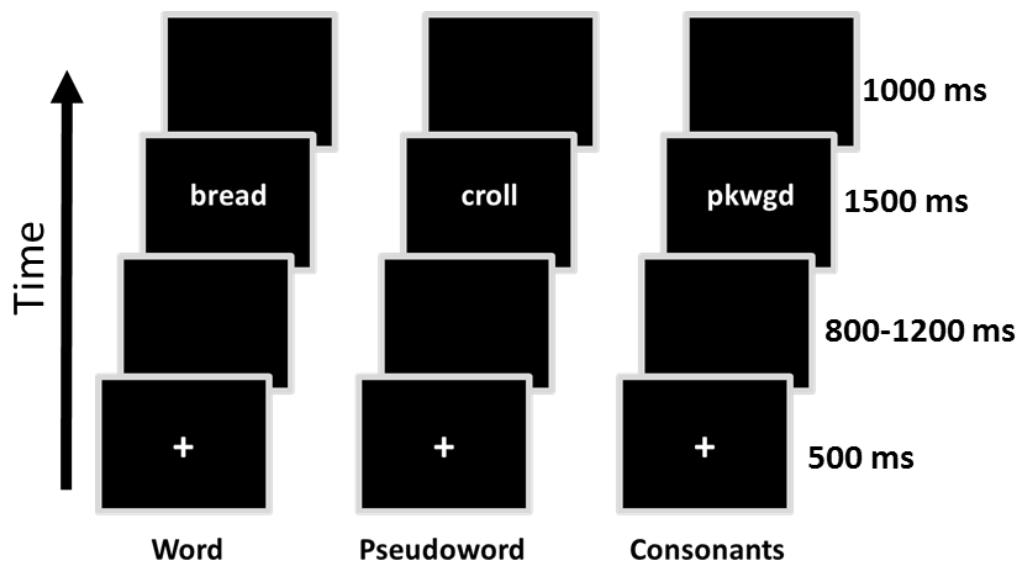


Figure 5.1. Schematic of phonological lexical decision task. Participants were required to judge whether or not a letter string was a real word.

Presentation software (Neurobehavioral Systems, USA) was used to present stimuli in white font on a black background. All stimuli were centered on a 17-inch computer monitor placed 45 cm in front of the participants. All participants used their right hand to respond on the keyboard; however, the response buttons used for “Yes” and “No” were counterbalanced across subjects.

EEG Acquisition

A portable BioSemi system was used to record continuous EEG from 64 active electrodes at equidistant locations based on the International 10–10 system of electrode placement, referenced to the average of all scalp signals (except Iz). EEG signals were amplified and sampled at 512 Hz through an analog passband of 0.16–100 Hz. Eye muscle activity was recorded by electro-oculogram (EOG) from two periocular electrodes. All electrode impedances were below 20 kΩ.

All further offline processing and analysis was performed using MATLAB software (Mathworks, Natick, USA). All signals were re-referenced to an average reference, resampled to 256 Hz, and digitally filtered from 1-100 Hz using EEGLAB software (Delorme & Makeig, 2004), an open source MATLAB toolkit, and custom scripts. A digital notch filter between 55 Hz to 65 Hz was applied to reduce line noise. The continuous data were epoched into 3500 ms bins time-locked to the presentation of the letter strings, capturing 1500 ms before and 2000 ms after word presentation.

Current Source Density

The methods for deriving CSD were identical to those used in Chapter 2, with some minor differences based on the EEG system used to collect data. CSD Toolbox for MATLAB was used to compute the CSD values (Kayser, 2009; Kayser & Tenke, 2006a; Kayser & Tenke, 2006b). Cortical regions of interest for further analysis were selected based on reading-related brain areas as revealed in previous research (Table 5.1; Jobard et al., 2003). The cortical Talairach coordinates of these sites were then cross-referenced to anatomical locations of electrodes based on the 10-10 system (Koessler et al., 2009). The nearest electrodes to these sites, as measured by Euclidean distance, were then selected for further analysis. The subset of electrodes selected in this manner were CP5, CP6, F5, F6, FT7, FT8, O1, O2, P7, P8, TP7, and TP8 (Figure 5.2). For ease of exposition the ROIs will be referred to by their cortical locations from now on, but it must be remembered that in fact the data to be analysed are the CSD values computed for the electrode locations nearest those cortical locations and not the activation levels of dipoles or other types of cortical sources inferred by localization analysis.

Table 5.1. Reading-related Brain Regions and Their Corresponding EEG Channels.

EEG channel	Talairach coordinates			Corresponding Brain Region
	x	y	z	
F5	-51	27	25	L. IFG
F6	51	27	25	R. IFG
FT7	-59	3	-2	L. PreCG
FT8	59	3	-2	R. PreCG
CP5	-62	-46	23	L. AG/SMG
CP6	62	-46	23	R. AG/SMG
TP7	-64	-45	-4	L. MTG/STG
TP8	64	-45	-4	R. MTG/STG
P7	-56	-65	0	L. Fusiform
P8	56	-65	0	R. Fusiform
O1	-26	-93	8	L. Occip
O2	26	-93	8	R. Occip

Table 5.1. EEG channels and their corresponding brain regions. EEG channels were selected for further analysis based on their proximity to previously established ROIs (Jobard et al., 2003) and their cross-hemispheric counterparts. Anatomic locations of EEG channels in Talairach space were derived from Koessler et al. (2009).

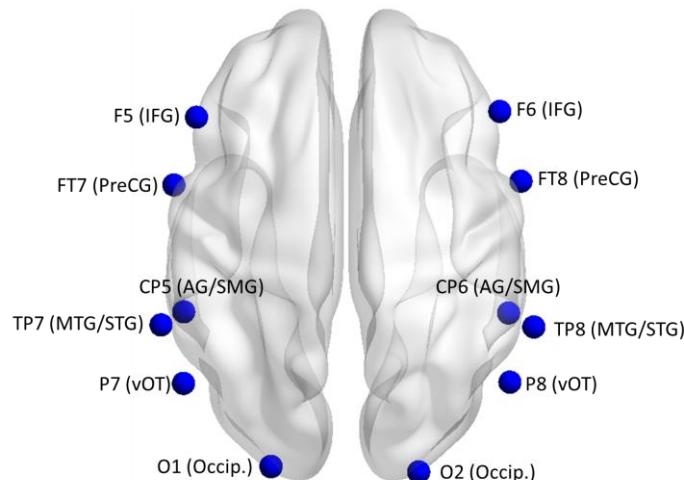


Figure 5.2. Selected electrodes that overlap with reading-related brain areas. Visual representation of anatomical locations of channels described in Table 5.1.

Event-Related Potentials (ERPs)

ERP parameters and rejection criteria were nearly identical to those used in Chapter 4. ERPs were computed by averaging each participant's epoched EEG activity across trials. This was done separately for each condition. ERPs were baseline corrected relative to a 100 ms pre-stimulus window and low-pass filtered at 20 Hz. ERPs from PRE and POST sessions were then compared using pairwise *t*-tests at each time point. Instances of significant differences between sessions sustained across multiple time points then informed the subsequent connectivity analyses as to which moments might provide insights into important network differences.

Event-Related Spectral Perturbations (ERSPs)

The ERSP processing and analysis procedures for this experiment were identical to those explained in Chapter 4. ERSPs allow us to observe the moment-to-moment fluctuations in oscillatory power at various oscillatory frequencies (i.e. 3-100 Hz) relative to a 100 ms pre-stimulus baseline. ERSPs were computed across trials for each subject separately. This technique produced an output 400 time points in length, capturing ERSPs from -940 to 1440 ms of the original epoch, as per EEGLab's *newtimes()* function. ERSPs from PRE and POST sessions were then compared using pairwise *t*-tests at each time point.

Phase Synchrony

The phase synchrony processing and analysis procedures for this experiment were nearly identical to those explained in Chapter 4. Phase synchrony analyses were conducted in order to assess inter-regional functional connectivity, or the degree to which two brain areas are sharing information, in particular, theta- (3-8 Hz) and gamma- (30-50

Hz) bands.

In order to assess the connectivity patterns before and after intervention individually, two-tailed one-sample *t*-tests ($\alpha = 0.001$) were employed to determine the statistical significance of these PLVs relative to zero at each time point. For PRE-POST comparisons, two-tailed pairwise *t*-tests ($\alpha = 0.01$) were conducted at each time point.

In addition to pairwise comparisons, the POST data from the dyslexic group was compared to the PRE data from the typically developing readers. As a means to differentiate PLV connectivity patterns between groups, two-tailed independent *t*-tests ($\alpha = 0.01$) were used comparing POST dyslexic data to PRE typical data at each time point.

To assess the statistical reliability of these *t*-tests, time points from 0 to 900 ms following the stimulus onset were divided into non-overlapping 50 ms time bins (i.e., 18 such bins). To control for multiple comparisons, and to exclude meaningless interactions, we adopted a conservative criterion and considered a 50 ms bin to contain meaningful evidence of greater functional connectivity for one group than for the other if at least half (5 or more of 9) of the time points in that bin reached the statistical threshold described earlier for either POST > PRE, or vice versa, and none did for the opposite comparison. To assess the experiment-wise error of this procedure, we used $p = 0.01$ ($q = 1 - p = 0.99$) as the probability of a success in a single binomial trial to compute the binomial probability of getting 5 or more significant time points by chance out of the total of 9 time points in each 50-ms bin (Onton, et al., 2005). This probability is 1.21×10^{-8} if all of the time points in a bin represented independent tests. This assumption of independence is probably not precisely correct as using consecutive time points will lack complete independence. Since we made 66 (inter-regional) comparisons (each possible pairing of

12 different brain ROIs) for 18 time bins, there were 1188 such tests. At most ($p = 0.01$, with the minimum 5 of 9 significant data points per bin), the experiment-wise error probability for each set of *t*-tests, assuming independence, was $1188 \times 1.21 \times 10^{-8} = .0000144$.

Transfer Entropy

The NBTE processing and analysis procedures for this experiment were nearly identical to those explained in Chapter 2. Theta-band (3-8 Hz) oscillatory time series were obtained by filtering the CSD activations in the epochs using EEGLab's digital FIR filter. NBTE was then computed across trials for each subject at 30 ms and 50 ms lags. The lags used here span the range of lags found to contain significant NBTE in previous similar investigations (Bedo, et al., 2014; Wibral et al., 2011).

In order to assess the connectivity patterns before and after intervention individually, two-tailed one-sample *t*-tests ($\alpha = 0.001$) were employed to determine the statistical significance of these NBTE values relative to zero at each time point. For PRE-POST comparisons, two-tailed pairwise *t*-tests ($\alpha = 0.01$) were conducted at each time point.

In addition to pairwise comparisons, the POST data from the dyslexic group was compared to the PRE data from the typically developing readers. As a means to differentiate NBTE connectivity patterns between groups, two-tailed independent *t*-tests ($\alpha = 0.01$) were used comparing POST dyslexic data to PRE typical data at each time point.

To assess the experiment-wise error of this procedure, we used $p = 0.05$ ($q = 1 - p = 0.95$) as the probability of a success in a single binomial trial to compute the binomial

probability of getting 7 or more significant time points by chance out of the total of 13 time points in each 50-ms bin (Onton, et al., 2005). This probability is 9.85×10^{-7} if all of the time points in a bin represented independent tests. This assumption of independence is probably not precisely correct as using consecutive time points will lack complete independence. Since we made 132 (inter-regional) comparisons (each possible pairing of 12 different brain ROIs in both directions) for 18 time bins, there were 2376 such tests. At most ($p = 0.05$, with the minimum 7 of 13 significant data points per bin), the experiment-wise error probability for each set of t-tests, assuming independence, was $2376 \times 9.85 \times 10^{-7} = 0.00234$.

Just as with PLVs, instances of significant effective connectivity by NBTE were then visualized using the BrainNet Viewer toolbox for MATLAB (Xia et al., 2013). This process was performed for analysis of gamma (30-50 Hz) NBTE, as well.

Connectivity Correlations

Measuring the brain activity from the participants at two distinct time points gives us the unique opportunity to examine the relationship between the gains in reading performance and the changes in connectivity. Correlations were computed at each time point between participant assessment scores (WJ-WA and WJ-LW tests) and connectivity measures (PLVs and NBTE). This process followed the exact set of methods in the synchrony and transfer entropy process, but used the difference in assessment scores (POST – PRE) and the differences in connectivity values (POST – PRE).

Correlations were employed to determine the statistical significance of these associations between brain connectivity and assessment scores at each time point ($\alpha = 0.01$ for PLVs, 0.05 for NBTE).

To assess the experiment-wise error of this procedure, we used $p = 0.01$ ($q = 1 - p = 0.99$) as the probability of a success in a single binomial trial to compute the binomial probability of getting 5 or more significant time points by chance out of the total of 9 time points in each 50-ms bin for correlations with PLVs. This probability is 1.21×10^{-8} if all of the time points in a bin represented independent tests. This assumption of independence is probably not precisely correct as using consecutive time points will lack complete independence. Since we made 66 (inter-regional) comparisons (each possible pairing of 12 different brain ROIs) for 18 time bins, there were 1188 such tests. At most ($p = 0.01$, with the minimum 5 of 9 significant data points per bin), the experiment-wise error probability for each set of t-tests, assuming independence, was $1188 \times 1.21 \times 10^{-8} = .0000144$.

The experiment-wise error for the NBTE correlations required 7 or more significant time points out of 13 time points ($p = 0.05$) to consider a 50 ms to be significant. This probability is 9.85×10^{-7} if all of the time points in a bin represented independent tests. Since we made 132 (inter-regional) comparisons (each possible pairing of 12 different brain ROIs in both directions) for 18 time bins, there were 2376 such tests. At most ($p = 0.05$, with the minimum 7 of 13 significant data points per bin), the experiment-wise error probability for each set of t-tests, assuming independence, was $2376 \times 9.85 \times 10^{-7} = .000234$.

Results

Reading Assessments

While both WJ-WA and WJ-LW reading assessments saw slight improvements after training, neither test's improvements were statistically significant. Participants

showed increased scores for WJ-WA in the second session ($M=18.73$, $SD=4.34$) compared to session one ($M=16$, $SD=6.54$), though these gains were not statistically significant, $t(8)=0.14$, $p>0.05$. In the WJ-LW assessment, participants showed increased scores in the second session ($M=44.64$, $SD=6.86$) compared to session one ($M=41.67$, $SD=7.75$), although again not reaching statistical significance, $t(8)=0.15$, $p>0.05$.

Accuracy

No significant difference in accuracy on the experimental task was observed between sessions (Table 5.2; Fig. 5.3).

<i>Condition</i>	<i>Pre</i>		<i>Post</i>			
	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>t(8)</i>	<i>p</i>
<i>Consonants</i>	78.36	23.69	73.16	29.49	0.59	0.57
<i>Pseudowords</i>	35.47	27.67	44.60	26.09	1.02	0.34
<i>Real Words</i>	69.24	18.77	53.90	27.77	1.98	0.08

Table 5.2. Dependent sample t-tests revealed no significant differences in accuracy (percent correct) between sessions. M = Mean; SD = Standard Deviation.

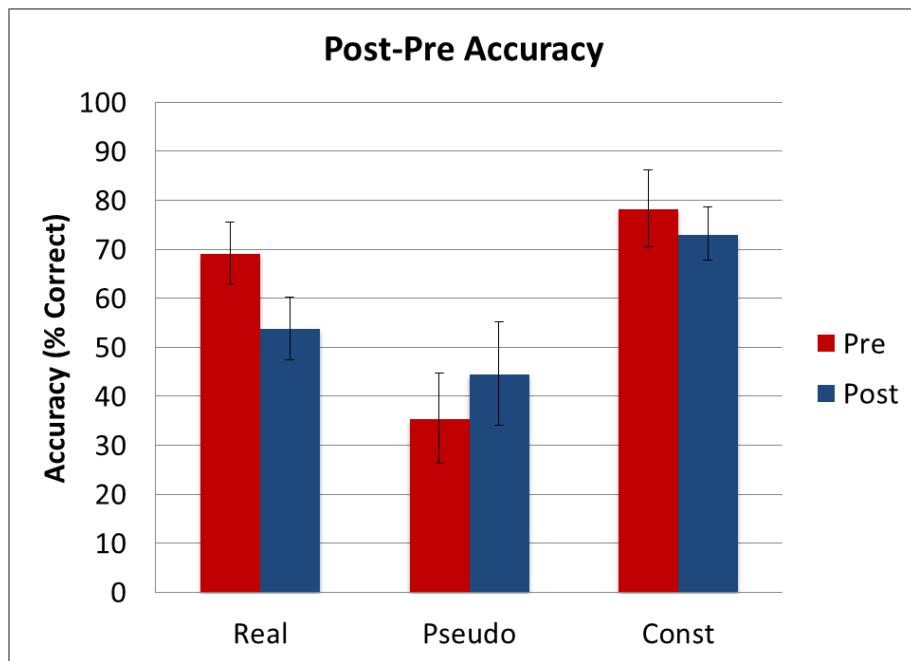


Figure 5.3. Lexical decision task accuracy before and after reading intervention. Error bars represent the standard error of the mean. Real = Real Word, Pseudo = Pseudoword, Const = Consonant Strings. Error bars represent one standard deviation.

Reaction Time

No significant difference in reaction times on the experimental task was observed between sessions (Table 5.3; Fig. 5.4).

Condition	Pre		Post		$t(8)$	p
	M	SD	M	SD		
Consonants	943	132	871	123	1.69	0.13
Pseudowords	1134	130	1045	136	1.99	0.08
Real Words	1064	146	1012	128	1.14	0.29

Table 5.3. Dependent sample t-tests revealed no significant differences in reaction times (in milliseconds) between sessions. Error bars represent the standard error of the mean. M = Mean; SD = Standard Deviation.

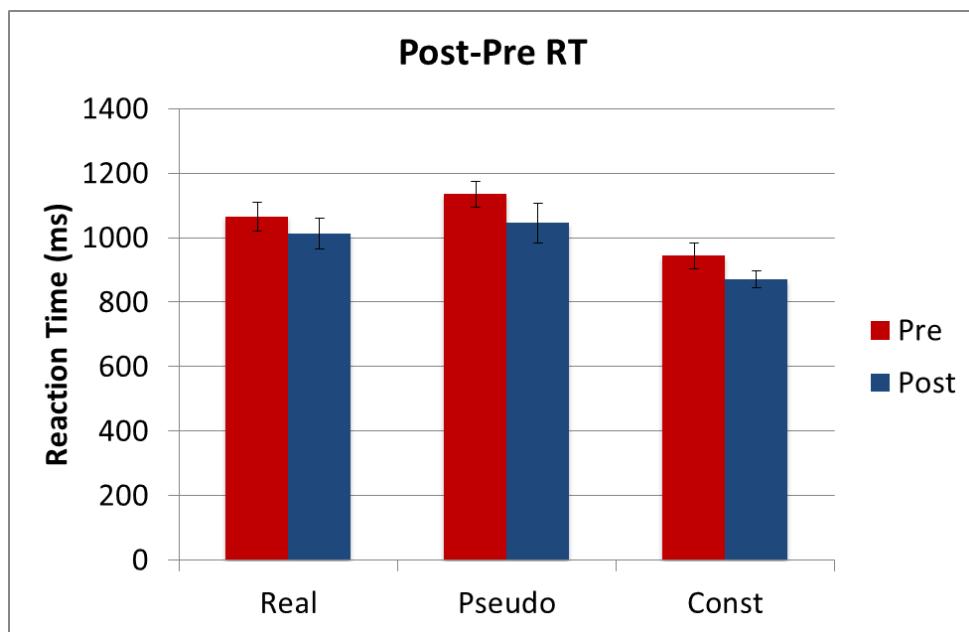


Figure 5.4. Lexical decision task reaction times before and after reading intervention. Dyslexic children did not show any differences in their reaction times. Error bars represent the standard error of the mean. Real = Real Word, Pseudo = Pseudoword, Const = Consonant Strings. Error bars represent one standard deviation.

ERPs

In L.vOT, the POST session yielded a less pronounced N170 negative peak from 170-190 ms in the Pseudoword condition ($p<0.05$, Fig. 5.5). In R.vOT, the POST session yielded a less pronounced negative peak from 195-240 ms in the Consonant condition, as well as deduced activation from 70-110 ms in the Pseudoword condition, and greater activation in the Word condition from 640-715 ms.

In L.AG, the PRE session showed greater activations from 730-800 ms in the Consonant condition, while the POST session showed greater activations from 95-140 ms in the Pseudoword condition. The PRE session showed greater activity from 290-315 ms in the Word condition, with the POST session showing greater activity from 525-550 ms.

In R.AG, the POST session showed greater activity from 10-40 ms in the Consonant condition, while the PRE session showed greater activity from 415-435 ms. The PRE session yielded a greater response from 280-310 ms in the Pseudoword condition. In the Word condition, the PRE session showed greater activity from 290-315 and 425-505 ms.

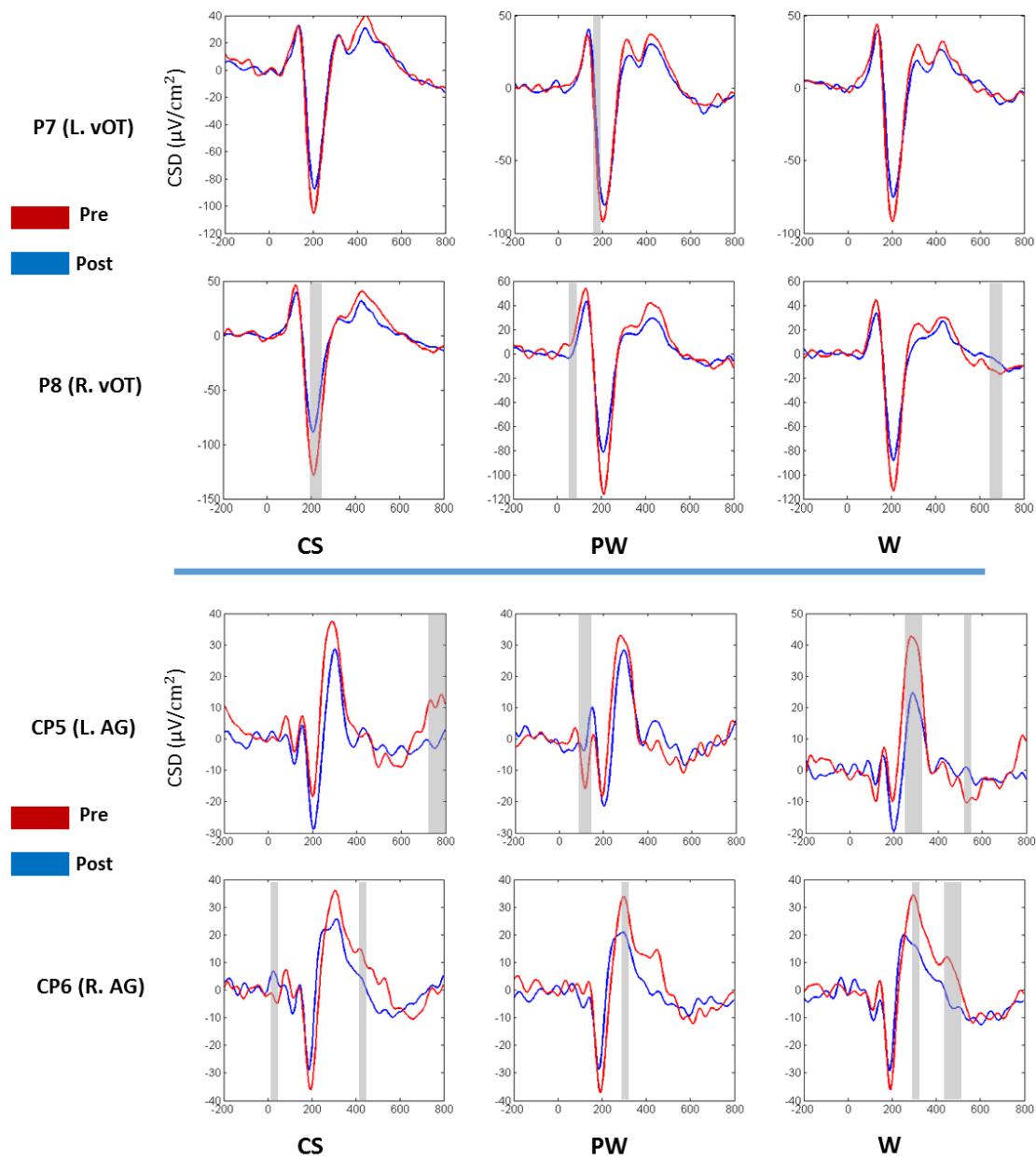


Figure 5.5. ERPs comparing reading-related brain regions between sessions. While not always significant, there is a general trend of post-intervention ERP peaks being less pronounced compared to the same peaks in the first session, especially around ~ 210 ms at vOT sites. As well, the left and right AG regions tend to show more prominent positive peaks after ~ 300 ms in the first session. CS = Consonant String; PW = Pseudoword; W = Word; vOT = ventral Occipito-Temporal cortex; AG = Angular Gyrus.

Phase Synchrony

Theta

Both sessions showed distributed theta-band network functional connectivity relative to baseline across all conditions in the 200-250 ms window ($p<0.001$; Fig. 5.6). Supplementary Figures 3 and 4 depict the broader time course of theta-band synchrony.

Comparing sessions, the POST session showed greater theta synchrony between L.STG and R.IFG in the Pseudoword condition, and between left and right PreCG regions and left and right STG sites in the Word condition ($p<0.01$).

The PRE session showed greater theta PLVs between R.vOT and R.AG sites, as well as between R.vOT and R.PreCG in the Consonant condition. The PRE session yielded greater PLVs between R.AG and R.IFG for Pseudowords. In the Word condition, the PRE session showed greater PLVs between L.vOT and R.PreCG, between R.vOT and R.AG, and between L.PreCG and right occipital cortex.

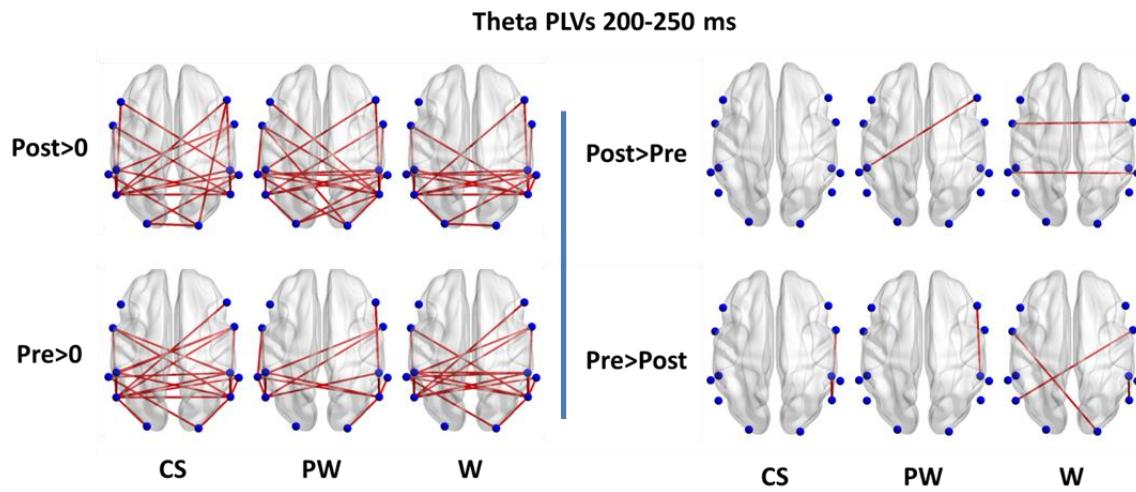


Figure 5.6. Theta (3-8 Hz) phase synchrony from 200-250 ms. (Left) Theta PLVs, when compared to baseline ($p<0.001$), show distributed connectivity among reading-related brain areas in both PRE and POST sessions. (Right) Theta PLVs, when comparing sessions ($p<0.01$) indicate distinct connectivity increases and decreases relative to the PRE session (i.e. greater connectivity in the PRE session suggests a significant decrease in the POST session). CS = Consonant String; PW = Pseudoword; W = Word.

Gamma

Both sessions showed distributed gamma-band network functional connectivity relative to baseline across all conditions in the 200-250 ms window ($p<0.001$; Fig. 5.7).

However, when comparing groups, neither session showed any instances of greater gamma-band network functional connectivity ($p<0.01$).

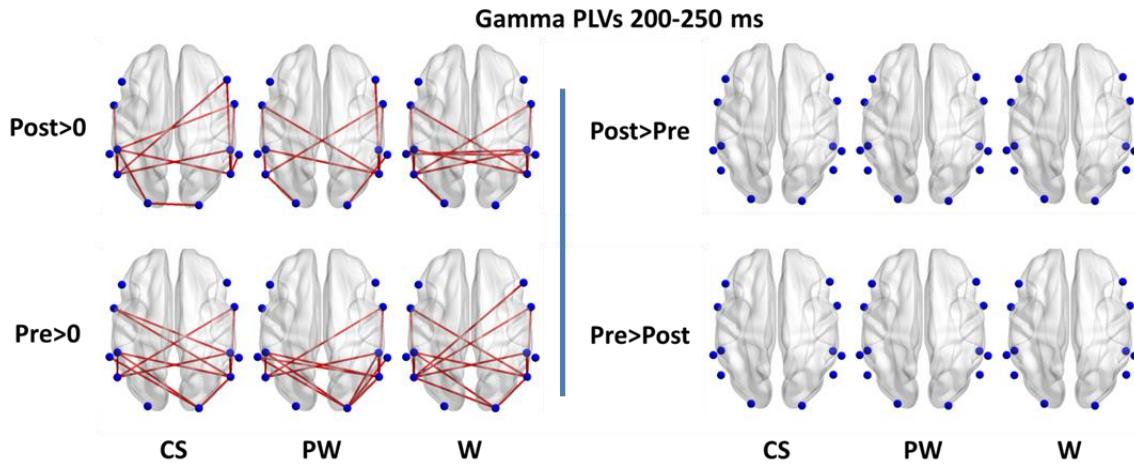


Figure 5.7. Gamma (30-50 Hz) phase synchrony from 200-250 ms. Both sessions showed distributed networks of gamma synchrony relative to baseline ($p<0.001$). However, no significant differences were observed between sessions ($p<0.01$).

Transfer Entropy

Theta

In the 200-250 ms window, the POST session showed significant theta NBTE from R.AG to R.STG, as well as bi-directional connectivity between left and right vOT sites in the Consonant condition ($p<0.05$; Fig. 5.8). In the Pseudoword condition, the POST session showed significant connectivity from R.AG to R.STG, from L.vOT to R.vOT, and from R.STG to right occipital cortex. In the Word condition, the POST session showed theta NBTE from L.STG to R.vOT, as well as bi-directional connectivity between left and right vOT regions.

The PRE session showed significant connectivity from R.STG to L.AG and L.STG, and between left and right vOT sites in the Consonant condition. For Pseudowords, the PRE session showed theta NBTE from L.PreCG to R.PreCG, and between L.vOT and R.vOT. In the Word condition, connectivity was observed from R.vOT to L.vOT, and from L.IFG to R.IFG and L.STG.

Comparing groups, the POST session showed greater theta NBTE from R.STG to left occipital cortex in the Pseudoword condition, and from L.AG to R.vOT in the Word condition ($p<0.01$). The PRE session showed greater connectivity from L.IFG to R.IFG in the Word condition.

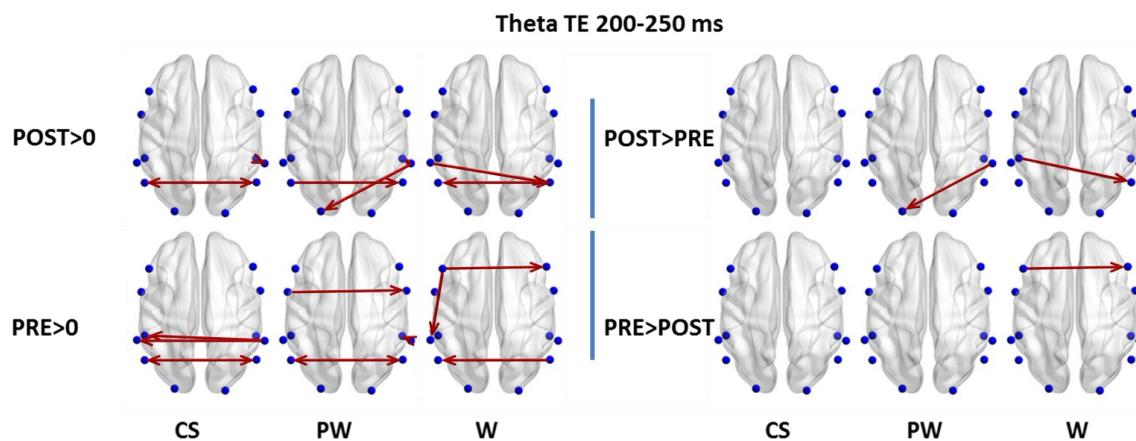


Figure 5.8. Theta (3-8 Hz) NBTE from 200-250 ms. CS = Consonant String; PW = Pseudoword; W = Word.

Gamma

In the 200-250 ms window, the POST session showed significant gamma NBTE from R.PreCG to L.STG, and from R.IFG to L.PreCG in the Consonant condition ($p<0.05$; Fig. 5.9). In the Pseudoword condition, the POST session showed significant connectivity from L.AG to L.PreCG, from L.IFG to R.AG, from R.AG to L.AG and left occipital cortex, and from right occipital cortex to R.AG. In the Word condition, the POST session showed gamma NBTE from R.PrecCG to L.vOT and from L.vOT to R.vOT.

The PRE session showed significant connectivity from L.AG to R.PreCG, from L.STG to R.STG, and from right occipital cortex to L.vOT in the Consonant condition. For Pseudowords, the PRE session showed gamma NBTE from L.PreCG to R.PreCG, and between L.vOT and R.vOT. In the Word condition, connectivity was observed from R.vOT to L.vOT, and from L.IFG to R.IFG and L.STG.

Comparing groups, the POST session showed greater gamma NBTE from R.AG to left occipital cortex in the Consonant condition ($p<0.01$).

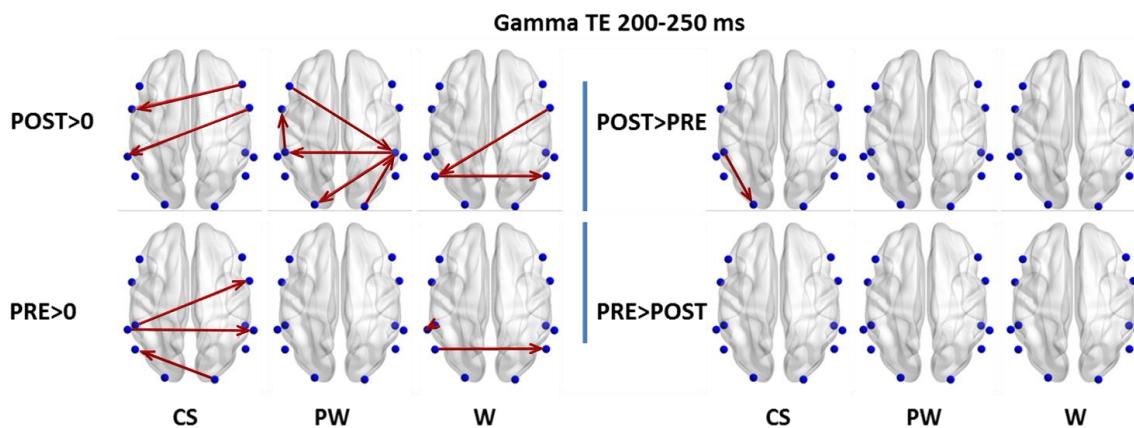


Figure 5.9. Gamma (30-50 Hz) NBTE from 200-250 ms. CS = Consonant String; PW = Pseudoword; W = Word.

Correlations Between Connectivity and Assessment Scores

Gains in performance (POST-PRE scores) on two reading assessments – WJ-WA and WJ-LW – were correlated with gains in brain connectivity (Figure 5.10).

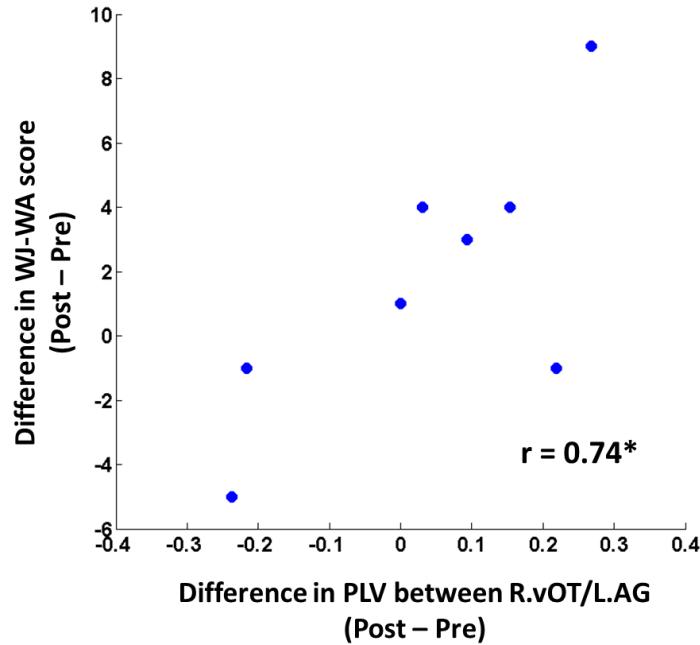


Figure 5.10. Example of a correlation between gains in reading performance and gains in phase synchrony at a single time point. In this instance, the theta PLV gains between R.vOT and L.AG were positively correlated with the gains in reading assessment scores (WJ-WA), such that readers who showed greater PLVs over time between these regions also tended to show greater improvements in reading performance. These correlations were performed at each time point, and were then subjected to the same binning as the PLV and NBTE procedures. This particular example uses data from eight participants.
* $p<0.01$

Theta PLVs

In the 200-250 ms window, gains in theta synchrony between R.vOT and R.IFG in the Pseudoword condition were significantly correlated to WJ-WA performance gains ($p<0.01$, Fig. 5.11). Significant correlations were also observed between R.vOT and L.IFG for Words.

Negative correlations in the Consonant condition were observed between R.AG and L.AG, between R.AG and L.STG, and between R.vOT and right occipital cortex. In

the Word condition, correlations were observed between R.STG and L.PreCG, and between R.vOT and R.STG.

Gains in theta synchrony between R.vOT and R.PreCG in the Consonant condition were significantly correlated to WJ-LW performance gains ($p < 0.01$). In the Pseudoword condition, correlations were observed between R.vOT and L.IFG and between L.vOT and R.STG. Correlations were also observed between R.vOT and L.IFG, between R.vOT and R.AG, and between R.AG and R.PreCG for Words.

Negative correlations in the Pseudoword condition were observed between L.AG and R.STG, between R.AG and L.STG, and in the Word condition between L.IFG and R.IFG, and between right occipital cortex and R.STG, L.STG, and left occipital cortex.

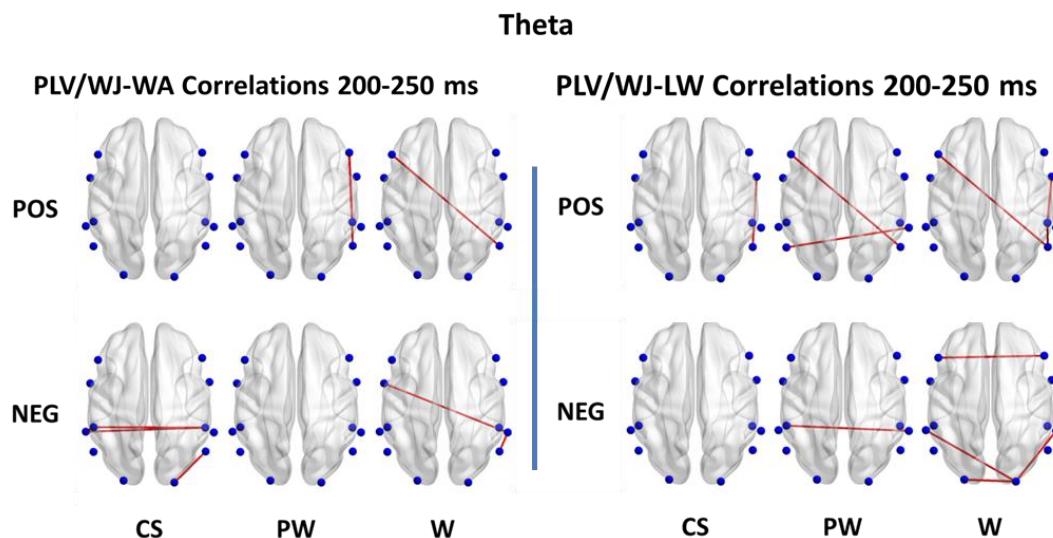


Figure 5.11. Correlation between gains in theta PLVs from 200-250 ms and gains in behavioral performance in WJ-WA (left) and WJ-LW (right) assessments. CS = Consonant String; PW = Pseudoword; W = Word.

Gamma PLVs

In the 200-250 ms window, gains in gamma synchrony between L.vOT and R.PreCG in the Consonant condition were significantly correlated to WJ-WA performance gains ($p<0.01$, Fig. 5.12).

Negative correlations in the Consonant condition were observed between L.IFG and left occipital cortex. In the Word condition, negative correlations were observed between L.AG and right occipital cortex.

Gains in gamma synchrony between L.IFG and left occipital cortex in the Pseudoword condition were significantly correlated to WJ-LW performance gains ($p<0.01$). In the Word condition, correlations were observed between R.IFG and left and right vOT regions, as well as with left occipital cortex.

Negative correlations in the Consonant condition were observed between R.PreCG and L.IFG, and between R.PreCG and R.IFG. In the Pseudoword condition, negative correlations were observed between R.PreCG and right occipital cortex. In the Word condition, negative correlations were observed between R.PreCG and left and right occipital cortex sites.

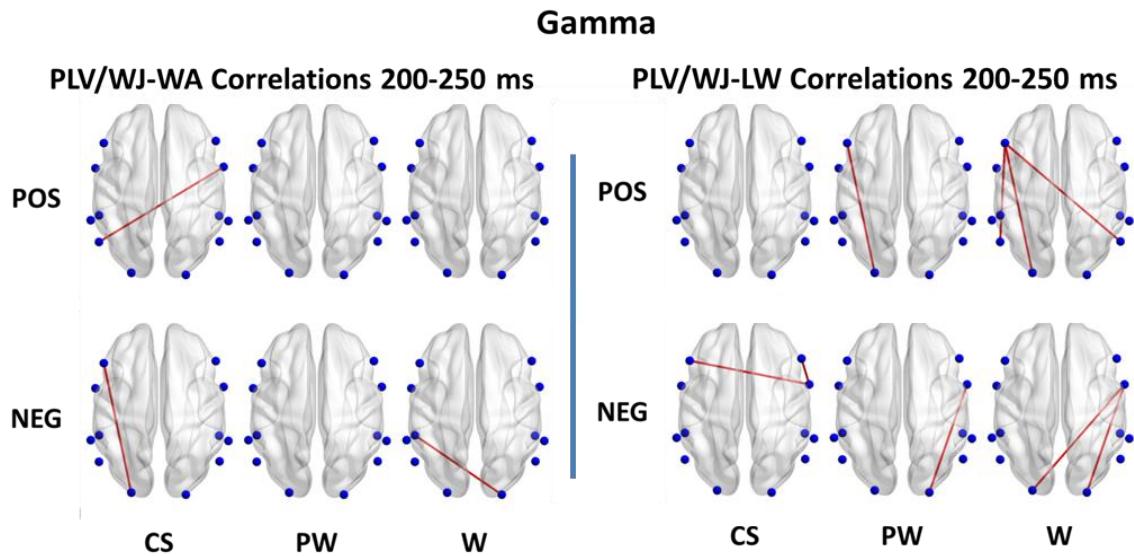


Figure 5.12. Correlation between gains in gamma PLVs from 200-250 ms and gains in behavioral performance in WJ-WA (left) and WJ-LW (right) assessments. CS = Consonant String; PW = Pseudoword; W = Word.

Theta NBTE

In the 200-250 ms window, gains in theta NBTE from L.AG and R.PreCG to right occipital cortex in the Pseudoword condition were significantly correlated to WJ-WA performance gains ($p < 0.05$, Fig. 5.13). Significant correlations were also observed from L.IFG to L.PreCG for Words.

Negative correlations in the Consonant condition were observed from L.AG to L.vOT, and from left occipital cortex to right occipital cortex. In the Pseudoword condition, correlations were observed from left occipital cortex to L.vOT.

Gains in theta NBTE from L.AG to R.IFG were significantly positive correlated to WJ-LW performance gains in the Pseudoword condition ($p < 0.05$), and from R.IFG to L.vOT in the Word condition.

Negative correlations in the Consonant condition were observed from L.AG to L.vOT.

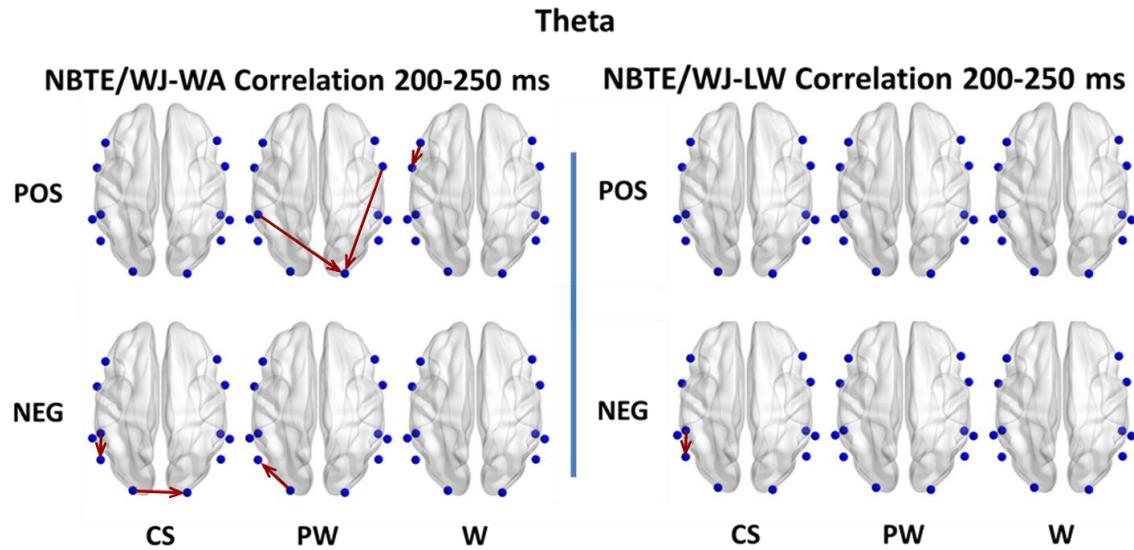


Figure 5.13. Correlation between gains in theta NBTE from 200-250 ms and gains in behavioral performance in WJ-WA (left) and WJ-LW (right) assessments. CS = Consonant String; PW = Pseudoword; W = Word.

Gamma NBTE

In the 200-250 ms window, gains in gamma NBTE from R.IFG to left occipital cortex in the Consonant condition were significantly correlated to WJ-WA performance gains ($p < 0.05$, Fig. 5.14). Significant negative correlations in the Word condition were observed from L.AG to L.PreCG.

Gains in gamma NBTE did not show significant positive correlations with WJ-LW performance gains in any condition ($p < 0.05$). Negative correlations in the Consonant condition were observed from L.AG to L.IFG.

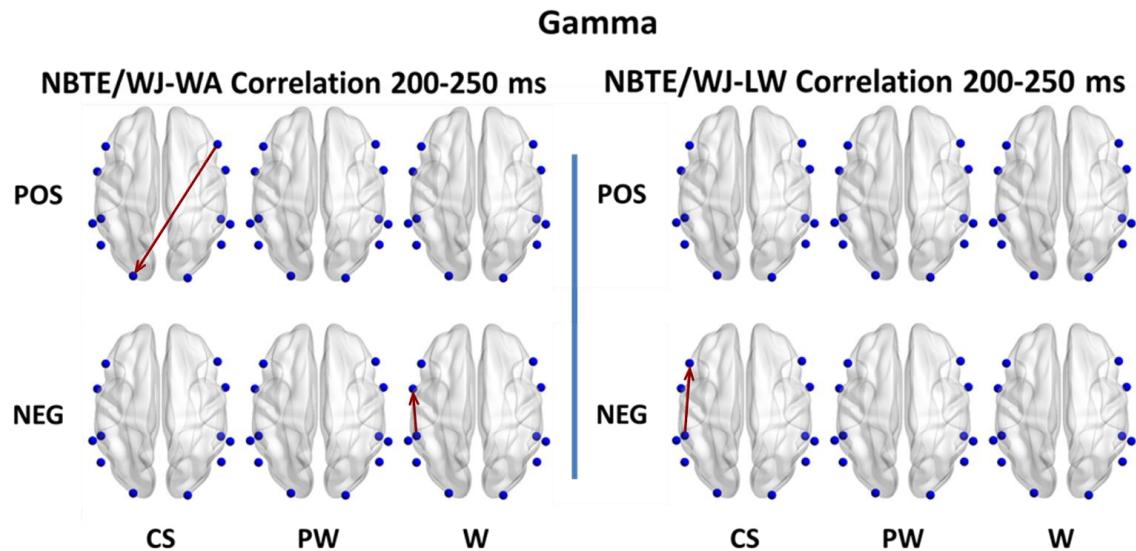


Figure 5.14. Correlation between gains in gamma NBTE from 200-250 ms and gains in behavioral performance in WJ-WA (left) and WJ-LW (right) assessments. CS = Consonant String; PW = Pseudoword; W = Word.

Comparing Post-intervention Dyslexic and Typical Reading Networks

In the 200-250 ms window, the FastForWord (dyslexic) group's phase synchrony measures from both PRE and POST sessions were compared to the networks of typical readers from the original PRE session.

Theta

Across all conditions in the PRE session, FFW readers showed widespread occipito-temporal theta connectivity that was significantly greater than TYP readers (Fig. 5.15; $p<0.05$). Supplementary Figures 4 and 6 depict the broader time course of theta-band synchrony.

In the POST session FFW readers showed occipito-temporal theta connectivity that was significantly greater than TYP readers in the pseudoword and word conditions, but show no differences in the consonant condition ($p<0.05$).

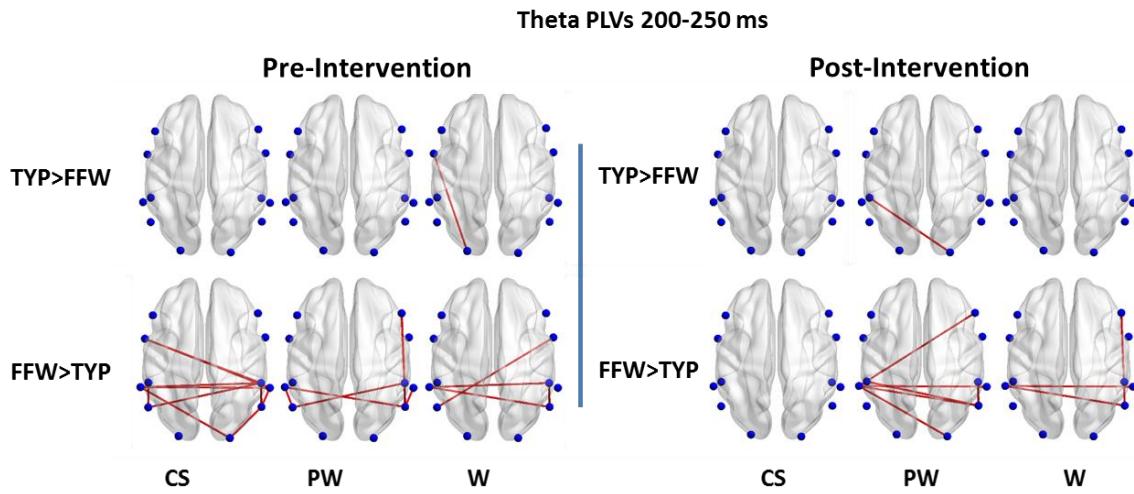


Figure 5.15. Comparing dyslexic and typical theta-band networks before and after intervention. (Left) Theta PLVs, comparing the dyslexic group to their typically-developing classmates prior to intervention. (Right) Comparing the dyslexic group after six months to the typical group from the first session. Following the intervention program, the reading networks of dyslexic children resemble those of typically-developing classmates when processing basic orthography (consonants). However, pseudowords and words continued to use pathways that were not in line with how the typical children were processing the information. CS = Consonant String; PW = Pseudoword; W = Word.

Gamma

Across all conditions in the PRE session, FFW readers showed occipito-temporal gamma connectivity (Fig. 5.16), as well as occasional engagement of frontal sites, that was significantly greater than in TYP readers ($p<0.05$).

In the POST session, FFW readers showed single instances of greater gamma-band connectivity between L.AG and R.PreCG in the consonant and pseudoword conditions, as well as occipito-temporal connectivity in the word condition.

Comparing PRE and POST sessions, the gamma connectivity in the pseudoword condition is much more sparse following intervention.

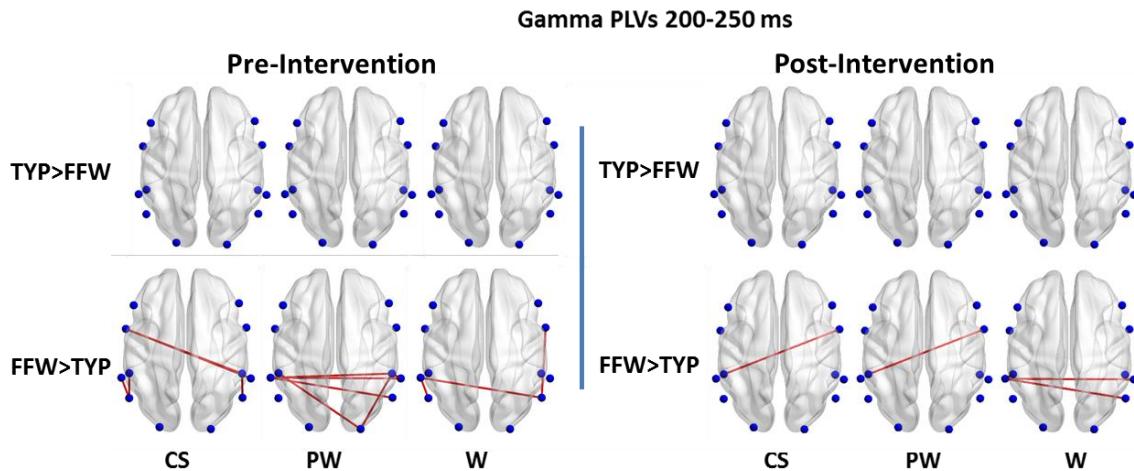


Figure 5.16. Comparing dyslexic and typical gamma-band networks before and after intervention. (Left) Gamma PLVs, comparing the dyslexic group to their typically-developing classmates prior to intervention. (Right) Comparing the dyslexic group after six months to the typical group from the first session. Following the intervention program, the reading networks of dyslexic children more closely resembled those of typically-developing classmates, particularly in the pseudoword condition. CS = Consonant String; PW = Pseudoword; W = Word.

Discussion

In order to investigate the development of brain networks involved in reading, nine dyslexic readers from the FFW group described in Chapter 4 completed the same tasks 5-6 months following the first session. Assessment scores, lexical decision task performance, and brain activity were then compared between sessions.

Across all behavioral scores – reading assessments (WJ-WA and WJ-LW), task accuracy, and reaction time – participants showed no significant differences in task accuracy or reaction time. However, despite the group lacking significant gains in aggregate, some readers did improve after intervention.

Between sessions, localized brain activity (ERPs) at reading-related sites showed a general reduction in intensity, such that positive and negative peaks of interest (e.g.

N170 component) were less pronounced in the POST session (Dujardin et al., 2011; Hasko et al., 2013; Hasko et al., 2014; Jucla et al., 2010; Mahe et al., 2012). These findings are in line with other neuroimaging (Schlagger & Chuch, 2009; Shaywitz et al., 2002) studies of dyslexia interventions, whereby improved reading ability was linked to decreases in general activation due to more efficient and specialized processing, as well as a shifting in regional activations.

Development of Brain Connectivity

Functional connectivity results, as measured by phase synchrony, displayed several differences in connectivity patterns between sessions and across conditions.

Theta-band synchrony has been shown to reflect network connectivity patterns over time during reading (Bedo et al., 2014). In the present study, a reduction of theta synchrony was observed in the Consonant condition of the POST session at the time window most critical for pre-lexical orthographic processing in children (200-250 ms). Interestingly, the Consonant condition requires no additional reading training to identify its semantic or phonological properties, and yet orthographic expertise seems to have had an effect here. Just as with ERPs, this result suggests a reduction in executive engagement during orthographic processing, thus requiring fewer resources to accomplish the same task (Johnson, 2011; Price & Devlin, 2011).

Further supporting this account, the performance-connectivity correlations also showed significant negative correlations between occipito-temporal posterior connectivity and reading assessment scores. In other words, children who showed the smallest performance gains also tended to exert more resources among posterior sites

involved in the early stages of reading, whereas individuals who showed the largest performance gains in their reading assessments instead tended to show connectivity engaging frontal sites, suggesting the engagement of higher-level language areas.

Price and Devlin (2011) have argued for a framework of occipito-temporal cortical dominance in word reading that emphasizes the role of connectivity and communication between these and other regions, such that orthographic information is resolved by comparing bottom-up inputs with top-down expectations. In this framework, unfamiliar or difficult content would require substantially more frequent evaluations to resolve the perceptual inputs and send that information to higher-level language-processing regions, resulting in slower overall performance. The results presented here suggest that readers who showed the greatest behavioral improvements required fewer resources at earlier stages, allowing for earlier engagement from frontal sites.

In general, the most improved readers showed greater theta-band connectivity with frontal sites in the 200-250 ms window while the least improved readers showed greater posterior occipito-temporal connectivity. Following Price and Devlin's framework, whereas poor readers are still resolving the orthographic and initial linguistic content, more developed readers are evaluating (or at least engaging with) higher-level linguistic content in the frontal language processing centers. In this case, I posit that the higher levels of occipito-temporal connectivity in the poor readers reflect a delay in processing, in that more experienced readers are already accessing linguistic information beyond simple pre-lexical orthography (Wolf, 2008).

Frontal lobe connectivity changes have been shown to be a predictor of reading performance gains. Hoeft and colleagues (2011) have shown that structural connectivity linked to R.IFG is a predictor of performance gains in children with developmental dyslexia. In the present study, our functional and effective connectivity results did not clearly corroborate this account, since R.IFG showed distinct instances of increased connectivity both in PRE and in POST sessions, as well as both positive and negative correlations to gains in assessment scores. Thus it seems that structural connectivity alone is not enough – there must be functional and effective connectivity accompanying it for reading performance to be bettered.

Although we did not measure the TYP group's reading networks a second time, a meaningful comparison is still possible to address the question of whether the intervention (plus the intervening time period and other school activities) caused the FFW reading networks to more closely resemble the already more skilled TYP reading networks. We found that indeed there was some closer resemblance in theta-band connectivity in the POST session, but only for the consonant strings. Even after six months of intervention, however, the FFW group's theta networks in the pseudoword and word conditions remained robustly distinct from the TYP group. These findings suggest that whereas some aspects of the reading network may have altered connectivity to resemble typical processing at early (i.e. pre-lexical) stages, the later stage processes still utilize alternative pathways. It remains unclear if this is because of a developed efficiency in alternative pathways or because of poor coordination from typical regions (e.g. ectopias in the left hemispheric language areas), or both.

In the gamma band, PRE and POST session differences were somewhat less pronounced, but it is clear that the FFW network connectivity in the pseudoword condition more closely resembles the TYP group after the POST session. The nature of the task is such that the pseudoword condition is particularly taxing on phonological processing skills of the reader, forcing them to sound out the letter strings. In this regard, their improved performance in reading assessments may be related to their networks being more optimal (i.e. closer to the typical organization).

The underlying premise for this comparison between post-intervention FFW and TYP readers was to examine if a targeted reading intervention would shape the reading network in dyslexic children to be more closely aligned to their typically-developing classmates, or if the training would instead optimize their existing networks. These results suggest that for early orthographic processing, FFW readers' theta-band networks do seem to shift in such a way that orthographic processing follows the same pathways as TYP readers. However, after this initial processing, as the orthographic information needs to be made available to the rest of the reading network (e.g. for phonological or semantic processing), FFW readers continue to use alternative pathways to achieve these results.

This divergence in results between theta and gamma bands may be addressed by explanations proposing different functional properties of each frequency band, whereby theta PLVs represent long distance communication (e.g. occipito-frontal; Ward, 2003), whereas gamma oscillations work in conjunction with theta oscillations to aid in more localized computations. As for gamma connectivity, Lehongre and colleagues (2011) showed a reduced ability for dyslexic individuals to synchronize their auditory processing at a gamma rate compared to controls. Goswami (2011) went on to posit that this gamma

synchrony deficit might account for phonological processing difficulties seen in dyslexic readers, as the average speed at which phonemes are read is at a gamma rate, such that when dyslexic readers attempt to string together speech sounds from text, they do so in an uncoordinated manner, resulting in poor reading performance. What remains unclear is why phonological processing networks in the gamma band would shift to a more typical organization, but the orthographic (consonant strings) or semantic processing (words) did not show so drastic a change.

Another perspective to consider is whether or not the presence of ectopias has altered the micro-structure of the reading-related brain regions to the point that pathways connected to these regions are under-utilized by the dyslexic reading networks in favor of alternative pathways (e.g. right hemisphere). If ectopias in the left hemisphere disrupted the brain's ability to develop effective pathways and networks in the left hemisphere, then the coordination is disrupted, and perhaps accounts for the challenges in phonological processing. These results suggest that, at least in the gamma band, enough coordination was shored up to the extent that the FFW networks statistically more closely resembled the TYP network, compared to the PRE session.

Limitations

Given our small sample size of nine participants after training, a replication at a larger scale with more participants would strengthen our results. Increasing our sample size would bolster our statistical power, adding confidence to the connectivity findings. More participants would also allow for a stronger experimental design that directly tests the contributions of the training program. As it stands, even though the readers went through training, the effects of the program are not able to be distinguished from normal

development or classroom instruction. With more participants, a variant of this experiment could also include a group of dyslexic students who would not participate in the training (e.g. waitlist), and could then be compared to the trained readers, thus more formally analyzing the additive effects of training on top of classroom instruction and general development.

Chapter 6: General Discussion

In a series of experiments, I have studied the fast dynamics of functional and effective connectivity in the brain during word reading in adults, as well as in typically developing and dyslexic children.

In Chapter 2, adult readers were examined to understand the typical developmental trajectory and time course of network connectivity in a reading task. This experiment showed how increasing the cognitive demands of written words elicits significant and widespread connectivity among reading-related sites. Stimuli with linguistic content (words) engaged frontal and temporal regions involved in semantic and phonological processing, whereas stimuli lacking this linguistic content (consonant strings) showed little-to-no such engagement.

Chapter 3 examined the differences in connectivity between dyslexic and typically developing 8-9 year old children during a lexical decision task. In particular, focusing on a critical moment in orthographic processing occurring 200-250 ms after word presentation, results indicated that dyslexic readers showed greater connectivity, especially among posterior occipito-temporal sites.

Just as with Chapter 3, Chapter 4 investigated the connectivity patterns of dyslexic children and typically developing readers prior to a reading intervention, again in this critical time window, showing comparable results between the two study populations. Chapter 5 then compared the connectivity patterns of the dyslexic children pre- and post-intervention. Following intervention, challenged readers showed significant improvements in assessment scores, which were coupled with a shift from posterior to anterior engagement of language regions.

Phase synchrony in the theta band proved to be the most revealing analysis throughout this program of research. First, showing in Chapter 2 how the brain processes linguistic content after the critical moment of orthographic processing and decoding in adults. In this same window of early decoding (200-250 ms) these connectivity results highlighted the involvement of right hemispheric processing in grade 2 dyslexic readers (Chapter 3). In a separate population (Chapter 4), theta-band synchrony showed how dyslexic and neurotypical readers diverge further in the organization of their reading networks by grades 4 and 5. Finally, after an intervention program (Chapter 5), the changes in this connectivity were correlated with reading performance, showcasing the importance of the right-hemispheric analog to the so-called visual word form area (VWFA) and its engagement with language processing areas in the prefrontal cortex.

Increased Connectivity, Cognitive Engagement, and Speed of Processing

The PLV and NBTE results from Chapter 2 suggest that an increase in cognitive engagement (words versus consonant strings) generates greater connectivity in a distributed fashion. As readers have to process additional levels of information (e.g. phonology, semantics), more connectivity is seen. Connectivity measures derived from oscillatory dynamics (PLVs and NBTE) have been shown to increase as a function of cognitive engagement (Palva et al., 2005; Shovon et al., 2014a; Shovon et al., 2014b; Shovon et al., 2016). However, this issue is not simply about whether the stimuli are more or less complex, but rather it is relative to each individual's required engagement during a task. It therefore makes sense that dyslexic readers would show greater connectivity in reading tasks compared to neurotypical readers, as they must exert more resources to accomplish the same goal. This phenomenon is reminiscent of general

learning studies which show increased activation of executive processing centers in the brain early in the learning process (Luna et al., 2001; Maurer et al., 2006; Maurer et al., 2008; Schlagger et al., 2002). However, as expertise in a skill increases, less active engagement is required. Price and Devlin (2011) address this in the context of reading, explaining how bottom-up sensory information and top-down predictions in reading networks are resolved in the visual word form area. This framework suggests that as a reader gains expertise, the top-down predictions in the reading network become more accurate, which facilitates the reading process and allows for faster, more efficient processing (see also: Johnson, 2011). However, during the early stages of learning or when encountering challenging or unfamiliar stimuli, more evaluation is needed to resolve the difference between these top-down predictions and bottom-up signals, increasing connectivity in the process. This principle appears especially strongly in Chapters 3 and 4, which demonstrate that dyslexic children displayed more connectivity compared to typical readers in the critical 200-250 ms window. Furthermore, the Pre-Post comparisons in Chapter 5 showed a reduction in connectivity after training, which was correlated to an increase in Woodcock-Johnson reading assessments. That said, the neural correlates of learning are not simply reflected as a uniform increase or decrease of network activity. Indeed, as a network becomes more efficient in certain types of processing, the timing of coordination with other regions may lead to increased activity therein. For example, after training in Chapter 5, greater improvements in reading performance were correlated with greater temporo-frontal connectivity, which typically would not be expected to occur until slightly later in time. We posit that this increase reflects a faster overall reading network that spends less time processing earlier

orthographic decoding, allowing for the earlier engagement of phonological processing centers.

It is tempting to expect a uniform reduction in activations and connectivity after training due to increasing expertise. Not all sites show reductions in activation, however. Temple and colleagues (2003) have shown activation increases in both left and right hemispheres, particularly in occipito-temporal and inferior frontal sites after training (see also: Eden et al., 2004). Other research groups have identified R.IFG as a key predictor of reading performance gains in dyslexic children, because increases in activation in this region during a reading task were correlated with improved performance (Hoeft et al., 2011).

If cognitive engagement for reading is indeed correlated with connectivity, this concept may be leveraged to get a sense of the developmental timing of critical checkpoints in the network dynamics underlying word reading. Just as with non-connectivity measures (e.g. ERPs), reductions in specific activity may signify increased experience and efficiency, such as in the prefrontal cortex as a skill becomes more practiced and expertise for this particular skill increases (Johnson, 2011). As well, reductions in activity may instead signify that the processing has sped up so as to be less apparent in the same time window as was originally observed. For example, when responding to novel stimuli, the latency for the P300 ERP component in babies occurs much later than in adults. However, we do not say that the babies show reduced activity over time; rather, the activity occurred sooner for the adults. As they become more proficient readers, we posit that the post-intervention connectivity reductions reflect, in fact, a faster shift in the network processing which allows for earlier engagement of

frontal regions.

This idea is partly why the window of 200-250 ms was chosen for scrutiny. The reason for such close examination of the 200-250 ms window is that it captures the transition from bottom-up, early visual and pre-lexical orthographic processing (i.e. the N170 component that in children occurs at ~220 ms in area vOT) and the engagement of later-stage processes, such as phonology and semantics. If the N170 represents the interface between bottom-up visual processing and top-down linguistic processes (Price & Devlin, 2011), then the connectivity patterns surrounding this moment should show increased posterior connectivity (occipito-temporal) before intervention, and greater anterior engagement after (e.g. fronto-temporal). Prior to the reading intervention, challenged readers showed theta-band connectivity primarily in posterior cortical regions, suggesting that even though orthographic processing was occurring (i.e. the N170 peak at ~220 ms), frontal sites were engaged only at a minimal level. However, after the intervention, these readers showed increased frontal engagement.

Ultimately, as a group, challenged readers did not show significant gains in behavioural performance. However, for children who *did* improve after training, their gains were correlated with connectivity involving the vOT region in the right hemisphere. These underlying network patterns did not fully resemble those of typically developing readers, suggesting the usage of alternative pathways even after training. However, regardless of which pathways were used, the increased speed at which challenged readers' networks eventually shifted out of posterior low-level processing, along with the engagement of frontal sites, seems like a promising outcome.

Limitations

CSD and Localization

It is a worthwhile endeavor to implement source localization techniques when attempting to answer questions about brain activity, as raw scalp data can be noisy and highly inter-correlated. One limitation of CSD is that it is essentially still “just” scalp data, albeit refined and de-correlated to some extent from the contributions of neighboring regions. Many studies have found success with this technique, as it is particularly well-suited for localizing shallow sources (i.e. cortical sources near the scalp; Hjorth, 1975; Hjorth, 1991). However, CSD may not be the most accurate form of source localization.

In a more comprehensive follow-up study, it may be wise to use structural MRI scans from the children being assessed in order to aid the localization of EEG activity so that a more complete understanding of the underlying connectivity may be developed. Alternatively, representative structural scans may be taken from existing repositories that may be used as surrogates for the children in the study. Improved head models based on these scans might contribute to more accurate representations of connectivity in the brain by reducing spurious artefacts generated by other nearby sources.

An alternative to CSD and the localization techniques used here is independent component analysis (ICA) coupled with dipole fitting to localize EEG activity (Bedo et al., 2014; Makeig and Delorme, 2004). Through an iterative computational process, ICA produces independent sources of activity derived directly from the EEG signal; dipole fitting then spatially maps these independent signals onto head models to localize the “true” underlying activity from the EEG. This process is distinct from CSD in that it

produces mathematically independent signals, whereas CSD effectively increases the contrast to minimize the impact of each signal on the other neighboring signals. ICA and dipole fitting are not without their faults, however, as the techniques can sometimes over- or under-fit the activity to the head space, as well as making signals “too” independent, splitting a true source into two distinct sources based on different features of that brain activity. Moreover, since these techniques are used in conjunction with EEG, they still highly benefit from MRI scans to improve their fidelity. Some studies have actually found success in combining ICA and CSD to localize brain activity as well as correct for artefacts (Fitzgibbon et al., 2015).

Missing Expected Connectivity

One of the main concerns when performing many statistical tests is the emergence of spurious false positives. One aspect of the statistical techniques used here was a binomial test as a means of consolidating the results of significant t -tests into 50 ms bins. Rather than worrying about experiment-wise error generated by so many individual tests, we believe that this approach is actually quite conservative, and thus is probably missing some real connectivity rather than showing spurious connectivity. The approach used here requires substantially consistent connectivity over time within a particular frequency band to be considered significant, which almost certainly guarantees omission of spurious connectivity, but also may exclude instances of “real” connectivity that lasts less than 25 ms.

This approach likely also misses some important connectivity because we are working with children. There is a huge variation in the neuro-cognitive developmental process across participants. At the age of these participants (6-10 years old), brains are

extremely plastic, and in the case of reading, may not yet be sufficiently specialized. This includes even the good readers. This affects not only the activation amplitudes and latencies, but also the spatial distribution of activity (Brem et al., 2010; Johnson, 2011; Shaywitz et al., 2002); so even if our techniques can localize the relevant brain activity, the sources are more diffuse. Moreover, very little research exists showing the development of dyslexic brain activity over time, and even less so the connectivity dynamics. As such, since we do not fully understand the developmental trajectories of these regions and their overarching networks, it is difficult to pinpoint specific instances of connectivity as being atypical or developmentally perturbed.

Consider, for example, area L.vOT. In typically developing readers, this region becomes more specialized and efficient with more practice and experience (Cohen et al., 2000; Dehaene, 2009). This outcome is much less reliable in dyslexia, given the functional and neuro-anatomical differences throughout development (Galaburda et al., 1985; Galaburda, 2004; Stein, 2001; Stein & Talcott, 1999). Dyslexic brains do not follow this trajectory in the same way, in that they also utilize their right hemisphere analog (R.vOT) much more than controls, to the point of being almost bilateral (compared to being almost completely localized to the left hemisphere in typical fluent readers). So when dyslexic readers “naturally” improve in reading ability, it is unclear whether one should expect the left hemisphere to improve in efficiency, or if it makes more sense to optimize the bilateral networks already in place. Furthermore, when reading interventions target the underlying issues of dyslexia (e.g. phonological processing, frequency discrimination, and sound segmenting), do *those* improvements reflect a shift to a “repaired” left-lateralized reading network? Or again, is it about

optimizing the existing neural architecture? These considerations are not adequately addressed by the literature at present, and so it is difficult to know what sorts of activation and connectivity dynamics are expected or typical or atypical, especially at later stages of processing (>300 ms).

Many more studies will be required to understand the developmental course for typical readers' networks, and probably even longer for dyslexic readers.

PLV and NBTE Discrepancies and Limitations

When comparing PLV and NBTE results, it is clear that the results from the two techniques diverge considerably at times, which impacts their interpretability. Ultimately, phase synchrony and transfer entropy are very different mathematically and address the data in very different ways (simultaneous oscillatory phase difference measure versus information measure computed using lagged phase and amplitude). Thus, somewhat different results are expected based on the distinct theoretical assumptions underlying each technique (see Chapter 2 methods). Ultimately, the detailed relationships between these and other techniques used to reveal interactions between brain regions, such as dynamic causal modeling, remain to be explored further.

Finally, both our PLV and TE analyses were bivariate (computed on individual pairs of channels) and thus we could have some spurious PLV or TE results if a third source was functionally or causally involved with both of the channels in a given pair. Given our conservative criteria, we do not believe this is a serious problem, but it could be alleviated by further implementation of multivariate PLV and TE analyses.

Future Directions

The experiment in Chapter 5 measured connectivity after an intervention

program, but due to our limited pool of participants, we could not include a “waiting list” group to see the additive effect of the intervention over normal school instruction. This was the first experiment out of a more comprehensive campaign to understand dyslexia, so a larger-scale study would allow us to specifically target this question.

In general, the results from these studies highlight the need to understand the developmental trajectories of reading networks in typical and dyslexic readers. Currently, there is much uncertainty as to how a lot of these results should be interpreted because the existing information about brain connectivity is extremely limited. If connectivity patterns were tracked throughout development, we might come to understand the neural connectivity signatures of a typical reader or that of a dyslexic reader. Further, these signatures could be adapted into machine learning algorithms that can make predictions about the performance outcomes of developing children based on their connectivity patterns.

Conclusion

Over a series of experiments, I examined the brain connectivity dynamics of neurotypical and dyslexic readers in two distinct populations and showed that these two groups utilize different networks to process written language. Not only were these networks different in general configuration, but also in the amount of resources and time needed to process the same information. The reading networks of the dyslexic children suggested that they spent more time evaluating the visual and orthographic properties of words, while the typically developing classmates were already engaging brain regions responsible for higher-level language processing. However, after targeted reading training, the challenged readers’ brain networks seemed more closely aligned with those

of their classmates with regard to the general progression of activity (a shift from posterior to anterior processing), while still utilizing distinct pathways to accomplish this. These findings highlight the value of connectivity analyses in understanding the nuances of reading in the brain, and how remediation programs such as FastForWord alter brain development as a means of improving reading performance.

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Appendix A: Time Course of Theta PLVs

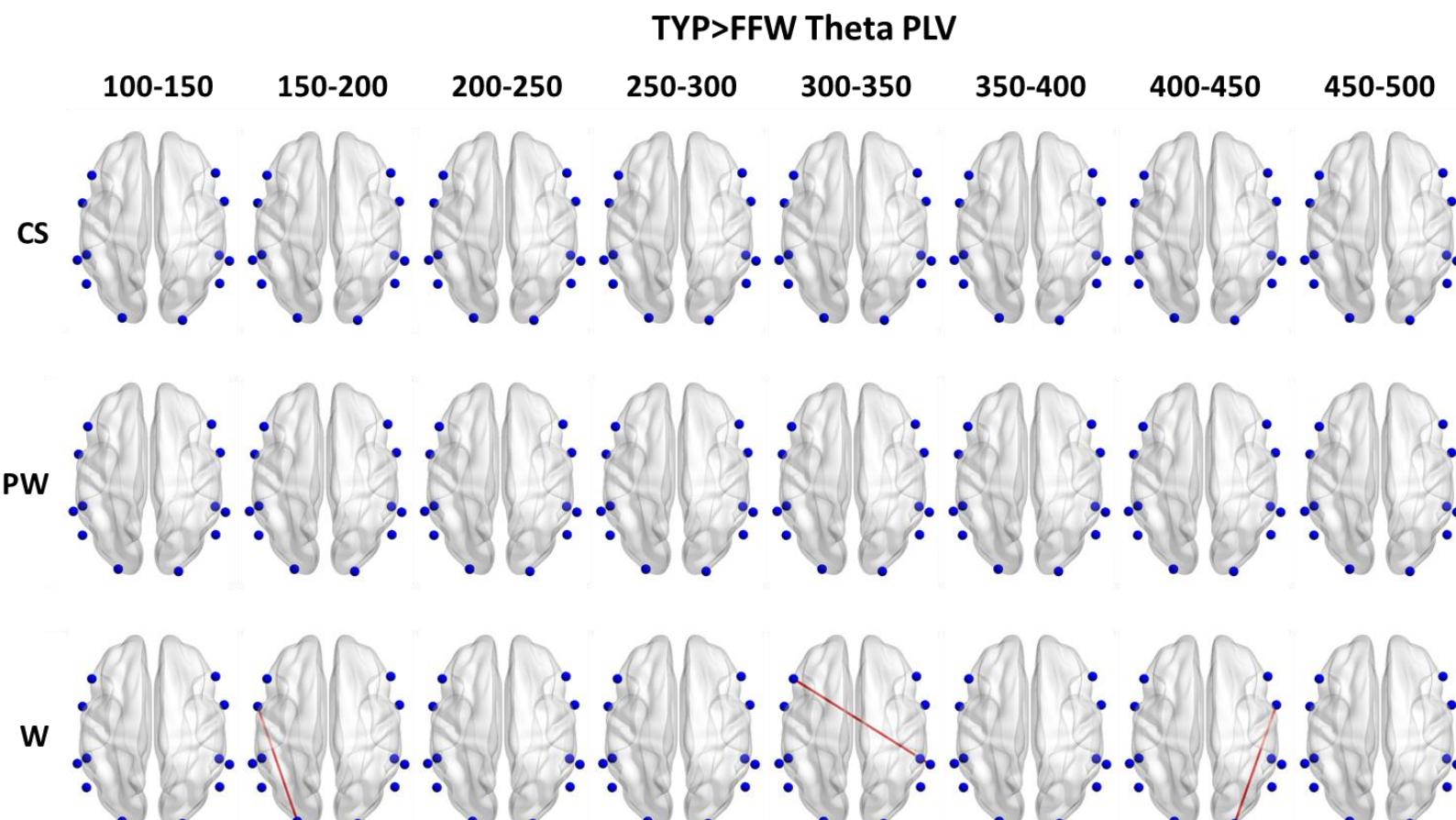


Figure A.1. Time course of theta-band synchrony (functional connectivity) where typically developing readers (TYP) showed greater connectivity than readers enrolled in the FastForWord (FFW) intervention program. Time bins are in milliseconds following stimulus presentation. CS=Consonant Strings; PW=Pseudowords; W=Words.

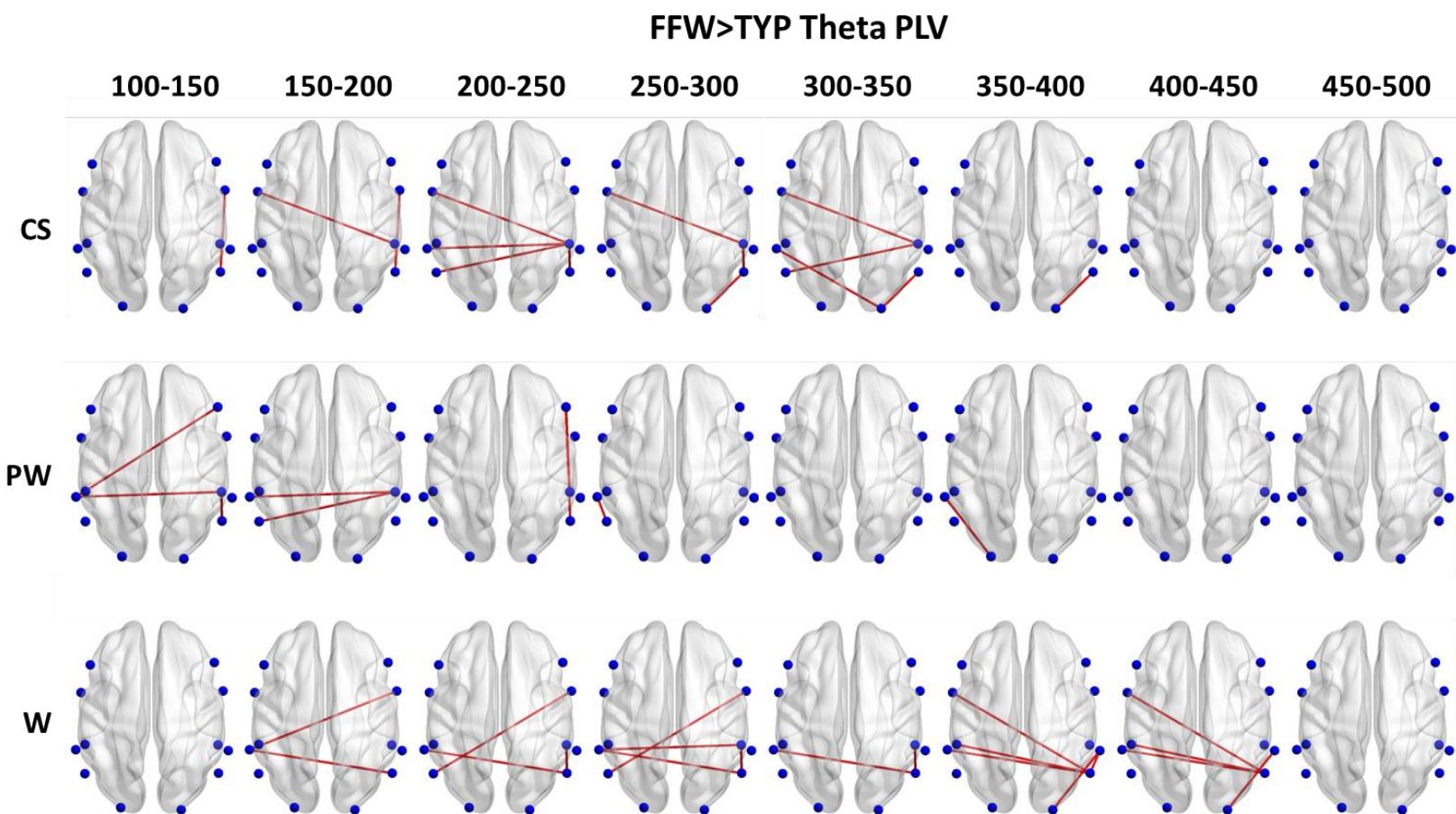


Figure A.2. Time course of theta-band synchrony (functional connectivity) in which FFW readers showed greater connectivity than TYP readers. Time bins are in milliseconds following stimulus presentation. CS=Consonant Strings; PW=Pseudowords; W=Words.

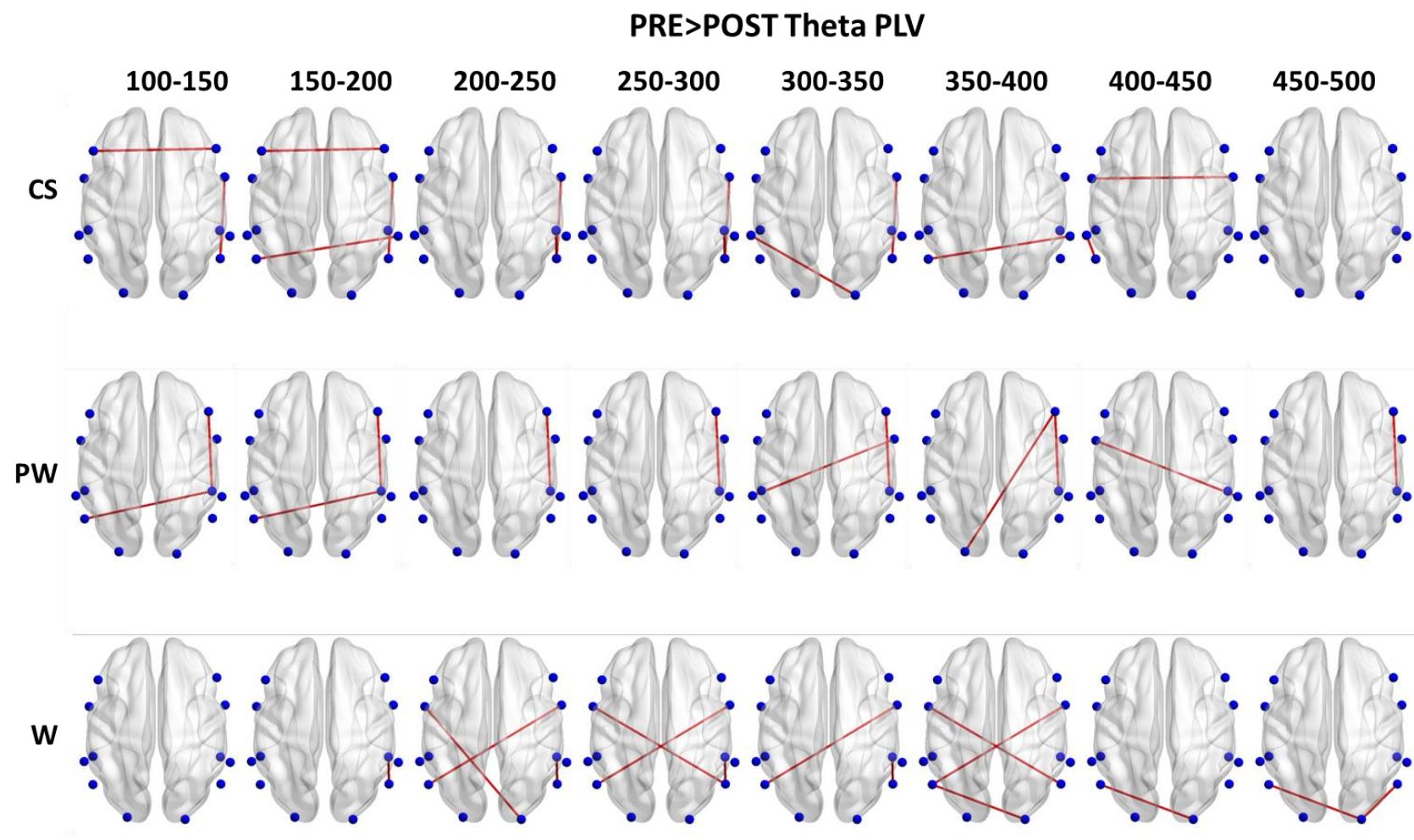


Figure A.3. Time course of theta-band synchrony in which FFW readers showed greater connectivity before intervention (PRE) than after intervention (POST). Time bins are in milliseconds following stimulus presentation. CS=Consonant Strings; PW=Pseudowords; W=Words.

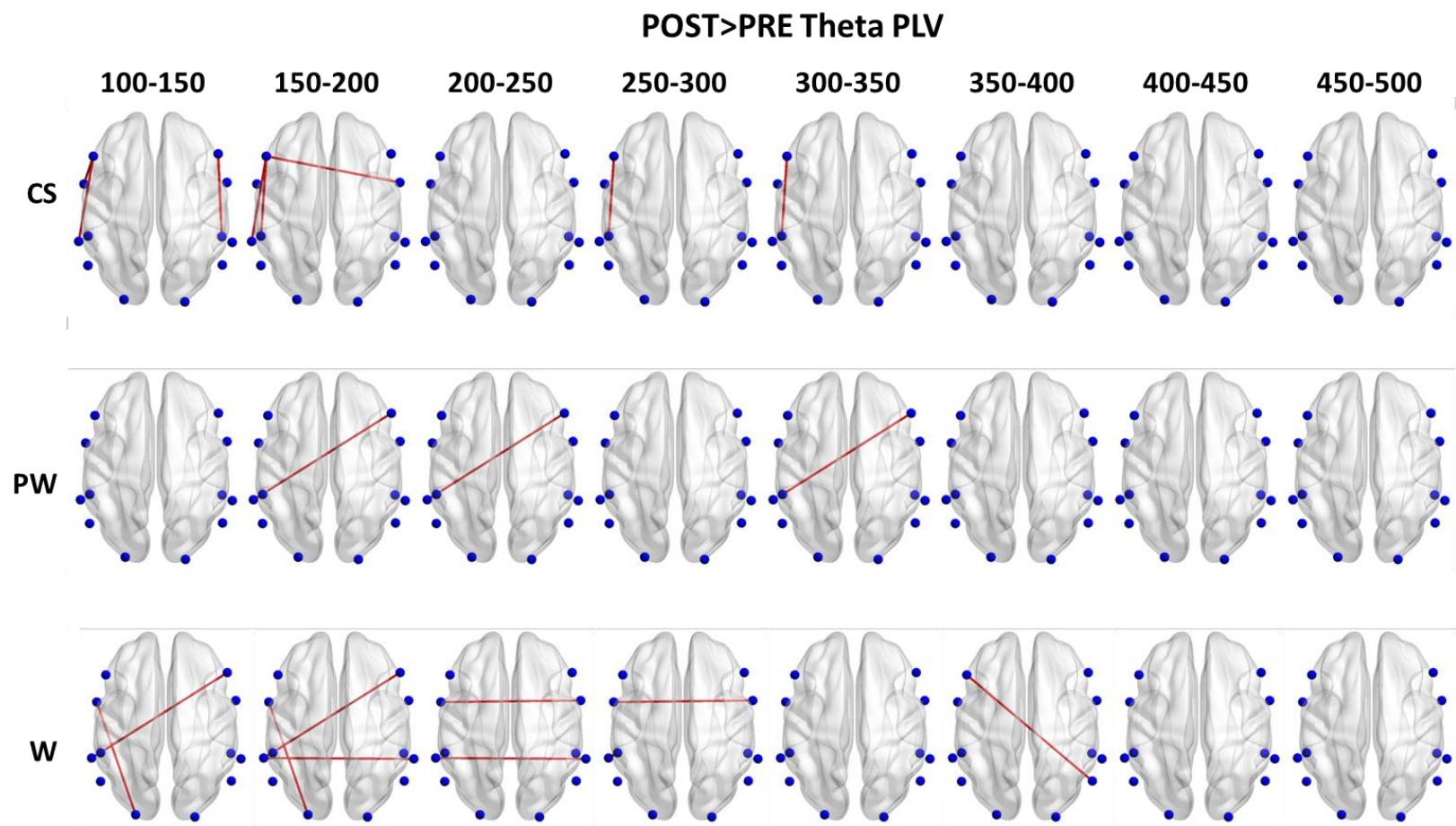


Figure A.4. Time course of theta-band synchrony in which FFW readers showed greater connectivity after intervention (POST) than before intervention (PRE). Time bins are in milliseconds following stimulus presentation. CS=Consonant Strings; PW=Pseudowords; W=Words.

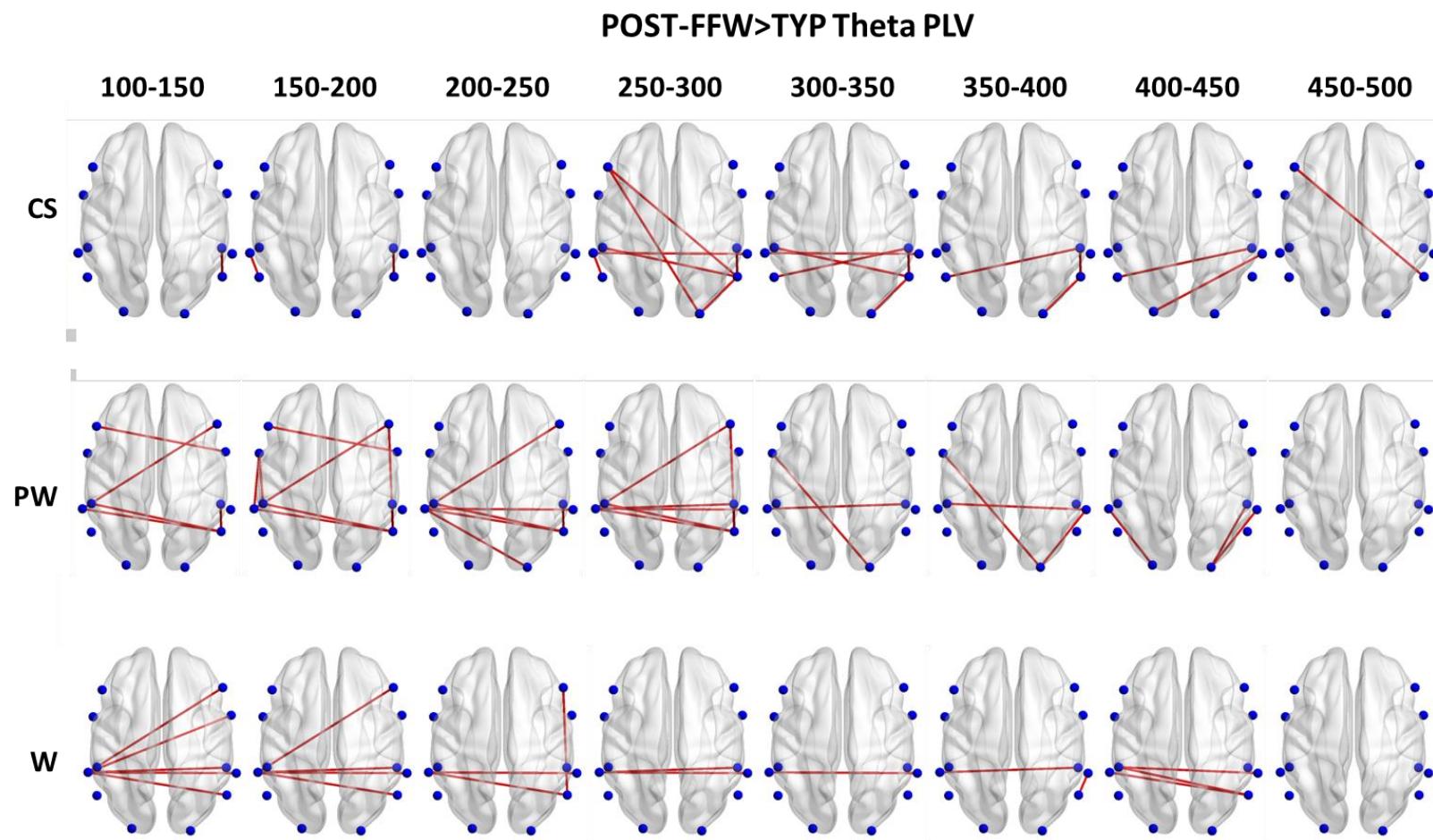


Figure A.5. Time course of theta-band synchrony in which FFW readers after intervention (POST-FFW) showed greater connectivity typically developing readers (TYP). Time bins are in milliseconds following stimulus presentation. CS=Consonant Strings; PW=Pseudowords; W=Words.

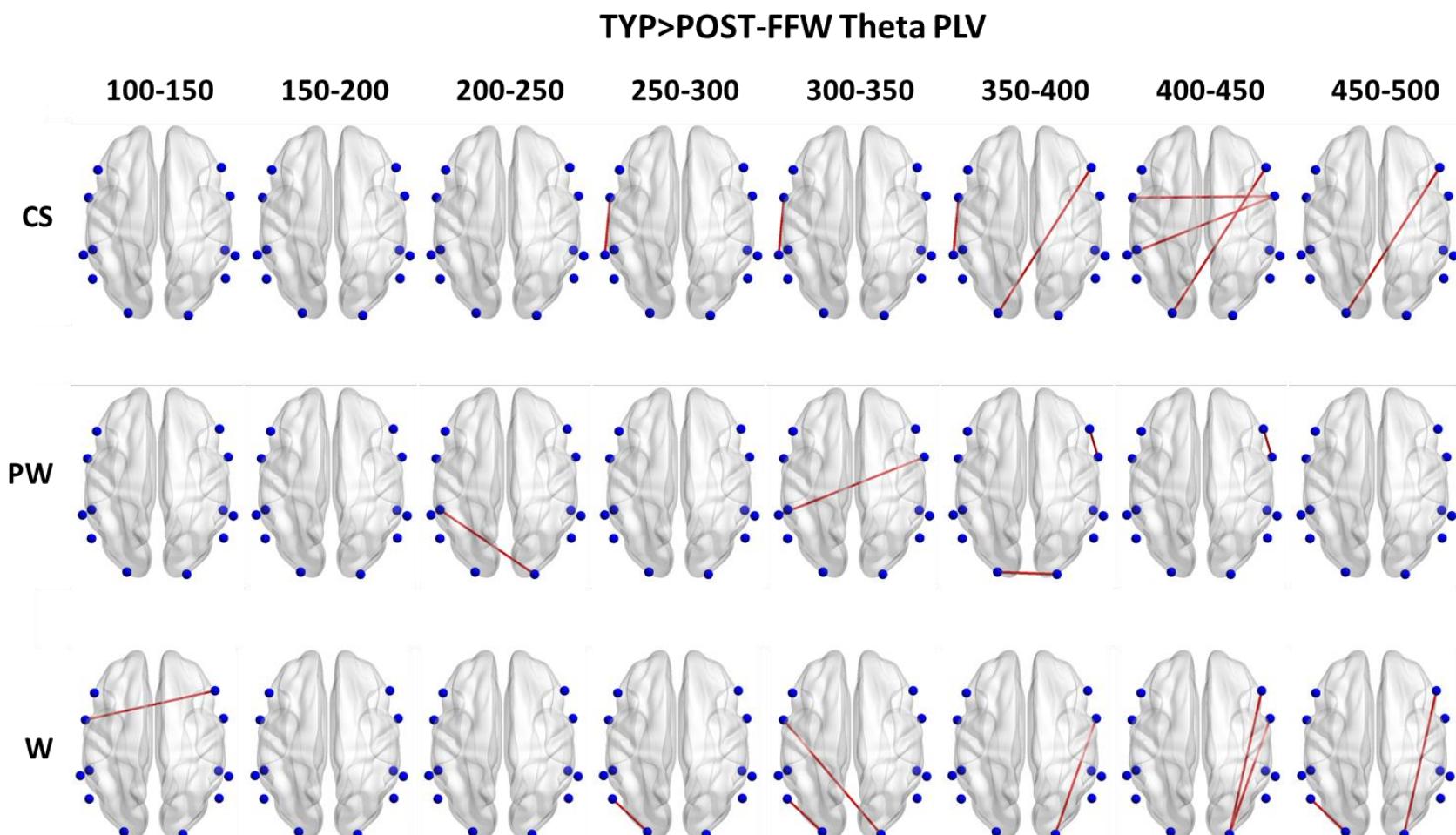


Figure A.6. Time course of theta-band synchrony in which typically developing readers (TYP) showed greater connectivity than FFW readers after intervention (POST-FFW). Time bins are in milliseconds following stimulus presentation. CS=Consonant Strings; PW=Pseudowords; W=Words.