

Electronic Thesis and Dissertation Repository

---

10-7-2020 10:00 AM

## Examining Brain Connectivity and Reading Ability in Children

Alexandra M. Cross, *The University of Western Ontario*

Supervisor: Archibald, Lisa M. D., *The University of Western Ontario*

Co-Supervisor: Joannis, Marc F., *The University of Western Ontario*

A thesis submitted in partial fulfillment of the requirements for the Doctor of Philosophy degree in Health and Rehabilitation Sciences

© Alexandra M. Cross 2020

Follow this and additional works at: <https://ir.lib.uwo.ca/etd>



Part of the [Neurosciences Commons](#)

---

### Recommended Citation

Cross, Alexandra M., "Examining Brain Connectivity and Reading Ability in Children" (2020). *Electronic Thesis and Dissertation Repository*. 7356.

<https://ir.lib.uwo.ca/etd/7356>

This Dissertation/Thesis is brought to you for free and open access by Scholarship@Western. It has been accepted for inclusion in Electronic Thesis and Dissertation Repository by an authorized administrator of Scholarship@Western. For more information, please contact [wlsadmin@uwo.ca](mailto:wlsadmin@uwo.ca).

## **Abstract**

In this thesis, I investigated the relationship between functional and structural connectivity and reading ability in children. Prior research has tended to use single word reading measures or composite measures, however this is problematic as reading is a complex skill relying on multiple subskills, such as decoding efficiency, sight word reading efficiency, reading comprehension, and rapid automatized naming. As a result, the multifaceted relationship between brain connectivity and reading ability is not well understood. I aimed to address this issue by considering multiple reading subskills while examining the neural substrates of reading. In Chapter 2, I examined how individual differences in decoding efficiency, sight word reading efficiency, reading comprehension, and rapid automatized naming relate to resting-state functional connectivity from regions of the brain's reading network. I found that distinct functional networks in both hemispheres of the brain support different components of reading in children. In Chapter 3, I built on these findings to examine how individual differences in the same reading subskills are associated with structural connectivity in reading-related white matter tracts, as measured by diffusion tensor imaging. Similar to Chapter 2, the results of Chapter 3 suggested that different components of reading ability are supported by structural characteristics in distinct bilateral tracts of the brain. Importantly, many of the effects observed in Chapters 2 and 3 were found to be specific to reading subskills and were not associated with more general cognitive abilities. In Chapter 4, I examined how improvements in reading ability are related to changes in structural and functional connectivity, by measuring brain connectivity pre- and post-intervention in a group of children with reading disability. I also investigated whether individual differences in the amount of improvement in reading ability post-intervention was

predicted by pre-intervention brain connectivity. I found that gains in reading ability were associated with changes in resting-state functional connectivity, particularly between reading-related regions and frontal regions as well as regions of the default mode network. Changes in white matter microstructure of the right arcuate fasciculus were strongly associated with gains in single word reading abilities. Additionally, results showed that distinct pre-intervention characteristics of resting-state functional connectivity and white matter integrity predicted the magnitude of subsequent gains in reading ability following the reading intervention. Chapter 5 summarizes the findings of this thesis in relation to the current literature and presents recommendations for future research on reading ability and brain connectivity.

**Keywords**

Reading ability, reading disability, reading development, resting-state functional connectivity, magnetic resonance imaging, diffusion tensor imaging

## Lay Summary

Reading is an extraordinarily complex skill. Readers must fluently integrate visual information about letters and words with their knowledge of the sounds of their language, and map this onto their existing conceptual knowledge in order to successfully understand what they are reading. Many previous neuroimaging studies have shown that the brain regions supporting reading are widely distributed across the brain, and that connections between these brain regions are important for supporting coordinated processing across this complex, widespread network. However, as previous studies have tended to use composite measures of reading ability, the distinct roles of these connections in supporting different types of skills involved in reading are not well understood. For example, reading relies on one's ability to rapidly recognize letters and familiar words, decode unfamiliar words, and understand sentences. The goal of this thesis was to explore the role of connectivity between these brain areas in supporting different aspects of reading in school-aged children.

In the first two studies described in this thesis, I investigated how coordinated activity among different brain regions and anatomical connections between these regions were associated with different subskills of reading in children. The results of these studies showed that distinct networks of coordinated activity and distinct anatomical connections in both hemispheres of the brain were important for supporting different components of reading ability. In my third study, I was interested in extending these findings to examine how improvements in reading ability are related to changes in brain connectivity. Children in this final study were struggling readers who were participating in an intensive reading intervention program at their school. Results showed that improvements in reading ability were associated with measurable changes in anatomical connections and coordination of activity in the brain. Overall, the findings of the present thesis further our understanding of

the role of brain connectivity in supporting distinct aspects of reading ability. Additionally, they shed new light on the changes in the brain that underlie improvements in reading ability in struggling readers who receive reading intervention.

## **Co-Authorship Statement**

The chapters of this dissertation are being prepared for submission to scientific journals. The presented data are based on a series of collaborative research projects; however all analyses were performed and manuscripts were written by Alexandra M. Cross with feedback from Marc F. Joannis and Lisa M.D. Archibald.

## Acknowledgments

First and foremost, thank you to my co-supervisors Drs. Lisa Archibald and Marc Joannisse. Marc, thank you for taking a chance on me 7 years ago, and keeping me on 5 years ago, despite my insistence that I did not have the prerequisites needed for the programs I was applying to. Lisa, thank you for welcoming me to the lab and to elevenses before I was even an official LWM lab member. Both of you have gone out of your way to open new doors for me, both as a graduate student and as a future speech-language pathologist. While I have learned a great deal from each of you about being a good scientist, I have learned even more about being an excellent mentor.

I would also like to acknowledge the other scientists and clinicians I have worked with along the way. Thank you to my advisory committee member, Dr. Janis Cardy, for your valuable insight and guidance throughout the development and completion of this thesis and throughout the combined program. Thank you to the HRS Speech and Language Sciences students and faculty for helpful feedback during many SLS seminar presentations. Thank you to members of the Brain and Mind Institute, for creating such a rich and welcoming research environment, and to BrainsCAN, for the reduced scanning rates that helped make this longitudinal MRI project possible. Thank you to collaborators on these projects, including Karen Steinbach, Maureen Lovett, and Jan Frijters, for your thoughtful feedback and your support of this work over the course of the last five years.

I would like to thank the past and present members of the LRCN lab, Nicolette, Emily, Joe, Christine, Leah, Chenglin, Felix, Christina, Lien, Jessica, Krystal; the LWM lab, Areej, Laura, Nicolette, Meghan, Alyssa, Theresa, Taylor; and the Elborn shared lab, for your academic support, friendship, and lunchtime entertainment over the years. Thank you especially to Rachael for always being there to chat about speech or research or life, and for

keeping me on track with our writing goal calendar and Zoom writing sessions when everything shut down for COVID-19.

To my family, thank you for being the most loving and supportive family I could ever ask for. Dad: thank you for spending a great deal of your free time thinking about my research and various problems I encountered along the way. Your thoughtful questions and countless diagrams helped me a great deal in writing this thesis. Mom: thank you for your endless encouragement and for reminding me to be a Cross-boss like you when I needed to be one.

And finally, to Ryan: I am certain that without you, writing this dissertation would have been a much longer and more unpleasant process. Thank you for making the last few years the happiest years of my life.



# Table of Contents

Abstract.....	ii
Lay Summary.....	iv
Co-Authorship Statement.....	vi
Acknowledgments.....	vii
Table of Contents.....	ix
List of Tables.....	xi
List of Figures.....	xii
List of Appendices.....	xiv
Chapter 1: Introduction.....	1
1.1 Cognitive Models of Reading and RD.....	2
1.2 Cognitive Subskills Associated with Reading.....	7
1.2.1 Single word reading skills.....	7
1.2.2 Reading comprehension.....	8
1.2.3 Rapid naming.....	9
1.2.4 Summary.....	10
1.3 Neural Basis of Reading and RD.....	10
1.3.1 Neuroimaging studies of reading ability and RD.....	10
1.3.2 Brain connectivity.....	14
1.4 Relevant Issues in Brain Connectivity Research of Reading.....	20
1.5 Objectives and Overview.....	21
Chapter 2: Resting-State Functional Connectivity Correlates of Reading Subskills in Children.....	34
2.1 Introduction.....	34
2.2 Methods.....	41
2.2.1 Participants.....	41
2.2.2 Procedures.....	41
2.2.3 MRI acquisition and processing.....	43
2.3 Results.....	47
2.3.1 Behavioural results.....	47
2.3.2 Functional connectivity results.....	49
2.4 Discussion.....	60
2.4.1 Positive RSFC-behaviour relationships.....	60
2.4.2 Negative RSFC-behaviour relationships.....	64
2.4.3 Conclusions.....	68
Chapter 3: DTI Connectivity Correlates of Reading Subskills in Children.....	78
3.1 Introduction.....	78
3.2 Methods.....	85
3.2.1 Participants.....	85
3.2.2 Behavioural measures.....	86
3.2.3 MRI acquisition and processing.....	87
3.3 Results.....	90
3.3.1 Behavioural results.....	90
3.3.2 DTI connectivity results.....	91
3.4 Discussion.....	105
3.4.1 Conclusion.....	111

Chapter 4: Functional and Structural Connectivity and Reading Intervention in Children	119
4.1 Introduction	119
4.2 Methods	127
4.2.1 Participants	127
4.2.2 Procedures	127
4.2.3 Intervention	129
4.2.4 MRI acquisition and processing	131
4.2.5 Resting-state fMRI data processing and analysis	131
4.2.6 DTI data processing and analysis	134
4.3 Results	137
4.3.1 Behavioural results	137
4.3.2 Changes in resting-state functional connectivity over time	140
4.3.3 Changes in DTI connectivity over time	144
4.3.4 Resting-state functional connectivity predictors of response following intervention	147
4.3.5 DTI predictors of behavioural response following intervention	150
4.4 Discussion	152
4.4.1 Resting-state functional connectivity and reading intervention	153
4.4.2 DTI connectivity and reading intervention	158
4.4.3 Conclusions	162
Chapter 5: General Discussion	172
5.1 Relevant Findings	172
5.1.1 Brain connectivity correlates of individual differences in reading subskills	172
5.1.2 Brain connectivity and reading intervention in RD	177
5.2 Directions for Future Research	181
Appendices	189
Curriculum Vitae	201

## List of Tables

<b>Table 2.1</b> MNI Coordinates of Seed ROIs. ....	45
<b>Table 2.2</b> Descriptive statistics for behavioural tasks. ....	48
<b>Table 2.3</b> Pearson’s correlations among behavioural measures and motion parameters. ....	49
<b>Table 3.1</b> Descriptive statistics for behavioural tasks. ....	91
<b>Table 3.2</b> Pearson’s correlations among behavioural measures. ....	92
<b>Table 4.1</b> MNI coordinates of centre of seed ROIs. ....	133
<b>Table 4.2</b> Demographic characteristics of the sample. ....	138
<b>Table 4.3</b> Intervention progress monitoring data collected in RI group. ....	138
<b>Table 4.4</b> Summary of significant interaction effects in resting-state functional connectivity data. ....	141

## List of Figures

<b>Figure 2.1</b> Seed regions of interest.....	46
<b>Figure 2.2</b> Significant seed-to-voxel clusters for the decoding task (A and B) and sight word reading task (C and D) by seed region.....	51
<b>Figure 2.3</b> Significant seed-to-voxel clusters for the reading comprehension task (A, B, C, and D) and RAN task (E) by seed region. ....	52
<b>Figure 2.4</b> Significant seed-to-voxel clusters for the decoding task when controlling for sight word reading (A), nonverbal intelligence (B), and RAN (C&D). ....	54
<b>Figure 2.5</b> Significant seed-to-voxel clusters for the reading comprehension task when controlling for sight word reading (A&B), decoding (C), RAN (D), and nonverbal intelligence (E).....	58
<b>Figure 2.6</b> Significant seed-to-voxel clusters for connectivity from IFGtri seed for the RAN task when controlling for sight word reading (A), decoding (B), reading comprehension (C), and nonverbal intelligence (D). ....	59
<b>Figure 3.1</b> White matter correlations of FA and reading sub-skills in the left arcuate fasciculus, controlling for age.....	96
<b>Figure 3.2</b> White matter correlations of FA and reading sub-skills in the right arcuate fasciculus, controlling for age.....	97
<b>Figure 3.3</b> White matter correlations of FA and reading sub-skills in the left uncinate fasciculus, controlling for age.....	101
<b>Figure 3.4</b> White matter correlations of FA and reading sub-skills in the right uncinate fasciculus, controlling for age.....	102
<b>Figure 3.5</b> White matter correlations of FA and reading comprehension in the right ILF, controlling for age.....	103
<b>Figure 4.1</b> Seed regions of interest.....	134
<b>Figure 4.2</b> Percent change from pre- to post-intervention for each progress monitoring task. ....	139
<b>Figure 4.3</b> Seed-to-voxel clusters showing significant group by time interaction.....	142
<b>Figure 4.4</b> Seed-to-voxel clusters showing significant association with change in behavioural scores .....	144

<b>Figure 4.5</b> Significant main effects of time in the right arcuate fasciculus (A) and right uncinata fasciculus (B).....	146
<b>Figure 4.6</b> Correlation between change in FA and change in multi-syllabic reading scores within the right arcuate fasciculus. ....	147
<b>Figure 4.7</b> Seed-to-voxel clusters showing significant association between Time 1 RSFC and change in reading skills.....	149
<b>Figure 4.8</b> Correlations between FA and change in reading skills. ....	152

## List of Appendices

<b>Appendix A:</b> Letter RAN task administered in studies in Chapters 2 and 3 .....	189
<b>Appendix B:</b> Informal intervention progress monitoring materials administered in study described in Chapter 4 .....	190
<b>Appendix C:</b> Ethics approval for the studies described in Chapters 3, 4, and 5.....	200

## Chapter 1: Introduction

Reading is a complex skill involving many different cognitive processes and types of representations. Readers must fluently integrate visual information about letters and words with their knowledge of the sounds of their language, and map this onto semantic knowledge in order to successfully understand what they are reading. Advances in neuroimaging technology have significantly increased understanding of the neural substrates of this complex process, showing that proficient reading relies on activity in regions distributed across all lobes of the brain. However, studies of localized brain activity can only capture a part of the neurobiology of reading, as fluent and accurate reading requires coordinated processing among these localized brain regions. Much remains to be understood regarding the role of structural connections and coordinated activity among brain regions in order to support the different cognitive processes involved in reading. My research seeks to examine the brain networks underlying reading ability in children, specifically with respect to the functional and structural connections in the brain that support reading processes and skill development.

Much of previous neuroimaging research on reading has focused on comparisons of typical readers and individuals with reading disability (RD), also known as developmental dyslexia, with the goal of elucidating the neural bases of reading ability. Approximately 10% of otherwise typically developing children have RD (Lyon, Shaywitz, & Shaywitz, 2003), which is characterized by difficulty reading words fluently and accurately. RD has been linked to specific differences in localized brain function (Maisog, Einbinder, Flowers, Turkeltaub, & Eden, 2008; Paulesu, Danelli, & Berlinger, 2014; Richlan, Kronbichler, & Wimmer, 2009, 2011). However, research has only

recently begun to uncover differences in RD with respect to structural connections and coordinated activity among these localized brain regions.

Thus, although more recent neuroimaging research has begun to capture the role of the brain in reading ability and disability, the relationship between brain connectivity and individual differences in reading is not well understood. In this chapter, I will describe current cognitive and neurobiological models of reading and RD. I will then discuss the potential application of recent methodologies for examining functional and structural brain connectivity, and briefly detail current gaps in the literature with respect to brain connectivity research on reading.

### **1.1 Cognitive Models of Reading and RD**

In order to understand the neural bases of reading, it is necessary to understand the complex cognitive processes involved in integrating visual and auditory information that are necessary for efficient reading. Many models of reading have been proposed to explain the cognitive processes underlying reading and to account for the impairments observed in RD. Two models of word identification that have received the most research attention are the *dual route cascaded* model (Coltheart, Rastle, Perry, Langdon, & Ziegler, 2001) and various *connectionist* models of reading (Harm & Seidenberg, 1999, 2004; Plaut, McClelland, Seidenberg, & Patterson, 1996; Seidenberg & McClelland, 1989; for a review see Seidenberg, 2005).

The dual route cascaded model proposes that words can be identified via either a direct or indirect route (Coltheart et al., 2001). The more direct, lexical non-semantic route involves mapping orthographic representations of words directly onto phonological representations, while the indirect grapheme-phoneme correspondence route requires



application of knowledge of grapheme-phoneme correspondence rules in order to map graphemes onto phonological representations. The lexical non-semantic route is thought to be used for reading of familiar words and words with irregular spellings, while the grapheme-phoneme correspondence route allows for decoding of words that are unfamiliar to the reader.

In contrast, the connectionist models of reading assume that words are read via activation that propagates from units representing orthography to units representing phonology (Harm & Seidenberg, 1999, 2004; Plaut, McClelland, Seidenberg, & Patterson, 1996; Seidenberg & McClelland, 1989). Rather than representing words locally, as is proposed by dual route models, connectionist models propose distributed representation, in which the activation of many units in the system represent a word. Typically, connectionist models include layers of “hidden” units in between levels of representations, which allow the model to learn and represent more complex relationships between representations. Importantly, orthographic and phonological information contain statistical regularities, allowing these models to learn rules via repeated exposure to quasi-regular patterns in language and strengthening of the activated connections. As a result, words that are encountered frequently can be read more quickly and accurately than infrequent or novel words. While the dual route model distinguishes between two discrete routes for reading, connectionist models posit that reading is always a division of labour among the two routes, such that no single word is read by relying solely on one pathway.

A number of theories of RD have also been proposed in order to explain the impairments observed in individuals with RD. The most prominent of these theories are

phonological theories of RD, which propose that the core feature of RD is an impairment in representation, storage, or retrieval of speech sounds (Liberman, Shankweiler, & Liberman, 1989; Ramus et al., 2003). Because learning to read relies on learning associations between orthographic and phonological information, degraded phonological representations or an impairment in storing and/or retrieving these representations can greatly impact learning of these relationships and, in turn, the ability to decode words. Neurologically, this is generally attributed to dysfunction of brain areas supporting representation of phonological information or connections between areas supporting phonological and orthographic information.

Alternatives to phonological theories have also been proposed to explain the broader deficits that are sometimes linked to RD. Evidence that rapid naming and phonological processing were independent predictors of RD led Wolf and Bowers (1999) to propose the double deficit hypothesis. This hypothesis proposes that rapid naming deficits can cause RD, either in the absence of or in addition to phonological deficits. The rapid auditory processing theory (Tallal, 1980) postulates that phonological impairments in RD are caused by deficits in rapid auditory processing. Within this view, RD involves an impairment in perceiving brief or rapidly changing sounds, resulting in a secondary deficit in phonological representations. Visual theories of RD (Livingstone, Rosen, Drislane, & Galaburda, 1991; Lovegrove, Bowling, Badcock, & Blackwood, 1980) consider RD to be an impairment in visual processing of letters and words. Biologically, this is proposed to be associated with a disruption of the magnocellular pathway of the visual system, impacting binocular control and visuospatial attention (Hari, Renvall, & Tanskanen, 2001; Stein & Walsh, 1997). The cerebellar theory of RD (Nicolson &

Fawcett, 1990; Nicolson, Fawcett, & Dean, 2001) postulates that RD results from dysfunction of the cerebellum. Within this view, the cerebellum's role in motor control is thought to result in poor articulation, leading to impaired phonological representations. Additionally, cerebellar involvement in automatization of tasks is thought to impact ability to learn grapheme-phoneme correspondences. The magnocellular theory of RD (Galaburda, Menard, & Rosen, 1994; Livingstone et al., 1991; Stein, 2003; Stein & Walsh, 1997) further expands on visual, auditory, and cerebellar theories to propose that magnocellular impairments in RD also extend to auditory and tactile domains, and that this impacts the cerebellum as it receives a large degree of input from magnocellular systems (Stein, 2001).

In general, phonological theories of RD are thought to best describe the core impairments observed in individuals with RD. Sensory-motor deficits, which are predicted by the rapid auditory processing, visual, cerebellar, and magnocellular theories of RD, are not consistently found in individuals with RD and are sometimes only identified in a subgroup of individuals with RD (for a review see Ramus (2003) and Ramus et al., 2003) Although the phonological theory fails to explain the presence of sensory and/or motor deficits in some individuals with RD, proponents of this theory argue that these are not core features of RD and are not causally related to RD (e.g. Ramus et al., 2003; Snowling, 2000). In support of phonological theories of RD, phonological deficits have been consistently and robustly associated with reading disability (Desroches, Joanisse, & Robertson, 2006; Fletcher et al., 1994; Morris et al., 1998; Ramus et al., 2003; Shaywitz et al., 1999; Stanovich & Siegel, 1994). Even prior to reading instruction, individuals with RD struggle to identify and manipulate sounds in

speech (Ball & Blachman, 1991; Bradley & Bryant, 1983; Fletcher et al., 1994; Shankweiler & et al, 1979; Wagner & Torgesen, 1987), a skill known as phonological awareness, which is an important precursor to learning to read (Wagner, Torgesen, & Rashotte, 1994). A strong body of evidence also demonstrates that phonology-based interventions are effective in improving reading in children with RD (Bus & Van Ijzendoorn, 1999; Duff & Clarke, 2011; Report of the National Reading Panel, 2000; Torgesen et al., 2001).

In line with phonological theories of RD, the dual route cascaded model and connectionist models also suggest that the impairment in RD is primarily a phonological deficit. In the context of the dual route model of reading, RD is characterized as a selective impairment to the grapheme-phoneme correspondence route (Castles & Coltheart, 1993), resulting in great difficulty retrieving grapheme-phoneme rules and applying these rules to decode words. In connectionist models of reading, RD is proposed to involve degraded phonological representations, leading to difficulty learning associations between orthographic and phonological information and generalizing pronunciations to read novel words (Harm & Seidenberg, 1999). Although the exact nature of the predicted impairment differs between the two models, both suggest that RD is characterized by a phonological impairment resulting in difficulty reading unfamiliar words.

Much of recent research on RD has focused on phonological skills as phonology is a strong correlate of poor reading and phonological theories of RD are supported in cognitive models of reading. However, research identifying subgroups of poor readers suggest that the field's focus on phonological deficits may not fully capture possible

subtypes or multiple etiologies of reading difficulties. For example, studies have documented subgroups of “poor comprehenders” with deficits specific to reading comprehension (Yuill & Oakhill, 1991), individuals with “surface dyslexia”, who show delays in reading skills but do not exhibit phonological impairments relative to their word reading ability (Castles & Coltheart, 1993; Joanisse, Manis, Keating, & Seidenberg, 2000; Manis, Seidenberg, Doi, McBride-Chang, & Petersen, 1996; Stanovich, Siegel, & Gottardo, 1997), and children with rapid naming deficits uniquely contributing to reading difficulties (Wolf & Bowers, 1999). These findings highlight the heterogeneity of profiles of poor reading and the multi-componential nature of reading ability. Previous neuroimaging research focusing on phonological skills in RD may therefore not fully capture the multi-faceted relationship between reading and brain structure and function. In my research, I focus on measuring individual differences in multiple cognitive subskills associated with reading, to better characterize the complex neural substrates of reading ability and disability.

## **1.2 Cognitive Subskills Associated with Reading**

### **1.2.1 Single word reading skills**

Although the dual route cascaded model and connectionist models characterize representation and processing of written language very differently, both predict that words can be recognized more quickly and automatically when they are familiar to the reader. This process is referred to as *sight word reading*, and is distinguished from *decoding*, in which readers must use knowledge of grapheme-phoneme correspondences to decode an unfamiliar word. Typical readers learn to read initially by decoding, but with repeated experiences with a word, they can recognize the word more fluently and

accurately without relying on mapping individual letters to sounds. Reading in RD is characterized by difficulty decoding words accurately and fluently. Children with RD also tend to struggle with sight word reading, although this can often be attributed to difficulty accurately decoding words as this results in reduced experience and weaker associations between the orthographic form of a word and its corresponding phonological form.

### **1.2.2 Reading comprehension**

While the dual route and connectionist models capture the processes involved in single word recognition, an additional component of reading is comprehension (Gough & Tunmer, 1986). This is the process by which words, sentences, and discourse are mapped onto semantic representations, allowing the reader to comprehend the piece of written text. The *simple view of reading* posits that reading comprehension is determined by a combination of word recognition abilities and listening comprehension abilities (Catts, Hogan, & Adlof, 2005; Catts, Hogan, & Fey, 2003; Hoover & Gough, 1990). According to this view, a child may have poor reading comprehension due to impaired word recognition abilities, impaired listening comprehension abilities, or a combination of both impairments. In the context of RD, children who struggle with decoding and identifying words accurately and fluently are likely to struggle to draw meaning from text. Importantly, this reading comprehension deficit is a product of their phonological impairment and does not reflect a listening comprehension impairment. However, other subgroups of children may also have poor reading comprehension abilities for other reasons including children who have developmental language disorder (for a review see Bishop, 1997) or subclinical language weaknesses (Nation & Snowling, 1998, 1999,

2000; Yuill & Oakhill, 1991), as well as children with comorbid RD and developmental language disorder (Catts et al., 2003). Reading comprehension difficulties in children with developmental language disorder or subclinical language weaknesses are generally related to an impairment in listening comprehension and aspects of spoken language processing (Nation & Snowling, 1998, 1999, 2000), whereas children with comorbid RD and developmental language disorder tend to struggle with reading comprehension as a result of impairments in both word recognition and listening comprehension.

### **1.2.3 Rapid naming**

One important predictor of reading in both developing readers and adults is *rapid automatized naming* (RAN) (for a review see Norton & Wolf, 2012). RAN tasks involve rapid naming of an array of items, such as colours, objects, letters, or numbers.

Importantly, RAN tasks involve a recurring set of items, for example a set of four letters recurring in random order throughout the array, requiring rapid recognition of these items and inhibition of previously activated items. RAN performance is thought to index the fluent perceptual, attentional, and motoric processes involved in reading aloud (Arnell, Klein, Joanisse, Bussen, & Tannock, 2009).

While RAN and phonological awareness are both known to be robust early predictors of later reading abilities (Pennington & Lefly, 2001; Scarborough, 1998; Schatschneider, Fletcher, Francis, Carlson, & Foorman, 2004), they have been shown to each have independent contributions to predicting reading (Wolf & Bowers, 1999). This demonstrates the importance of considering RAN in addition to phonology as a measure of reading success and difficulty. In school-age years, with frequent exposure to letters and numbers, alphanumeric RAN tasks are stronger predictors of reading ability than

colour or object RAN tasks (Meyer, Wood, Hart, & Felton, 1998; Wolf, 1986).

Performance on RAN tasks remains strongly associated with reading ability throughout later school-age years and adolescence, particularly in poor readers (van den bos, Zijlstra, & Iutje Spelberg, 2002; Vukovic, Wilson, & Nash, 2004). The relationship between RAN and reading fluency has been consistently documented across many orthographies (Georgiou, Parrila, & Liao, 2008; Tan, Spinks, Eden, Perfetti, & Siok, 2005).

#### **1.2.4 Summary**

In summary, reading is a complex cognitive skill relying on many component skills, including decoding, sight word reading, comprehension, and rapid naming. Children with RD mainly have difficulty performing fluently and accurately on decoding and rapid naming tasks but tend to also struggle with sight word reading and comprehension, as a result of inaccurate and disfluent decoding. Because reading impairment is multi-factorial, it is necessary to take a similarly multi-factorial approach to fully understand its neural substrates.

### **1.3 Neural Basis of Reading and RD**

#### **1.3.1 Neuroimaging studies of reading ability and RD**

The development of functional neuroimaging technologies over the last three to four decades has allowed significant growth in our understanding of the neural systems that support reading ability. Specifically, technologies such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET), which measure changes in blood flow and metabolic activity in the brain have allowed researchers to capture what brain areas are active during different types of reading tasks.



Various models of reading in the brain have been developed as a result of converging fMRI and PET evidence. In a neurobiological model of reading and RD, Pugh, Mencl, Jenner, et al. (2000) proposed that three major left hemisphere systems are involved in word recognition: a dorsal, ventral, and anterior system. Recognition of familiar words, via sight word reading, is associated with left ventral occipito-temporal areas, while reading unfamiliar or low frequency words by decoding relies on left dorsal temporo-parietal regions and anterior areas located in the left inferior frontal gyrus. Children learning to read tend to rely largely on left temporo-parietal regions for integrating orthographic and phonological information to decode words. These left temporo-parietal regions are thought to support the subsequent development of occipito-temporal regions of the brain, allowing for faster word form identification in more experienced readers. The integration of phonological and semantic representations in overlapping neural circuits in these regions is thought to be essential for development of typical reading skills. Pugh et al. (2000) suggest that children with RD, who have difficulty with temporo-parietal phonological processing, rely more on the left inferior frontal gyrus and posterior right hemisphere regions to support compensatory strategies such as covert pronunciation and visual strategies.

Sandak, Mencl, Frost, and Pugh (2004) further specified the regions implicated in Pugh et al.'s (2000) model, suggesting that regions of the supramarginal gyrus (within the dorsal system) and inferior frontal gyrus (within the anterior system) are crucial in early reading for binding orthographic and phonological information, with additional contributions from the angular gyrus to link semantic representations to these words. During reading development, strong orthographic-phonological integration is proposed to

contribute to the development of the ventral system in the occipito-temporal regions and middle and inferior temporal gyri, which allows for fast and efficient sight word reading. Sandak et al. (2004) theorize that children with RD have deficits in temporo-parietal areas, which impair development of the ventral system and result in development of compensatory responses in the anterior system and in right hemisphere regions.

A more recent model of reading (Dehaene, 2009) furthered Pugh et al.'s (2000) and Sandak et al.'s (2004) model, highlighting the role of ventral occipito-temporal regions in reading. This model proposes that visual input is first processed in the occipital lobe, with the left ventral occipito-temporal area involved specifically in visual analysis of letter and word shape. Numerous cortical areas, including inferior frontal regions, anterior temporal regions, anterior fusiform regions, middle temporal regions, and angular gyrus, are then thought to be involved in accessing word meaning. Dehaene (2009) proposes that access to pronunciation and articulation are associated with parietal, temporal, and frontal regions, including the supramarginal gyrus, superior temporal regions, precentral gyrus, and anterior insula, while posterior parietal regions exert a top-down influence on visual attention and serial reading. This model also emphasizes the role of connectivity between these regions in reading, noting that the connections are all bidirectional and that many functions are operating in parallel during reading.

Similar patterns have emerged in research measuring functional brain activation while participants complete reading tasks, suggesting that reading involves regions distributed across the cortex. Numerous meta-analyses of neuroimaging studies of reading have linked the left occipital temporal junction and left fusiform gyrus to pre-lexical processing of letter patterns, left dorsal temporo-parietal areas to integrating

orthographic and phonological information for decoding unfamiliar words, left ventral occipito-temporal regions to extracting the phonology of familiar words, and the left inferior frontal gyrus and left precentral gyrus in phonological output processes, particularly when reading aloud (Cattinelli, Borghese, Gallucci, & Paulesu, 2013; Houdé, Rossi, Lubin, & Joliot, 2010; Jobard, Crivello, & Tzourio-Mazoyer, 2003; Taylor, Rastle, & Davis, 2013; Turkeltaub, Eden, Jones, & Zeffiro, 2002). As expected, comparisons of neuroimaging findings in children and adults suggest some developmental shifts in the brain's role in reading, with both common and divergent patterns of reading-related functional activation observed between children and adults (Martin, Schurz, Kronbichler, & Richlan, 2015). Specifically, Martin et al. (2015) observed a common network including left ventral occipito-temporal areas, left inferior frontal gyrus, left posterior parietal cortex, and bilateral supplementary motor area. In children, the bilateral supplementary motor area and left superior temporal gyrus were most consistently found to be activated during reading across the meta-analysis of studies, while in adults more consistent activation was observed in the bilateral cerebellum, left middle frontal gyrus, left precentral gyrus, and left middle occipital gyrus. This body of research demonstrates that both children and adults rely on a distributed network of brain regions during reading, and some changes in the specific brain areas recruited for reading occur throughout reading development.

Meta-analyses of functional neuroimaging studies of RD have also identified atypical brain activation in regions of the reading network in struggling readers. Specifically, meta-analyses of fMRI and PET studies of reading suggest that RD is consistently characterized by underactivation in left temporo-parietal regions (Maisog et

al., 2008; Paulesu et al., 2014; Richlan et al., 2009, 2011), left occipito-temporal regions (Maisog et al., 2008; Richlan et al., 2009), and left inferior frontal regions (Maisog et al., 2008; Richlan et al., 2009). Additionally, overactivation has been found in the left precentral regions (Richlan et al., 2009, 2011) and right thalamus and insula (Maisog et al., 2008), which is suggested to be related to compensatory processes during reading. Together, the existing literature demonstrates that reading in RD is characterized by underactivation of dorsal areas associated with decoding, and of ventral and anterior areas associated with sight word reading, as well as compensatory reliance on left precentral and right hemisphere regions.

### **1.3.2 Brain connectivity**

Although much of previous neuroimaging research has focused on identifying localized brain regions that support reading or that differ between typical readers and individuals with RD, a deeper understanding the role of the brain in reading requires understanding of how localized regions distributed widely across the brain function in concert with one another. As efficient reading depends on coordinated processing amongst many cortical regions, connectivity between these brain regions is therefore important to ensure that signals can be transmitted efficiently across the brain (Friston, 2011). Neural connectivity can be measured both in terms of functional connectivity, which assesses the coordination of activity across brain regions, and in terms of structural connectivity, which assesses the integrity of brain anatomy connecting cortical regions. In the present dissertation, I focused on measuring functional and structural connectivity in children and examined how these measures relate to typical and impaired reading ability.

**1.3.2.1 Measuring functional connectivity.** Functional connectivity is measured by examining temporal correlations between regions of the cortex (Friston, Frith, Liddle, & Frackowiak, 1993; Friston, Jezzard, & Turner, 1994). This method was initially implemented in PET studies by examining the correlation in neural activity between regions of known cortical networks while participants completed a related task (Clark, Kessler, Buchsbaum, Margolin, & Holcomb, 1984; Horwitz, Duara, & Rapoport, 1984; Horwitz, Rumsey, & Donohue, 1998; Horwitz, 1990; Metter, Riege, Kuhl, & Phelps, 1984). Networks that are more functionally connected tend to be more correlated in their activity over time. Importantly, functional connectivity is distinct from structural connectivity (Horwitz et al., 1992; Horwitz, 1994). Two brain regions that are structurally connected may not always show functional connectivity, depending on the demands of the task. On the other hand, two regions that show functional connectivity may also not be directly connected structurally, as they could both receive input from a third brain region resulting in correlation in neural activity. These same principles have been more recently applied to fMRI, in which functional connectivity can be measured by examining correlations in the blood-oxygen level dependent (BOLD) response between cortical regions over the course of the fMRI scan.

Although many initial fMRI studies of functional connectivity used a task-based approach, in which participants completed a task during the fMRI scan, this method can also be adapted to use a resting-state approach, in which the fMRI scan is conducted while the participant is in a wakeful resting state. Resting-state fMRI measures correlations in low frequency (<0.1 Hz) spontaneous fluctuations in the BOLD response across brain regions (Biswal, Zerrin Yetkin, Haughton, & Hyde, 1995), which are

thought to reflect the brain's functional networks (see Fox & Raichle, 2007). The resting-state approach to measuring functional connectivity is advantageous because the data cannot be influenced by task demands or by differences in task performance or processing strategies. This is of particular relevance when studying reading, as task-based fMRI studies tend vary in terms of the type reading task used, and patterns of functional connectivity are known to differ for different types of reading tasks (Mechelli et al., 2005; Nakamura, Dehaene, Jobert, Le Bihan, & Kouider, 2007). When studying children, the resting-state technique also has the appreciable advantage that children do not need to be trained on a task prior to scanning and can simply rest quietly in the scanner.

Resting-state functional networks among reading-related regions have been shown to align closely with functional networks observed in task-based fMRI data (Hampson et al., 2006; Koyama et al., 2010), including positive correlations in activation between the left temporoparietal junction and left frontal and temporal areas and between the left fusiform gyrus and the left inferior frontal gyrus extending into the left precentral gyrus, as well as negative correlations between reading-related regions and areas associated with the default mode network, effortful control, and working memory. Resting-state functional connectivity (RSFC) in the reading network is also known to correlate with individual differences in single word reading abilities. Koyama et al. (2011) found that in both children and adults, reading performance was positively associated with RSFC from the left precentral gyrus seed to the left postcentral gyrus, bilateral supplementary motor area and posterior cingulate cortex, and right postcentral/precentral gyrus, as well as from the left inferior frontal gyrus pars opercularis seed to the left superior temporal gyrus. Children also exhibited negative

correlations between reading and RSFC from the left fusiform gyrus to the left inferior frontal gyrus and left superior temporal gyrus, and positive correlations between reading and RSFC from the left fusiform gyrus to the default mode network and from the left intraparietal sulcus to the bilateral thalami, while adults showed an inverse pattern of RSFC-behaviour correlations in these regions. These developmental differences in RSFC-behaviour relationships were proposed to be related to differences in functional segregation among networks associated with reading, rest, and visual attention, impacting efficiency and automaticity of reading processes.

Although the current literature shows the usefulness of the resting-state functional connectivity approach in characterizing the role of functional connectivity in reading, the relationship between RSFC and different components of reading is not well understood. In the present thesis, I sought to further examine how discrete subskills of reading in children were associated with RSFC within the brain's reading network.

**1.3.2.2 Measuring structural connectivity.** While functional connectivity assesses networks of coordinated activity, structural connectivity is a measure of anatomical connectivity between cortical regions. Diffusion tensor imaging (DTI) is a structural MRI technique which measures diffusion of water molecules in body tissues. When used for imaging of the brain, DTI can characterize the organization of tissues in the brain based on the direction of diffusion of water molecules (Basser, 1995; Basser & Pierpaoli, 1996; Pierpaoli & Basser, 1996; for a review see Feldman, Yeatman, Lee, Barde, & Gaman-Bean, 2010). In areas of the brain filled with cerebrospinal fluid, diffusion of water is largely isotropic, meaning water molecules can diffuse both in a relatively unconstrained way and in all directions. In areas of grey matter, cell membranes and structures inside

the cell force water molecules to take more convoluted paths of diffusion. This slows diffusion and decreases the mean displacement of the water molecules in grey matter relative to those in cerebrospinal fluid. Diffusion in grey matter is still isotropic as the orientation of each cell's membranes and structures is random relative to other cells, allowing water molecules to displace in all directions. Conversely, the myelinated axons in neurons of white matter tracts of the brain allow for relatively unimpeded diffusion parallel to the axon while greatly hindering diffusion perpendicular to the axon. This results in diffusion that is *anisotropic*: diffusion is greater in one direction than in other directions. Fractional anisotropy (FA) is a DTI measure which quantifies the degree of anisotropy, or directionality, of water diffusion in the brain. FA values range between 0 and 1, with higher values representing a greater degree of diffusion in a single direction relative to all other directions. FA can be used to characterize increased axon density, axonal diameter, and myelination (Basser & Pierpaoli, 1996). FA is first measured at the individual voxel level, and tractography techniques can then be used to trace a subject's fiber streamlines within a particular white matter tract by sequentially piecing together information about the directionality of individual neighbouring voxels (Basser, Pajevic, Pierpaoli, Duda, & Aldroubi, 2000; Conturo et al., 1999; Mori, Crain, Chacko, & Van Zijl, 1999). One such tractography technique is deterministic tractography, in which an algorithm moves sequentially from voxel to voxel along the principal diffusion direction and stops when a voxel is unlikely to be part of the same streamline based on its FA measurement or its angle relative to other voxels. This technique allows researchers to identify individual participants' white matter tracts and assess structural connectivity along these specific tracts.



The white matter tract most consistently linked to reading is the left arcuate fasciculus (Carter et al., 2009; Christodoulou et al., 2017; Deutsch et al., 2005; Gold, Powell, Xuan, Jiang, & Hardy, 2007; Klingberg et al., 2000; Nagy, Westerberg, & Klingberg, 2004; Richards et al., 2008; Rimrodt, Peterson, Denckla, Kaufmann, & Cutting, 2010; Steinbrink et al., 2008; Vandermosten et al., 2012), a dorsal tract connecting superior/middle temporal with inferior frontal regions and linked to oral and written language processing. Ventral tracts associated with reading include the left inferior fronto-occipital fasciculus, left inferior longitudinal fasciculus, and left uncinate fasciculus. The inferior fronto-occipital fasciculus includes fibers connecting occipital, temporal, and frontal grey matter regions, while the inferior longitudinal fasciculus links occipital and anterior temporal brain regions and the uncinate fasciculus links anterior temporal and ventral frontal regions. These ventral tracts have been implicated in orthographic, lexical, and semantic processing (Epelbaum et al., 2008; Grossman et al., 2004; Lu et al., 2002; Mandonnet, Nouet, Gatignol, Capelle, & Duffau, 2007; Marchina et al., 2011; Wilson et al., 2011). Although much of reading research has focused on left hemisphere white matter tracts, studies have also implicated white matter integrity in the right hemisphere in reading ability and RD (Frye et al., 2009; Lebel et al., 2013; Odegard, Farris, Ring, McColl, & Black, 2009; Richards et al., 2008; Vandermosten, Poelmans, Sunaert, Ghesquière, & Wouters, 2013), suggesting structural connectivity in both hemispheres plays a role in reading success.

DTI studies of reading clearly show the importance of white matter connectivity in supporting reading, however there is substantial variability in the tracts and hemispheres implicated and the types of reading tasks used in different studies. As a

result, there is no clear consensus regarding which tracts support different aspects of reading. My research aims to elucidate how integrity of different white matter tracts in the left and right hemisphere relate to individual differences in subskills of reading in children.

#### **1.4 Relevant Issues in Brain Connectivity Research of Reading**

Much of previous neuroimaging research examining reading has measured reading ability using only a measure of single word reading or a composite measure combining scores on multiple types of reading tasks. This is problematic as reading is known to be a complex process involving multiple cognitive subskills. Moreover, findings of studies with only single word reading measures are often used to draw conclusions about reading in general, however single word reading tasks only capture a small part of the cognitive processes involved in overall reading success. Similarly, studies using composite measures of reading which combine scores of different types of reading tasks cannot capture the neural basis for each of the distinct cognitive processes involved in reading.

An additional challenge is that much of reading research has focused on comparisons of typical readers to individuals with RD. Reading performance, like many other cognitive skills, is distributed normally within the population. RD does not represent a categorical distinction between typical and poor readers, rather, it represents the lower tail of the normal distribution (Gilger et al., 1996; Shaywitz, Shaywitz, Fletcher, & Makuch, 1992). In studies using group-based approaches to compare individuals with RD to typical readers, the thresholds for determining how to divide individuals into typically-developing and RD groups tend to be arbitrary (Lyon et al.,

2003) and variable across different studies (Siegel, 2006), leading to significant variability in findings across studies and difficulty generalizing findings to the greater population. Further research is therefore needed to characterize the roles of functional and structural brain connectivity in supporting individual differences in reading processes across the full range of the distribution of reading abilities.

Research measuring individual differences in reading abilities based on more than one type of skill has provided preliminary evidence that different subskills are supported by distinct patterns of DTI connectivity in adults (Horowitz-Kraus, Wang, Plante, & Holland, 2014; Welcome & Joanisse, 2014). However, the relationship between white matter connectivity and subskills of reading in children has only been studied in terms of sight word reading and decoding abilities (Niogi & McCandliss, 2006), and this multi-component approach has not yet been applied in studies of functional connectivity. The present thesis considers individual differences in component subskills of reading in children, in order to fully capture their discrete relationships to brain structure and function.

### **1.5 Objectives and Overview**

The central objective of this thesis is to examine how functional and structural connectivity relate to individual differences in reading. To summarize the above discussion, many previous studies of brain connectivity and reading have used single or composite measures of reading skill, however, reading is known to rely on multiple types of cognitive subskills. In addition, much of previous research has focused on comparing children with RD to typically reading peers, although reading ability is known to be distributed on a continuum and RD simply represents the lower tail end of the normal

distribution. By measuring reading based on multiple subskills in individuals with a wide range of reading abilities, I use an individual-differences approach to consider how subskills of reading may show distinct patterns in their relationships to brain connectivity, and how these measures of brain connectivity may change as an individual's reading ability improves.

Chapter 2 examines the relationship between reading subskills and resting-state functional connectivity. Prior studies have shown that resting-state functional connectivity in the reading network is related to individual differences in single word reading in children and adults (Koyama et al., 2011). In Chapter 2, I expand on this research to examine how individual differences in decoding, sight word reading, reading comprehension, and rapid naming correlate differently with resting-state functional connectivity in a sample of children with a wide range of reading abilities.

Chapter 3 extends this investigation of individual differences in reading subskills to examine their relationship with structural connectivity. Measures of fractional anisotropy (FA) are known to relate to individual differences in single word reading (Beaulieu et al., 2005; Cummine et al., 2013; Deutsch et al., 2005; Lebel et al., 2013; Nagy et al., 2004; Niogi & McCandliss, 2006; Odegard et al., 2009). Using DTI, I take an individual-differences approach to extend this body of research to multiple reading subskills, including decoding, sight word reading, reading comprehension, and rapid naming abilities, to characterize the roles that different neural pathways play in reading in children.

Given that individual differences in reading are known to be reflected in patterns of functional and structural connectivity in the brain, Chapter 4 considers the changes in

measures of connectivity observed following improvement in reading abilities as a result of phonology-based reading intervention. Many previous studies have focused on how brain activation or functional connectivity during a reading task changes as reading ability improves, however the present study aims to extend this research to examine how spontaneous patterns of brain activity and structural connections in the brain change with improvement in reading skills. Additionally, as there is significant variability in the degree to which children respond to reading intervention, Chapter 4 considers how pre-intervention structural and functional connectivity may predict the individual differences in the magnitude of change in behavioural reading skills observed post-intervention.

The findings of the present thesis will characterize the roles that different functional and structural connections play in supporting distinct subskills of reading in school-age children with a wide range of reading abilities. In addition, the findings will contribute to understanding of differences in neural connectivity underlying RD and response to intervention in struggling readers.

## References

- Arnell, K. M., Klein, R. M., Joanisse, M. F., Bussen, M. A., & Tannock, R. (2009). Decomposing the relation between rapid automatized naming (RAN) and reading ability. *Canadian Journal of Experimental Psychology*, *63*(3), 173–184. <https://doi.org/10.1037/a0015721>
- Ball, E. W., & Blachman, B. A. (1991). Does phoneme awareness training in kindergarten make a difference in early word recognition and developmental spelling? *Reading Research Quarterly*, *26*(1), 49–66. <https://doi.org/10.1598/rrq.26.1.3>
- Basser, P. J. (1995). Inferring microstructural features and the physiological state of tissues from diffusion-weighted images. *NMR in Biomedicine*, *8*(7), 333–344. <https://doi.org/10.1002/nbm.1940080707>
- Basser, P. J., Pajevic, S., Pierpaoli, C., Duda, J., & Aldroubi, A. (2000). In vivo fiber tractography using DT-MRI data. *Magnetic Resonance in Medicine*, *44*(4), 625–632. [https://doi.org/10.1002/1522-2594\(200010\)44:4<625::AID-MRM17>3.0.CO;2-O](https://doi.org/10.1002/1522-2594(200010)44:4<625::AID-MRM17>3.0.CO;2-O)
- Basser, P. J., & Pierpaoli, C. (1996). Microstructural and physiological features of tissues elucidated by quantitative-diffusion-tensor MRI. *Journal of Magnetic Resonance - Series B*, *111*(3), 209–219. <https://doi.org/10.1006/jmrb.1996.0086>
- Beaulieu, C., Plewes, C., Paulson, L. A., Roy, D., Snook, L., Concha, L., & Phillips, L. (2005). Imaging brain connectivity in children with diverse reading ability. *NeuroImage*, *25*(4), 1266–1271. <https://doi.org/10.1016/j.neuroimage.2004.12.053>
- Bishop, D.V.M. (1997). *Uncommon understanding: Development and disorders of language comprehension in children*. Hove: Psychology Press.
- Biswal, B., Zerrin Yetkin, F., Haughton, V. M., & Hyde, J. S. (1995). Functional connectivity in the motor cortex of resting human brain using echo-planar mri. *Magnetic Resonance in Medicine*, *34*(4), 537–541. <https://doi.org/10.1002/mrm.1910340409>
- Blachman, B. A. (2000). Phonological awareness. In M. L. Kamil, P. B. Mosenthal, P. D. Pearson, & R. Barr (Eds.), *Handbook of reading research, Vol. 3* (p. 483–502). Lawrence Erlbaum Associates Publishers.
- Bradley, L., & Bryant, P. E. (1983). Categorizing sounds and learning to read - A causal connection. *Nature*, *301*(5899), 419–421. <https://doi.org/10.1038/301419a0>
- Bus, A. G., & Van Ijzendoorn, M. H. (1999). Phonological awareness and early reading: A meta-analysis of experimental training studies. *Journal of Educational Psychology*, *91*(3), 403–414. <https://doi.org/10.1037/0022-0663.91.3.403>
- Carter, J. C., Lanham, D. C., Cutting, L. E., Clements-Stephens, A. M., Chen, X., Hadzipasic, M., ... Kaufmann, W. E. (2009). A dual DTI approach to analyzing white matter in children with dyslexia. *Psychiatry Research - Neuroimaging*, *172*(3), 215–219. <https://doi.org/10.1016/j.psychresns.2008.09.005>
- Castles, A., & Coltheart, M. (1993). Varieties of developmental dyslexia. *Cognition*, *47*(2), 149–180. [https://doi.org/10.1016/0010-0277\(93\)90003-E](https://doi.org/10.1016/0010-0277(93)90003-E)
- Cattinelli, I., Borghese, N. A., Gallucci, M., & Paulesu, E. (2013). Reading the reading brain: A new meta-analysis of functional imaging data on reading. *Journal of Neurolinguistics*, *26*(1), 214–238. <https://doi.org/10.1016/j.jneuroling.2012.08.001>
- Catts, H. W., Hogan, T. P., & Adlof, S. M. (2005). Developmental changes in reading and reading disabilities. In *The Connections Between Language and Reading*

- Disabilities*. <https://doi.org/10.4324/9781410612052>
- Catts, H. W., Hogan, T. P., & Fey, M. E. (2003). Subgrouping poor readers on the basis of individual differences in reading-related abilities. *Journal of Learning Disabilities, 36*(2), 151–164. <https://doi.org/10.1177/002221940303600208>
- Christodoulou, J. A., Murtagh, J., Cyr, A., Perrachione, T. K., Chang, P., Halverson, K., ... Gabrieli, J. D. E. (2017). Relation of white-matter microstructure to reading ability and disability in beginning readers. *Neuropsychology, 31*(5), 508–515. <https://doi.org/10.1037/neu0000243>
- Clark, C. M., Kessler, R., Buchsbaum, M. S., Margolin, R. A., & Holcomb, H. H. (1984). Correlational methods for determining regional coupling of cerebral glucose metabolism: A pilot study. *Biological Psychiatry, 19*(5), 663–678.
- Coltheart, M., Rastle, K., Perry, C., Langdon, R., & Ziegler, J. (2001). DRC: A dual route cascaded model of visual word recognition and reading aloud. *Psychological Review, 108*(1), 204–256. <https://doi.org/10.1037/0033-295X.108.1.204>
- Conturo, T. E., Lori, N. F., Cull, T. S., Akbudak, E., Snyder, A. Z., Shimony, J. S., ... Raichle, M. E. (1999). Tracking neuronal fiber pathways in the living human brain. *Proceedings of the National Academy of Sciences of the United States of America, 96*(18), 10422–10427. <https://doi.org/10.1073/pnas.96.18.10422>
- Cummine, J., Dai, W., Borowsky, R., Gould, L., Rollans, C., & Boliek, C. (2013). Investigating the ventral-lexical, dorsal-sublexical model of basic reading processes using diffusion tensor imaging. *Brain Structure and Function, 220*(1), 445–455. <https://doi.org/10.1007/s00429-013-0666-8>
- Dehaene, S. (2009). *Reading in the brain: The new science of how we read*. Penguin.
- Desroches, A. S., Joanisse, M. F., & Robertson, E. K. (2006). Specific phonological impairments in dyslexia revealed by eyetracking. *Cognition, 100*(3). <https://doi.org/10.1016/j.cognition.2005.09.001>
- Deutsch, G. K., Dougherty, R. F., Bammer, R., Siok, W. T., Gabrieli, J. D. E., & Wandell, B. (2005). Children's reading performance is correlated with white matter structure measured by diffusion tensor imaging. *Cortex, 41*(3), 354–363. [https://doi.org/10.1016/S0010-9452\(08\)70272-7](https://doi.org/10.1016/S0010-9452(08)70272-7)
- Duff, F. J., & Clarke, P. J. (2011). Practitioner Review: Reading disorders: What are the effective interventions and how should they be implemented and evaluated? *Journal of Child Psychology and Psychiatry and Allied Disciplines*. <https://doi.org/10.1111/j.1469-7610.2010.02310.x>
- Epelbaum, S., Pinel, P., Gaillard, R., Delmaire, C., Perrin, M., Dupont, S., ... Cohen, L. (2008). Pure alexia as a disconnection syndrome: New diffusion imaging evidence for an old concept. *Cortex, 44*(8), 962–974. <https://doi.org/10.1016/j.cortex.2008.05.003>
- Feldman, H. M., Yeatman, J. D., Lee, E. S., Barde, L. H. F., & Gaman-Bean, S. (2010). Diffusion tensor imaging: A review for pediatric researchers and clinicians. *Journal of Developmental and Behavioral Pediatrics*. <https://doi.org/10.1097/DBP.0b013e3181dcaa8b>
- Fletcher, J. M., Shaywitz, S. E., Shankweiler, D. P., Katz, L., Liberman, I. Y., Stuebing, K. K., ... Shaywitz, B. A. (1994). Cognitive profiles of reading disability: Comparisons of discrepancy and low achievement definitions. *Journal of Educational Psychology, 86*(1), 6–23. <https://doi.org/10.1037/0022-0663.86.1.6>

- Fox, M. D., & Raichle, M. E. (2007). Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nature Reviews Neuroscience*, *8*(9), 700–711. <https://doi.org/10.1038/nrn2201>
- Friston, K. J. (2011). Functional and effective connectivity: A review. *Brain Connectivity*, *1*(1), 13–36. <https://doi.org/10.1089/brain.2011.0008>
- Friston, K. J., Frith, C. D., Liddle, P. F., & Frackowiak, R. S. J. (1993). Functional connectivity: The principal-component analysis of large (PET) data sets. *Journal of Cerebral Blood Flow and Metabolism*, *13*(1), 5–14. <https://doi.org/10.1038/jcbfm.1993.4>
- Friston, K. J., Jezzard, P., & Turner, R. (1994). Analysis of functional MRI time-series. *Human Brain Mapping*, *1*(2), 153–171. <https://doi.org/10.1002/hbm.460010207>
- Frye, R. E., Ph, D., Hasan, K., Xue, L., Strickland, D., Malmberg, B., ... Papanicolaou, A. (2009). Splenium microstructure is related to two dimensions of reading skill. *Neuroreport*, *19*, 1627–1631. <https://doi.org/10.1097/WNR.0b013e328314b8ee.Splenium>
- Galaburda, A. M., Menard, M. T., & Rosen, G. D. (1994). Evidence for aberrant auditory anatomy in developmental dyslexia. *Proceedings of the National Academy of Sciences of the United States of America*, *91*(17), 8010–8013. <https://doi.org/10.1073/pnas.91.17.8010>
- Georgiou, G. K., Parrila, R., & Liao, C. H. (2008). Rapid naming speed and reading across languages that vary in orthographic consistency. *Reading and Writing*, *21*(9), 885–903. <https://doi.org/10.1007/s11145-007-9096-4>
- Gilger, J. W., Borecki, I. B., Smith, S. D., DeFries, J. C., & Pennington, B. F. (1996). The etiology of extreme scores for complex phenotypes: An illustration using reading performance. In C. H. Chase, G. D. Rosen, & G. F. Sherman (Eds.), *Developmental dyslexia: Neural, cognitive, and genetic mechanisms* (pp 63–85). York Press.
- Gold, B. T., Powell, D. K., Xuan, L., Jiang, Y., & Hardy, P. A. (2007). Speed of lexical decision correlates with diffusion anisotropy in left parietal and frontal white matter: Evidence from diffusion tensor imaging. *Neuropsychologia*, *45*(11), 2439–2446. <https://doi.org/10.1016/j.neuropsychologia.2007.04.011>
- Gough, P. B., & Tunmer, W. E. (1986). Decoding, reading, and reading disability. *Remedial and Special Education*, *7*(1), 6–10. <https://doi.org/10.1177/074193258600700104>
- Grossman, M., McMillan, C., Moore, P., Ding, L., Glosser, G., Work, M., & Gee, J. (2004). What's in a name: Voxel-based morphometric analyses of MRI and naming difficulty in Alzheimer's disease, frontotemporal dementia and corticobasal degeneration. *Brain*, *127*(3), 628–649. <https://doi.org/10.1093/brain/awh075>
- Hampson, M., Tokoglu, F., Sun, Z., Schafer, R. J., Skudlarski, P., Gore, J. C., & Constable, R. T. (2006). Connectivity-behavior analysis reveals that functional connectivity between left BA39 and Broca's area varies with reading ability. *NeuroImage*, *31*(2), 513–519. <https://doi.org/10.1016/j.neuroimage.2005.12.040>
- Hari, R., Renvall, H., & Tanskanen, T. (2001). Left minineglect in dyslexic adults. *Brain*, *124*(7), 1373–1380. <https://doi.org/10.1093/brain/124.7.1373>
- Harm, M. W., & Seidenberg, M. S. (1999). Phonology, reading acquisition, and dyslexia: Insights from connectionist models. *Psychological Review*, *106*(3), 491–528. <https://doi.org/10.1037/0033-295X.106.3.491>



- Harm, M. W., & Seidenberg, M. S. (2004). Computing the meanings of words in reading: Cooperative division of labor between visual and phonological processes. *Psychological Review*, *111*(3), 662-720. <https://doi.org/10.1037/0033-295X.111.3.662>
- Hoover, W. A., & Gough, P. B. (1990). The simple view of reading. *Reading and Writing*, *2*(2), 127-160. <https://doi.org/10.1007/BF00401799>
- Horowitz-Kraus, T., Wang, Y., Plante, E., & Holland, S. K. (2014). Involvement of the right hemisphere in reading comprehension: A DTI study. *Brain Research*, *1582*, 34-44. <https://doi.org/10.1016/j.brainres.2014.05.034>
- Horwitz, B., Duara, R., & Rapoport, S. I. (1984). Intercorrelations of glucosemetabolic rates between brain regions: Application to healthy males in a state of reduced sensory input. *Journal of Cerebral Blood Flow and Metabolism*, *4*(4), 484-499. <https://doi.org/10.1038/jcbfm.1984.73>
- Horwitz, B., Grady, C. L., Haxby, J. V., Schapiro, M. B., Rapoport, S. I., Ungerleider, L. G., & Mishkin, M. (1992). Functional associations among human posterior extrastriate brain regions during object and spatial vision. *Journal of Cognitive Neuroscience*, *4*(4), 311-322. <https://doi.org/10.1162/jocn.1992.4.4.311>
- Horwitz, B., Rumsey, J. M., & Donohue, B. C. (1998). Functional connectivity of the angular gyrus in normal reading and dyslexia. *Proceedings of the National Academy of Sciences of the United States of America*, *95*(15), 8939-8944. <https://doi.org/10.1073/pnas.95.15.8939>
- Horwitz, Barry. (1990). Simulating functional interactions in the brain: A model for examining correlations between regional cerebral metabolic rates. *International Journal of Bio-Medical Computing*, *26*(3), 149-170. [https://doi.org/10.1016/0020-7101\(90\)90039-W](https://doi.org/10.1016/0020-7101(90)90039-W)
- Horwitz, Barry. (1994). Data analysis paradigms for metabolic-flow data: Combining neural modeling and functional neuroimaging. *Human Brain Mapping*, *2*(1-2), 112-122. <https://doi.org/10.1002/hbm.460020111>
- Houdé, O., Rossi, S., Lubin, A., & Joliot, M. (2010). Mapping numerical processing, reading, and executive functions in the developing brain: An fMRI meta-analysis of 52 studies including 842 children. *Developmental Science*, *13*(6), 876-885. <https://doi.org/10.1111/j.1467-7687.2009.00938.x>
- Joanisse, M. F., Manis, F. R., Keating, P., & Seidenberg, M. S. (2000). Language deficits in dyslexic children: Speech perception, phonology, and morphology. *Journal of Experimental Child Psychology*, *77*(1), 30-60. <https://doi.org/10.1006/jecp.1999.2553>
- Jobard, G., Crivello, F., & Tzourio-Mazoyer, N. (2003). Evaluation of the dual route theory of reading: A metaanalysis of 35 neuroimaging studies. *NeuroImage*, *20*(2), 693-712. [https://doi.org/10.1016/S1053-8119\(03\)00343-4](https://doi.org/10.1016/S1053-8119(03)00343-4)
- Klingberg, T., Hedehus, M., Temple, E., Salz, T., Gabrieli, J. D. E., Moseley, M. E., & Poldrack, R. A. (2000). Microstructure of temporo-parietal white matter as a basis for reading ability: Evidence from diffusion tensor magnetic resonance imaging. *Neuron*, *25*(2), 493-500. [https://doi.org/10.1016/S0896-6273\(00\)80911-3](https://doi.org/10.1016/S0896-6273(00)80911-3)
- Koyama, M. S., di Martino, A., Zuo, X. N., Kelly, C., Mennes, M., Jutagir, D. R., ... Milham, M. P. (2011). Resting-state functional connectivity indexes reading competence in children and adults. *Journal of Neuroscience*, *31*(23), 8617-8624.

- <https://doi.org/10.1523/JNEUROSCI.4865-10.2011>
- Koyama, M. S., Kelly, C., Shehzad, Z., Penesetti, D., Castellanos, F. X., & Milham, M. P. (2010). Reading networks at rest. *Cerebral Cortex*, *20*(11), 2549–2559. <https://doi.org/10.1093/cercor/bhq005>
- Lebel, C., Shaywitz, B., Holahan, J., Shaywitz, S., Marchione, K., & Beaulieu, C. (2013). Diffusion tensor imaging correlates of reading ability in dysfluent and non-impaired readers. *Brain and Language*, *125*(2), 215–222. <https://doi.org/10.1016/j.bandl.2012.10.009>
- Lieberman IY, Shankweiler D, Liberman AM (1989): Phonology and reading disability: Solving the reading puzzle. In D. Shankweiler, I.Y. Liberman (Eds.), *International academy for research in learning disabilities monograph series* (1-33). University of Michigan Press.
- Livingstone, M. S., Rosen, G. D., Drislane, F. W., & Galaburda, A. M. (1991). Physiological and anatomical evidence for a magnocellular defect in developmental dyslexia. *Proceedings of the National Academy of Sciences of the United States of America*, *88*(18), 7943–7947. <https://doi.org/10.1073/pnas.88.18.7943>
- Lovegrove, W. J., Bowling, A., Badcock, D., & Blackwood, M. (1980). Specific reading disability: Differences in contrast sensitivity as a function of spatial frequency. *Science*, *210*(4468), 439–440. <https://doi.org/10.1126/science.7433985>
- Lu, L. H., Crosson, B., Nadeau, S. E., Heilman, K. M., Gonzalez-Rothi, L. J., Raymer, A., ... Roper, S. N. (2002). Category-specific naming deficits for objects and actions: Semantic attribute and grammatical role hypotheses. *Neuropsychologia*, *40*(9), 1608–1621. [https://doi.org/10.1016/S0028-3932\(02\)00014-3](https://doi.org/10.1016/S0028-3932(02)00014-3)
- Lyon, G. R., Shaywitz, S. E., & Shaywitz, B. A. (2003). A definition of dyslexia. *Annals of Dyslexia*, *53*(1), 1-14. <https://doi.org/10.1007/s11881-003-0001-9>
- Maisog, J. M., Einbinder, E. R., Flowers, D. L., Turkeltaub, P. E., & Eden, G. F. (2008). A meta-analysis of functional neuroimaging studies of dyslexia. In *Annals of the New York Academy of Sciences* (Vol. 1145, pp. 237–259). <https://doi.org/10.1196/annals.1416.024>
- Mandonnet, E., Nouet, A., Gatignol, P., Capelle, L., & Duffau, H. (2007). Does the left inferior longitudinal fasciculus play a role in language? A brain stimulation study. *Brain*, *130*(3), 623–629. <https://doi.org/10.1093/brain/awl361>
- Manis, F. R., Seidenberg, M. S., Doi, L. M., McBride-Chang, C., & Petersen, A. (1996). On the bases of two subtypes of development dyslexia. *Cognition*, *58*(2), 157–195. [https://doi.org/10.1016/0010-0277\(95\)00679-6](https://doi.org/10.1016/0010-0277(95)00679-6)
- Marchina, S., Zhu, L. L., Norton, A., Zipse, L., Wan, C. Y., & Schlaug, G. (2011). Impairment of speech production predicted by lesion load of the left arcuate fasciculus. *Stroke*, *42*(8), 2251–2256. <https://doi.org/10.1161/STROKEAHA.110.606103>
- Martin, A., Schurz, M., Kronbichler, M., & Richlan, F. (2015). Reading in the brain of children and adults: A meta-analysis of 40 functional magnetic resonance imaging studies. *Human Brain Mapping*, *36*(5), 1963–1981. <https://doi.org/10.1002/hbm.22749>
- Mechelli, A., Crinion, J. T., Long, S., Friston, K. J., Lambon Ralph, M. A., Patterson, K., ... Price, C. J. (2005). Dissociating reading processes on the basis of neuronal interactions. *Journal of Cognitive Neuroscience*, *17*(11), 1753–1765.

- <https://doi.org/10.1162/089892905774589190>
- Metter, E. J., Riege, W. H., Kuhl, D. E., & Phelps, M. E. (1984). Cerebral metabolic relationships for selected brain regions in healthy adults. *Journal of Cerebral Blood Flow and Metabolism*, *4*(1), 1–7. <https://doi.org/10.1038/jcbfm.1984.1>
- Meyer, M. S., Wood, F. B., Hart, L. A., & Felton, R. H. (1998). Selective predictive value of rapid automatized naming in poor readers. *Journal of Learning Disabilities*, *31*(2), 106–117. <https://doi.org/10.1177/002221949803100201>
- Mori, S., Crain, B. J., Chacko, V. P., & Van Zijl, P. C. M. (1999). Three-dimensional tracking of axonal projections in the brain by magnetic resonance imaging. *Annals of Neurology*, *45*(2), 265–269. [https://doi.org/10.1002/1531-8249\(199902\)45:2<265::AID-ANA21>3.0.CO;2-3](https://doi.org/10.1002/1531-8249(199902)45:2<265::AID-ANA21>3.0.CO;2-3)
- Morris, R. D., Shaywitz, S. E., Shankweiler, D. P., Katz, L., Stuebing, K. K., Fletcher, J. M., ... Shaywitz, B. A. (1998). Subtypes of reading disability: variability around a phonological core. *Journal of Educational Psychology*, *90*(3), 347–373. <https://doi.org/10.1037/0022-0663.90.3.347>
- Nagy, Z., Westerberg, H., & Klingberg, T. (2004). Maturation of white matter is associated with the development of cognitive functions during childhood. *Journal of Cognitive Neuroscience*, *16*(7), 1227–1233. <https://doi.org/10.1162/0898929041920441>
- Nakamura, K., Dehaene, S., Jobert, A., Le Bihan, D., & Kouider, S. (2007). Task-specific change of unconscious neural priming in the cerebral language network. *Proceedings of the National Academy of Sciences of the United States of America*, *104*(49), 19643–19648. <https://doi.org/10.1073/pnas.0704487104>
- Nation, K., & Snowling, M. J. (1998). Semantic processing and the development of word-recognition skills: Evidence from children with reading comprehension difficulties. *Journal of Memory and Language*, *39*(1), 85–101. <https://doi.org/10.1006/jmla.1998.2564>
- Nation, K., & Snowling, M. J. (1999). Developmental differences in sensitivity to semantic relations among good and poor comprehenders: Evidence from semantic priming. *Cognition*, *70*(1), B1–B13. [https://doi.org/10.1016/S0010-0277\(99\)00004-9](https://doi.org/10.1016/S0010-0277(99)00004-9)
- Nation, K., & Snowling, M. J. (2000). Factors influencing syntactic awareness skills in normal readers and poor comprehenders. *Applied Psycholinguistics*, *21*(2), 229–241. <https://doi.org/10.1017/S0142716400002046>
- Nicolson, R. I., & Fawcett, A. J. (1990). Automaticity: A new framework for dyslexia research? *Cognition*, *35*(2), 159–182. [https://doi.org/10.1016/0010-0277\(90\)90013-A](https://doi.org/10.1016/0010-0277(90)90013-A)
- Nicolson, Roderick I., Fawcett, A. J., & Dean, P. (2001). Developmental dyslexia: The cerebellar deficit hypothesis. *Trends in Neurosciences*, *24*(9), 508–511. [https://doi.org/10.1016/S0166-2236\(00\)01896-8](https://doi.org/10.1016/S0166-2236(00)01896-8)
- Niogi, S. N., & McCandliss, B. D. (2006). Left lateralized white matter microstructure accounts for individual differences in reading ability and disability. *Neuropsychologia*, *44*(11), 2178–2188. <https://doi.org/10.1016/j.neuropsychologia.2006.01.011>
- Norton, E. S., & Wolf, M. (2012). Rapid automatized naming (RAN) and reading fluency: Implications for understanding and treatment of reading disabilities. *Annual Review of Psychology*, *63*(1), 427–452. <https://doi.org/10.1146/annurev-psych->

120710-100431

- Odegard, T. N., Farris, E. A., Ring, J., McColl, R., & Black, J. (2009). Brain connectivity in non-reading impaired children and children diagnosed with developmental dyslexia. *Neuropsychologia*, *47*(8–9), 1972–1977.  
<https://doi.org/10.1016/j.neuropsychologia.2009.03.009>
- Paulesu, E., Danelli, L., & Berlinger, M. (2014). Reading the dyslexic brain: Multiple dysfunctional routes revealed by a new meta-analysis of PET and fMRI activation studies. *Frontiers in Human Neuroscience*, *8*, 830.  
<https://doi.org/10.3389/fnhum.2014.00830>
- Pennington, B. F., & Lefly, D. L. (2001). Early reading development in children at family risk for dyslexia. *Child Development*, *72*(3), 816–833. <https://doi.org/10.1111/1467-8624.00317>
- Pierpaoli, C., & Basser, P. J. (1996). Toward a quantitative assessment of diffusion anisotropy. *Magnetic Resonance in Medicine*, *36*(6), 893–906.  
<https://doi.org/10.1002/mrm.1910360612>
- Plaut, D. C., McClelland, J. L., Seidenberg, M. S., & Patterson, K. (1996). Understanding normal and impaired word reading: computational principles in quasi-regular domains. *Psychological Review*, *103*(1), 56–115. <https://doi.org/10.1037/0033-295X.103.1.56>
- Pugh, K. R., Einar Mencl, W., Jenner, A. R., Katz, L., Frost, S. J., Lee Ren, J., ... Laboratories, H. (2000). Functional neuroimaging studies of reading and reading disability (developmental dyslexia). *Mental Retardation and Developmental Disabilities Research Reviews*, *6*(3), 207–213. [https://doi.org/10.1002/1098-2779\(2000\)6:3<207::AID-MRDD8>3.0.CO;2-P](https://doi.org/10.1002/1098-2779(2000)6:3<207::AID-MRDD8>3.0.CO;2-P)
- Ramus, F. (2003). Developmental dyslexia: Specific phonological deficit or general sensorimotor dysfunction? *Current Opinion in Neurobiology*, *13*(2), 212–218.  
[https://doi.org/10.1016/S0959-4388\(03\)00035-7](https://doi.org/10.1016/S0959-4388(03)00035-7)
- Ramus, F., Rosen, S., Dakin, S. C., Day, B. L., Castellote, J. M., White, S., & Frith, U. (2003). Theories of developmental dyslexia: Insights from a multiple case study of dyslexic adults. *Brain*, *126*(4), 841–865. <https://doi.org/10.1093/brain/awg076>
- Report of the National Reading Panel (2000): *Teaching Children to Read: An Evidence Based Assessment of the Scientific Research Literature on Reading and its Implications for Reading Instruction* (Vol. NIH Pub. No. 00-4754): U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Institute of Child Health and Human Development.
- Richards, T., Stevenson, J., Crouch, J., Johnson, L. C., Maravilla, K., Stock, P., ... Berninger, V. (2008). Tract-based spatial statistics of diffusion tensor imaging in adults with dyslexia. *American Journal of Neuroradiology*, *29*(6), 1134–1139.  
<https://doi.org/10.3174/ajnr.A1007>
- Richlan, F., Kronbichler, M., & Wimmer, H. (2009). Functional abnormalities in the dyslexic brain: A quantitative meta-analysis of neuroimaging studies. *Human Brain Mapping*, *30*(10), 3299–3308. <https://doi.org/10.1002/hbm.20752>
- Richlan, F., Kronbichler, M., & Wimmer, H. (2011). Meta-analyzing brain dysfunctions in dyslexic children and adults. *NeuroImage*, *56*(3), 1735–1742.  
<https://doi.org/10.1016/j.neuroimage.2011.02.040>
- Rimrodt, S. L., Peterson, D. J., Denckla, M. B., Kaufmann, W. E., & Cutting, L. E.

- (2010). White matter microstructural differences linked to left perisylvian language network in children with dyslexia. *Cortex*, 46(6), 739–749. <https://doi.org/10.1016/j.cortex.2009.07.008>
- Sandak, R., Mencl, W. E., Frost, S. J., & Pugh, K. R. (2004). The neurobiological basis of skilled and impaired reading: Recent findings and new directions. *Scientific Studies of Reading*, 8(3), 273–292. [https://doi.org/10.1207/s1532799xssr0803\\_6](https://doi.org/10.1207/s1532799xssr0803_6)
- Scarborough, H. S. (1998). Predicting the future achievement of second graders with reading disabilities: Contributions of phonemic awareness, verbal memory, rapid naming, and IQ. *Annals of Dyslexia*, 48, 115–136. <https://doi.org/10.1007/s11881-998-0006-5>
- Schatschneider, C., Fletcher, J. M., Francis, D. J., Carlson, C. D., & Foorman, B. R. (2004). Kindergarten prediction of reading skills: A longitudinal comparative analysis. *Journal of Educational Psychology*, 96(2), 265–282. <https://doi.org/10.1037/0022-0663.96.2.265>
- Seidenberg, M. S. (2005). Connectionist models of word reading. *Current Directions in Psychological Science*, 14(5), 238–242. <https://doi.org/10.1111/j.0963-7214.2005.00372.x>
- Seidenberg, M. S., & McClelland, J. L. (1989). A distributed, developmental model of word recognition and naming. *Psychological Review*, 96(4), 523–568. <https://doi.org/10.1037/0033-295X.96.4.523>
- Shankweiler, D., & et al. (1979). The speech code and learning to read. *Journal of Experimental Psychology: Human Learning and Memory*, 5(6), 531–545. <https://doi.org/10.1037/0278-7393.5.6.531>
- Shaywitz, S. E., Fletcher, J. M., Holahan, J. M., Shneider, A. E., Marchione, K. E., Stuebing, K. K., ... Shaywitz, B. A. (1999). Persistence of dyslexia: The Connecticut Longitudinal Study at adolescence. *Pediatrics*, 104(6), 1351–1359. <https://doi.org/10.1542/peds.104.6.1351>
- Shaywitz, S. E., Shaywitz, B. A., Fletcher, J. M., & Makuch, R. (1992). Evidence that dyslexia may represent the lower tail of a normal distribution of reading ability. *New England Journal of Medicine*, 326(3), 145–150. <https://doi.org/10.1056/NEJM199201163260301>
- Siegel, L. S. (2006). Perspectives on dyslexia. *Paediatrics and Child Health*, 11(9), 581–587. <https://doi.org/10.1093/pch/11.9.581>
- Snowling, M.J. (2000). *Dyslexia* (2nd edition). Blackwell.
- Stanovich, K. E., & Siegel, L. S. (1994). Phenotypic performance profile of children with reading disabilities: A regression-based test of the phonological-core variable-difference model. *Journal of Educational Psychology*, 86(1), 24–53. <https://doi.org/10.1037/0022-0663.86.1.24>
- Stanovich, K. E., Siegel, L. S., & Gottardo, A. (1997). Converging evidence for phonological and surface subtypes of reading disability. *Journal of Educational Psychology*, 89(1), 114–127. <https://doi.org/10.1037/0022-0663.89.1.114>
- Stein, J. (2001). The magnocellular theory of developmental dyslexia. *Dyslexia*, 7(1), 12–36. <https://doi.org/10.1002/dys.186>
- Stein, J. (2003). Visual motion sensitivity and reading. *Neuropsychologia*, 41(13), 1785–1793. [https://doi.org/10.1016/S0028-3932\(03\)00179-9](https://doi.org/10.1016/S0028-3932(03)00179-9)
- Stein, J., & Walsh, V. (1997). To see but not to read; the magnocellular theory of

- dyslexia. *Trends in Neurosciences*, 20(4), 147–152. [https://doi.org/10.1016/S0166-2236\(96\)01005-3](https://doi.org/10.1016/S0166-2236(96)01005-3)
- Steinbrink, C., Vogt, K., Kastrup, A., Müller, H. P., Juengling, F. D., Kassubek, J., & Riecker, A. (2008). The contribution of white and gray matter differences to developmental dyslexia: Insights from DTI and VBM at 3.0 T. *Neuropsychologia*, 46(13), 3170–3178. <https://doi.org/10.1016/j.neuropsychologia.2008.07.015>
- Tallal, P. (1980). Auditory temporal perception, phonics, and reading disabilities in children. *Brain and Language*, 9(2), 182–198. [https://doi.org/10.1016/0093-934X\(80\)90139-X](https://doi.org/10.1016/0093-934X(80)90139-X)
- Tallal, P., Miller, S., & Fitch, R. H. (1993). Neurobiological basis of speech: A case for the preeminence of temporal processing. *Annals of the New York Academy of Sciences*, 682(1), 27–47. <https://doi.org/10.1111/j.1749-6632.1993.tb22957.x>
- Tan, L. H., Spinks, J. A., Eden, G. F., Perfetti, C. A., & Siok, W. T. (2005). Reading depends on writing, in Chinese. *Proceedings of the National Academy of Sciences of the United States of America*, 102(24), 8781–8785. <https://doi.org/10.1073/pnas.0503523102>
- Taylor, J. S. H., Rastle, K., & Davis, M. H. (2013). Can cognitive models explain brain activation during word and pseudoword reading? A meta-analysis of 36 neuroimaging studies. *Psychological Bulletin*, 139(4), 766–791. <https://doi.org/10.1037/a0030266>
- Torgesen, J. K., Alexander, A. W., Wagner, R. K., Rashotte, C. A., Voeller, K. K. S., & Conway, T. (2001). Intensive remedial instruction for children with severe reading disabilities: Immediate and long-term outcomes from two instructional approaches. *Journal of Learning Disabilities*, 34(1). <https://doi.org/10.1177/002221940103400104>
- Turkeltaub, P. E., Eden, G. F., Jones, K. M., & Zeffiro, T. A. (2002). Meta-analysis of the functional neuroanatomy of single-word reading: Method and validation. *NeuroImage*, 16(3 I), 765–780. <https://doi.org/10.1006/nimg.2002.1131>
- van den bos, K. P., Zijlstra, B. J. H., & Iutje Spelberg, H. C. (2002). Life-span data on continuous-naming speeds of numbers, letters, colors, and pictured objects, and word-reading speed. *Scientific Studies of Reading*, 6(1), 25–49. [https://doi.org/10.1207/s1532799xssr0601\\_02](https://doi.org/10.1207/s1532799xssr0601_02)
- Vandermosten, M., Boets, B., Poelmans, H., Sunaert, S., Wouters, J., & Ghesquière, P. (2012). A tractography study in dyslexia: Neuroanatomic correlates of orthographic, phonological and speech processing. *Brain*, 135(3), 935–948. <https://doi.org/10.1093/brain/awr363>
- Vandermosten, M., Poelmans, H., Sunaert, S., Ghesquière, P., & Wouters, J. (2013). White matter lateralization and interhemispheric coherence to auditory modulations in normal reading and dyslexic adults. *Neuropsychologia*, 51(11), 2087–2099. <https://doi.org/10.1016/j.neuropsychologia.2013.07.008>
- Vukovic, R. K., Wilson, A. M., & Nash, K. K. (2004). Naming speed deficits in adults with reading disabilities: A test of the double-deficit hypothesis. *Journal of Learning Disabilities*, 37(5), 440–450. <https://doi.org/10.1177/00222194040370050601>
- Wagner, R. K., & Torgesen, J. K. (1987). The nature of phonological processing and its causal role in the acquisition of reading skills. *Psychological Bulletin*, 101(2), 192–212. <https://doi.org/10.1037/0033-2909.101.2.192>

- Wagner, R. K., Torgesen, J. K., & Rashotte, C. A. (1994). Development of reading-related phonological processing abilities: New evidence of bidirectional causality from a latent variable longitudinal study. *Developmental Psychology, 30*(1), 73–87. <https://doi.org/10.1037/0012-1649.30.1.73>
- Welcome, S. E., & Joanisse, M. F. (2014). Individual differences in white matter anatomy predict dissociable components of reading skill in adults. *NeuroImage, 96*, 261–275. <https://doi.org/10.1016/j.neuroimage.2014.03.069>
- Wilson, S. M., Galantucci, S., Tartaglia, M. C., Rising, K., Patterson, D. K., Henry, M. L., ... Gorno-Tempini, M. L. (2011). Syntactic processing depends on dorsal language tracts. *Neuron, 72*(2), 397–403. <https://doi.org/10.1016/j.neuron.2011.09.014>
- Wolf, M. (1986). Rapid alternating stimulus naming in the developmental dyslexias. *Brain and Language, 27*(2), 360–379. [https://doi.org/10.1016/0093-934X\(86\)90025-8](https://doi.org/10.1016/0093-934X(86)90025-8)
- Wolf, M., & Bowers, P. G. (1999). The double-deficit hypothesis for the developmental dyslexias. *Journal of Educational Psychology, 91*(3), 415–438. <https://doi.org/10.1037/0022-0663.91.3.415>
- Yuill, N., & Oakhill, J.V. (1991). *Children's problems in text comprehension*. Cambridge: Cambridge University Press.

## **Chapter 2: Resting-State Functional Connectivity Correlates of Reading Subskills in Children**

### **2.1 Introduction**

Reading is a complex skill that relies on multiple cognitive processes and many different regions of the brain. Many previous studies examining the neural substrates of reading have used neuroimaging techniques to identify regions of the cortex associated with reading in both proficient readers and individuals with reading disability (RD) (see Price, 2012 for a review). However, these regions are distinct and are distributed across many areas of the cortex, and studies of regional activity only capture a part of the neural processes involved in reading. Recent developments in neuroimaging techniques such as functional magnetic resonance imaging (fMRI) have highlighted the importance of coordinated processing across functional networks of distinct brain regions in supporting proficient reading.

Neuroimaging studies examining connectivity among reading-related brain regions have provided insight into the importance of functional connectivity for efficient and accurate reading. For example, Pugh, Mencl, Shaywitz, et al. (2000) found that adults with RD exhibited reduced functional connectivity from the left angular gyrus to left occipito-temporal areas during tasks with high phonological processing demands, but no disruption in functional connectivity was observed on tasks with low phonological processing demands. Similarly, Horwitz, Rumsey, and Donohue (1998) observed reduced functional connectivity in adults with RD between the left angular gyrus and left frontal, temporal, and occipito-temporal areas during a single-word reading task. In children with RD, a disruption in functional connectivity between the fusiform gyrus and left inferior parietal and left inferior frontal language areas was observed during a phonological



lexical decision task (van der Mark et al., 2011). These studies all used task-based approaches, examining functional connectivity based on interregional correlations in activity while participants completed reading or related phonological processing tasks.

A limitation of task-based neuroimaging research is that there is a lack of consensus regarding the type of task that is optimal for characterizing brain networks for reading. Patterns of functional connectivity are known to differ significantly based on the type of task used in task-based fMRI studies (Mechelli et al., 2005; Nakamura, Dehaene, Jobert, Le Bihan, & Kouider, 2007). Because the process of reading can be decomposed into a number of different subskills, different types of reading tasks are likely to produce different types of connectivity patterns. Additionally, in group comparisons, differences observed in task-based connectivity data between a group with RD and a typically-developing group could be related to differences in task performance or processing strategies associated with that particular task. Findings of differences between groups with respect to fMRI findings are therefore confounded with behavioural differences in task performance, making it difficult to differentiate between the cause and effect of these differences.

A potential solution is to study functional networks while participants are in a resting-state rather than using a task-based paradigm. Resting-state fMRI is a task-free technique which measures temporal correlations in the low-frequency fluctuations ( $< 0.1$  Hz) in the fMRI signal of functionally-related brain areas (Biswal et al., 1995). These patterns of resting-state functional connectivity (RSFC) are thought to be specifically organized in a way that reflects the brain's functional networks (see Fox & Raichle, 2007). Regions that are functionally-related tend to be temporally correlated in terms of

their spontaneous BOLD activity. In contrast, regions that have opposing functionality tend to have negatively correlated BOLD activity during resting-states. Some advantages of the RSFC technique are that the neuroimaging data cannot be influenced by any particular task demands, differences in task performance, or differences in processing strategies.

With respect to reading, previous studies using an RSFC approach have shown that networks of functional connectivity align closely between task-based and task-free fMRI data. Using a seed-based approach, Hampson et al. (2006) observed consistent patterns of functional connectivity from the left inferior frontal gyrus in adults, both while they completed a sentence reading task and while they rested quietly in the scanner. The correlations observed from the seed region, the left inferior frontal gyrus, included positive correlations with areas adjacent to the inferior frontal gyrus, and positive correlations extending bilaterally to the superior and middle temporal gyri, the medial occipito-temporal cortex, middle frontal gyrus, and angular gyrus. Additionally, negative correlations were observed between the left inferior frontal gyrus and the bilateral anterior and posterior cingulate cortices. Koyama et al. (2010) extended these findings to examine functional connectivity from six seed regions in the left hemisphere, including the fusiform gyrus, the superior temporal gyrus, the precentral gyrus, the inferior frontal gyrus, the posterior area of the left inferior occipital gyrus, and the temporoparietal junction including the angular gyrus. RSFC from the left inferior frontal gyrus replicated the findings of Hampson et al. (2006). Additionally, patterns of RSFC aligned closely with the reading networks identified in previous task-based studies, including positive correlations between the left temporoparietal junction and left frontal and temporal areas,

as well as between the left fusiform gyrus and the left inferior frontal gyrus extending into the left precentral gyrus. Negative correlations with the seed regions included the medial prefrontal cortex, dorsolateral prefrontal cortex, anterior cingulate cortex, superior lateral parietal cortex, lateral temporal cortex, posterior cingulate cortex, and precuneus. The posterior cingulate and precuneus are areas associated with the default mode network, a network of brain regions in which activity is increased during rest and attenuated during other cognitive tasks (for a review see Raichle, 2015). Other negatively correlated areas such as the dorsolateral prefrontal and superior parietal cortices are regions associated with effortful control (Cazalis et al., 2003; MacDonald, 2008) and high working memory load (Marklund et al., 2007; Wendelken, Bunge, & Carter, 2008). The authors suggest that these negative correlations between areas of the reading network and other brain networks may reflect greater segregation of functional systems, possibly related to greater automatization of reading. Overall, these studies demonstrate the value of resting-state based approaches in examining functional connectivity independent of some confounds associated with task-based designs.

Differences in RSFC in the reading network have also been linked to behavioural reading ability, both in studies comparing individuals with RD to typical readers and by using an individual differences approach. In individuals with RD compared to typical readers, RSFC is characterized by reduced connectivity between the left and right inferior frontal gyri (Farris et al., 2011), between the left intraparietal sulcus and left middle frontal gyrus (Koyama et al., 2013), and between left inferior gyrus and left posterior temporal areas including the fusiform gyrus, and inferior, middle, and superior temporal gyri (Schurz et al., 2015). Additionally, adolescents and adults with RD have greater

RSFC between regions associated with reading and areas of the default mode network, particularly the precuneus (Schurz et al., 2015).

Studies using an individual differences approach have related behavioural reading ability in individuals with a wide range of reading proficiencies to differences in the strength of RSFC. Vogel et al. (2011) observed that in children aged 6 to 9 years old, RSFC of the putative visual word form area and the bilateral anterior inferior parietal sulcus increased with reading skill, as measured by a composite of single-word reading, reading comprehension, and decoding ability. In a study of children and adults, Koyama et al. (2011) found positive associations between single word reading ability and RSFC for both groups in connections from the left precentral gyrus seed to the left postcentral gyrus, bilateral supplementary motor area and posterior cingulate cortex, and right postcentral/precentral gyrus, as well as from the left inferior frontal gyrus pars opercularis seed to the left superior temporal gyrus. However, when the authors compared RSFC-behaviour relationships between children and adults, divergent patterns of results emerged. In adults only, positive RSFC-behaviour relationships were found for connections from the left fusiform gyrus seed to the left inferior frontal gyrus pars opercularis and the left inferior parietal lobule. For the same functional connections in children, negative correlations were observed between RSFC strength and word reading performance. The authors suggest this may be related to experience-dependent functional development of the fusiform gyrus. Additionally, a positive RSFC-behaviour relationship was observed for children for functional connections between the left fusiform gyrus seed and regions of the default mode network, whereas the same connections showed a negative relationship between RSFC strength and reading performance in adults similar

to that observed by Koyama et al. (2010). Finally, positive RSFC-behaviour correlations were observed for connections from the left intraparietal sulcus and the bilateral thalamus in children, but this relationship was negative in adults. Koyama et al. (2011) argue that these findings may be related to functional segregation among the networks associated with reading, rest, and visual attention processes. Although functional segregation among networks may be important for efficient and automatized reading in adults, a lack of segregation may not be detrimental to reading in children. Overall, these studies demonstrate that while the relationship between RSFC and behaviour changes throughout development, stronger reading in children is related to stronger functional connectivity among regions of the reading network as well as reduced segregation between areas of the reading network and other neural networks.

Put together, the present literature shows that RSFC in the reading network of the brain, as well as RSFC to other brain networks such as the default mode network, varies based on reading ability in children and adults. However, previous studies of reading and RSFC have examined reading skills using single word reading measures involving reading of words likely to be familiar to the reader, or composite measures of reading that combine scores across many types of reading tasks. Little research to date has examined whether the behaviour-RSFC relationship for reading differs across the many subskills associated with proficient reading. These include *decoding*, in which readers match orthographic representations onto phonological representations to decode words; *sight word reading*, in which skilled readers recognize familiar words without decoding; and *reading comprehension*, in which readers map lexical representations onto semantic representations to understand a word, sentence, or text. Finally, reading is also known to

be strongly associated with performance on *rapid automatized naming (RAN)* tasks (for a review see Norton & Wolf, 2012). In RAN tasks, an individual quickly names an array of familiar stimuli such as letters, digits, colours, or objects. This is thought to index the fluent perceptual, attentional, and motoric processes involved in reading aloud (Arnell et al., 2009; Kirby et al., 2010). Although phonological awareness and RAN are both strong early predictors of reading abilities (Pennington & Lefly, 2001; Scarborough, 1998; Schatschneider et al., 2004), studies of older children and adolescents suggest that performance on RAN tasks remains a strong predictor of reading ability throughout later school-age years, particularly with respect to RAN tasks involving naming letters or numbers (Meyer, Wood, Hart, & Felton, 1998; Wolf, 1986).

A study of task-based functional connectivity has demonstrated differences in functional connectivity observed in children with rapid naming deficits, with phonological awareness deficits, and with deficits in both skills, suggesting that patterns of functional connectivity are dissociable for different predictors of reading ability. However, these findings have not yet been extended to RSFC, or to other reading-related skills such as decoding and reading comprehension. In the present study, we aimed to examine individual differences in children's reading subskills, including decoding efficiency, sight word reading efficiency, comprehension, and RAN, and their relationship with RSFC in the brain's reading network. Nonverbal intelligence was also included as a measure in the present study to assess whether any effects observed were specific to reading ability or whether they could be attributed to more general cognitive factors. We focused on 11 regions of interest (ROIs) implicated in previous neuroimaging studies of reading (Bolger, Perfetti, & Schneider, 2005; Houdé, Rossi, Lubin, & Joliot,

2010; Koyama et al., 2010) and measured the correlation between performance on the behavioural tasks and functional connectivity from ROI seed regions to all other voxels in the brain. With this approach, we examined common and divergent relationships between RSFC and behaviour for different subskills associated with reading in children.

## **2.2 Methods**

### **2.2.1 Participants**

Participants were 83 children between 8 and 14 years old (mean age = 10.91 years, 45 female, 75 right-handed) in southwestern Ontario, Canada, recruited through local schools and social media advertisements. Some recruitment was targeted to children with reading disabilities participating in a reading intervention program in local schools. As a result, eighteen of the participants had been previously identified with reading difficulties by school professionals. The remaining participants had a wide range of reading abilities but any poor readers had not been formally identified with reading difficulties. All participants' parents reported that the children were native speakers of English and had normal hearing, normal or corrected-to-normal vision, and no known neurological impairments. All parents provided informed consent and children provided assent to participate at the beginning of the study.

### **2.2.2 Procedures**

One and three months prior to the MRI scanning session, all participants completed a battery of behavioural tests of reading and cognitive abilities and mock scanner training, as described below. The behavioural test battery included measures of sight word reading efficiency, decoding efficiency, reading comprehension, and rapid automatized naming.

**Sight word reading efficiency.** Children completed the *Test of Word Reading Efficiency-II* (TOWRE-2; Torgesen et al., 2012) *Sight Word Efficiency* subtest, in which they were given a list of words of increasing difficulty and were asked to read as many words aloud as possible in 45 seconds. This task measures fluency and accuracy of sight word reading.

**Decoding efficiency.** Fluency and accuracy of decoding was assessed using the *TOWRE-2 Phonemic Decoding Efficiency* subtest. Children were given a list of nonwords of increasing difficulty and were asked to read as many nonwords aloud as possible in 45 seconds.

**Reading comprehension.** Children completed the *Woodcock Johnson-III* (WJ-III; Woodcock et al., 2001) *Passage Comprehension* subtest as a measure of their ability to integrate syntactic and semantic information while reading. In this task, children read sentences and paragraphs of increasing difficulty and supplied a missing word.

**Rapid automatized naming (RAN) task.** Children were asked to name the items in the 5x10 array of letters (*k, r, m, g*) as quickly and accurately as possible (Howe, Arnell, Klein, Joanisse, & Tannock, 2006; see Appendix A). The task was scored based on the number of letters correctly named per second. This task was used to assess rapid naming abilities known to contribute to reading skill (Bowers & Wolf, 1993; Denckla & Rudel, 1976).

**Nonverbal intelligence.** Children completed the *Weschler Abbreviated Scale of Intelligence Second Edition* (WASI-II; Weschler, 2011) *Performance IQ* measures, which included the *Block Design* and *Matrix Reasoning* subtests, as a measure of nonverbal intelligence. The *Block Design* task involves viewing a sample model or a picture and



replicating the design as quickly as possible using red and white blocks. In the *Matrix Reasoning* task, participant view an unfinished matrix or series and are asked to select an item that completes the matrix from an array of five items. The scores on the *Block Design* and *Matrix Reasoning* subtests were combined to provide a standardized Performance IQ score measuring nonverbal intelligence. The nonverbal intelligence measures were administered in only 63 of the 83 participants.

***Mock scanner training.*** Participants were asked to lie still for 10 minutes in a mock MRI scanner while listening to an audiobook and recorded noises from an MRI scanner. The purpose of this training was to familiarize the participant with the safety rules, protocols, and environment associated with the MRI scan. Additionally, head movements were monitored via an electromagnetic position tracker (Polhemus FasTrack) during the simulated scan, which provided feedback about movement to the child and served as an informal assessment of whether they would be able to remain sufficiently still during the actual MRI scan to acquire good quality MRI images. No participants were excluded from the study based on movement in the simulated scan.

### **2.2.3 MRI acquisition and processing**

The imaging session was completed at the University of Western Ontario's Centre for Functional and Metabolic Mapping one to two weeks following the first session. MRI data was collected using a Siemens 3 Tesla Prisma scanner with a 32-channel head coil. Foam pads were used to minimize head movement. A six-minute T2-weighted resting-state fMRI scan was acquired using an echo planar imaging pulse sequence and oblique axial orientation (TR = 1000 ms; TE = 30ms; flip angle = 45; voxel size = 3 x 3 x 3 mm; FOV = 210 x 210 mm; 48 slices). During this scan, the participants were told to lie still

while looking at a fixation cross on a display. A high-resolution 3-D T1-weighted anatomical scan was also acquired in the sagittal plane (MPRAGE; GRAPPA acceleration factor = 2; TR = 2300 ms; TE = 2.98 ms; flip angle = 9; field of view = 256 x 256 mm; voxel size = 1 x 1 x 1 mm; 192 slices). Participants watched a movie during the anatomical scan, which lasted five minutes. In 63 participants, a diffusion tensor imaging scan was also acquired during the same session as part of the studies described in Chapters 3 and 4. In total, scan time for these participants was approximately 10-15 minutes. The remaining 20 participants completed three additional fMRI tasks as part of another study, with a total scan time of approximately 45 minutes for this group.

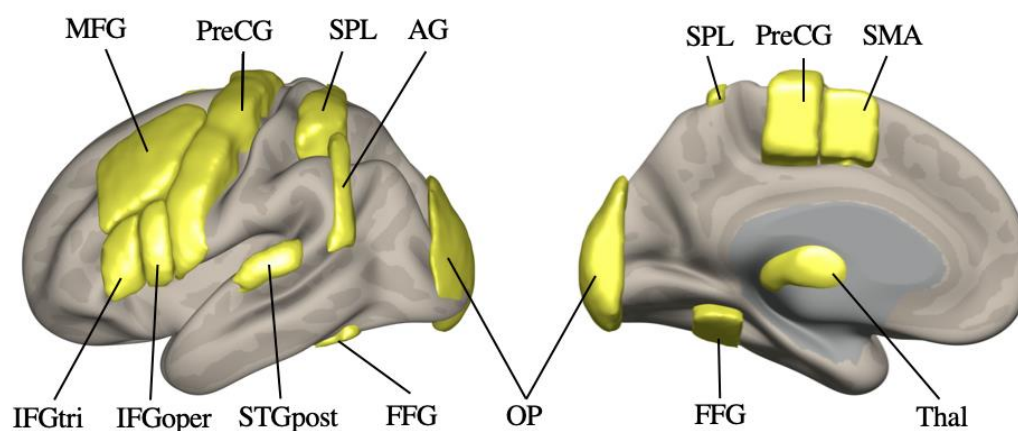
The resting-state fMRI data was pre-processed and denoised using the CONN-fMRI toolbox 17.a (Whitfield-Gabrieli & Nieto-Castanon, 2012) for SPM12 in Matlab R2016b. Pre-processing consisted of realignment, normalization to the MNI anatomical template, and spatial smoothing of the functional data using a Gaussian filter of 5mm. The structural data was segmented into gray matter, white matter, and cerebrospinal fluid. Using the aCompCor noise reduction method, the signal from white matter and cerebrospinal fluid masks were computed and included as nuisance parameters within the final analysis models (Behzadi, Restom, Liau, & Liu, 2007). Subject motion was estimated along three axes each of rotation and translation, and the resulting time series was regressed out of the BOLD functional data. Functional volumes that differed more than 95% from the mean BOLD signal amplitude were removed from analysis. Band pass filtering was performed between 0.008 Hz to 0.09 Hz on the resulting BOLD time-series.

Following preprocessing and denoising, analyses focused on the association between resting-state connectivity from seed regions of interest (ROIs) and individual

differences in reading subskills. Seed ROIs were selected based on a previous resting-state functional connectivity study of reading in children (Koyama et al., 2011) and a meta-analysis of brain areas associated with reading in children (Houdé et al., 2010): the middle frontal gyrus (MFG), inferior frontal gyrus pars opercularis (IFGoper), inferior frontal gyrus pars triangularis (IFGtri), precentral gyrus (PreCG), posterior superior temporal gyrus (STGpost), angular gyrus (AG), superior parietal lobule (SPL) including the intraparietal sulcus, supplementary motor area (SMA), posterior fusiform gyrus (FFG), occipital pole (OP), and thalamus (Thal), all within the left hemisphere. The seeds were all identified for analysis using the CONN atlas image volume which defines ROIs jointly across all subjects within MNI space (FSL Harvard-Oxford atlas and AAL atlas, developed based on: Desikan et al., 2006; Frazier et al., 2005; Goldstein et al., 2007; Makris et al., 2006; Tzourio-Mazoyer et al., 2002). The seed ROIs consisted of the entire anatomical parcels pictured in Figure 2.1 and their coordinates are detailed in Table 2.1.

**Table 2.1** MNI Coordinates of Seed ROIs.

Seed ROI (left hemisphere only)	MNI Coordinate of Seed Centre		
	<i>x</i>	<i>y</i>	<i>z</i>
MFG: Middle frontal gyrus	-38	18	42
IFGoper: Inferior frontal gyrus, pars opercularis	-51	15	15
IFGtri: Inferior frontal gyrus, pars triangularis	-50	29	9
PreCG: Precentral gyrus	-34	-12	49
STGpost: Superior temporal gyrus, posterior	-62	-29	4
AG: Angular gyrus	-50	-56	30
SPL: Superior parietal lobule	-29	-49	57
SMA: Supplementary motor area	-5	-3	56
FFG: Fusiform gyrus, posterior	-34	-54	-16
OP: Occipital pole	-17	-97	7
Thal: Thalamus	-10	-19	6



**Figure 2.1** Seed regions of interest, shown in a lateral and medial view.

Each subject's residual BOLD time course was extracted for each seed ROI by averaging across all voxels in the seed. A weighted general linear model was used to measure correlations between time series of the seed region and all other voxels in the brain for each subject, to estimate functional connectivity from each seed region to the rest of the brain. The correlation coefficients were Fisher transformed into z-scores to increase normality for the second-level analyses. As norms do not exist for the RAN task used in the present study, all subsequent analyses for all behavioural measures were performed using raw behavioural scores, with age added as a covariate to account for any confounding effects of age. Multiple regression analyses were then used to examine whether resting-state functional connectivity between seed ROIs and other voxels was uniquely associated with scores on any behavioural reading tasks, independent of age. False positive control was implemented using a cluster size threshold, defined by false-discovery rate (FDR) corrected p-values. With functional connectivity datasets, many statistical tests can be considered simultaneously to examine connectivity across multiple

regions of the brain, and standard procedures for correcting for multiple comparisons such as the Bonferroni correction tend to be overly conservative, eliminating both false and true positives when applied to large neuroimaging datasets. In contrast, the FDR is the proportion of false positives among only those tests for which the null hypothesis is rejected. This procedure is adaptable to the properties of the dataset and has been shown to have greater sensitivity and power than other methods for multiple correction when applied to fMRI datasets (Genovese, Lazar, & Nichols, 2002).

## **2.3 Results**

### **2.3.1 Behavioural results**

Descriptive statistics for standard scores on the behavioural measures are presented in Table 2.2. The descriptive statistics showed that the sample included a wide range of variability in sight word reading efficiency, decoding efficiency, reading comprehension, rapid naming, and nonverbal intelligence. Thirteen children met criteria for reading disability, defined as standard scores less than 1.5 standard deviations below the mean on at least two of the three normed reading measures. These thirteen children were all part of the subsample previously identified by school professionals as struggling readers.

Pearson's correlations among behavioural measures were calculated using standard scores for the TOWRE and WJ-III measures for descriptive purposes (Table 2.3). As the nonverbal intelligence measures were administered in only 63 of 83 participants, the Pearson's correlations examining nonverbal intelligence only included this subset of participants. To examine whether motion in the scanner was a significant confound, Pearson's correlations were also conducted between each of the behavioural

measures with maximum movement and mean movement during the resting-state scan (Table 2.3). This was completed because head motion during scanning can cause artifacts in fMRI data (Hajnal et al., 1994) and because ADHD is known to be unusually comorbid with RD in children (Semrud-Clikeman et al., 1992) and could contribute to increased motion in the MRI scan. A Bonferroni correction was used to correct all Pearson's correlations for multiple comparisons (corrected  $p < .0025$ ). Most behavioural measures were significantly correlated with one another, with the exception of RAN with reading comprehension, and nonverbal intelligence with decoding efficiency and RAN, each of which did not pass the Bonferroni correction. Maximum movement and mean movement were not significantly correlated with any behavioural measures, suggesting that motion during the resting-state scan is not a significant confound in the present study. All functional connectivity analyses also regressed out subject motion along three axes of rotation and translation, to account for the possibility of motion effects that were not completely captured by the Pearson's correlations.

**Table 2.2** Descriptive statistics for behavioural tasks.

	Mean (SD)	Range
Age (years)	10.91 (1.03)	8.83-14.68
Sight word reading efficiency (standard score)	94.13 (19.60)	55-139
Decoding efficiency (standard score)	95.16 (18.71)	56-131
Reading comprehension (standard score)	92.06 (12.42)	46-120
RAN (# correct/second)	1.88 (0.43)	0.90-2.90
Nonverbal intelligence (standard score)	108.68 (18.42)	63-147

**Table 2.3** Pearson's correlations among behavioural measures and motion parameters.

	1.	2.	3.	4.	5.	6.
1. Sight word reading efficiency	-					
2. Decoding efficiency	0.88*	-				
3. Reading comprehension	0.67*	0.68*	-			
4. RAN	0.61*	0.68*	0.30	-		
5. Nonverbal intelligence	0.39*	0.33	0.34*	0.11	-	
6. Maximum movement	-0.04	-0.09	-0.16	-0.12	0.05	-
7. Mean movement	-0.01	-0.01	-0.09	-0.23	0.08	0.40*

Note: \* denotes  $r$ -values that are significant at corrected  $p < .0024$ .

### 2.3.2 Functional connectivity results

Multiple regression analyses were conducted for each reading task to examine relationships between reading and RSFC from each seed region to other voxels of the brain, with age added as a covariate. For the phonemic decoding measure, positive relationships were observed between decoding efficiency and RSFC from the left AG seed to a right hemisphere cluster ( $p_{corr} < .01$ ; Figure 2.2A) including voxels in the right insular cortex, planum polare, central and frontal opercular cortex, temporal pole, and right IFGoper. Additionally, RSFC and decoding efficiency were negatively associated for connections from the left MFG seed to bilateral clusters of voxels in the lateral occipital cortex and AG ( $p_{corr} < .01$ ; Figure 2.2B).

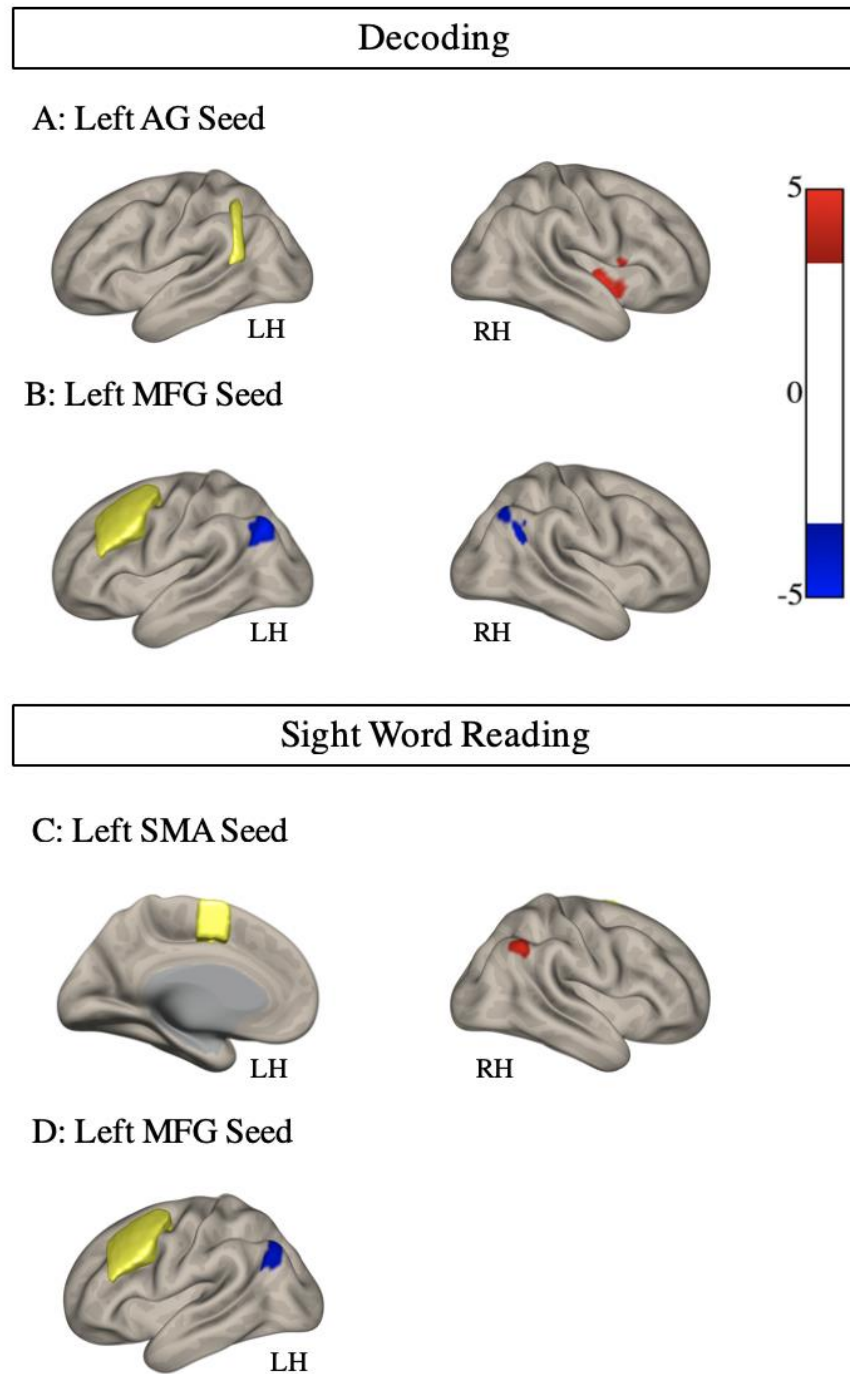
For the sight word efficiency measure, similar negative relationships were observed between sight word reading efficiency and RSFC from the left MFG seed to a cluster of voxels in the left lateral occipital cortex and left angular gyrus ( $p_{corr} < .01$ ; Figure 2.2D). Connectivity from the left SMA seed to a cluster in the right lateral

occipital cortex and right angular gyrus was positively related to sight word reading efficiency ( $p \text{ corr} < .01$ ; Figure 2.2C).

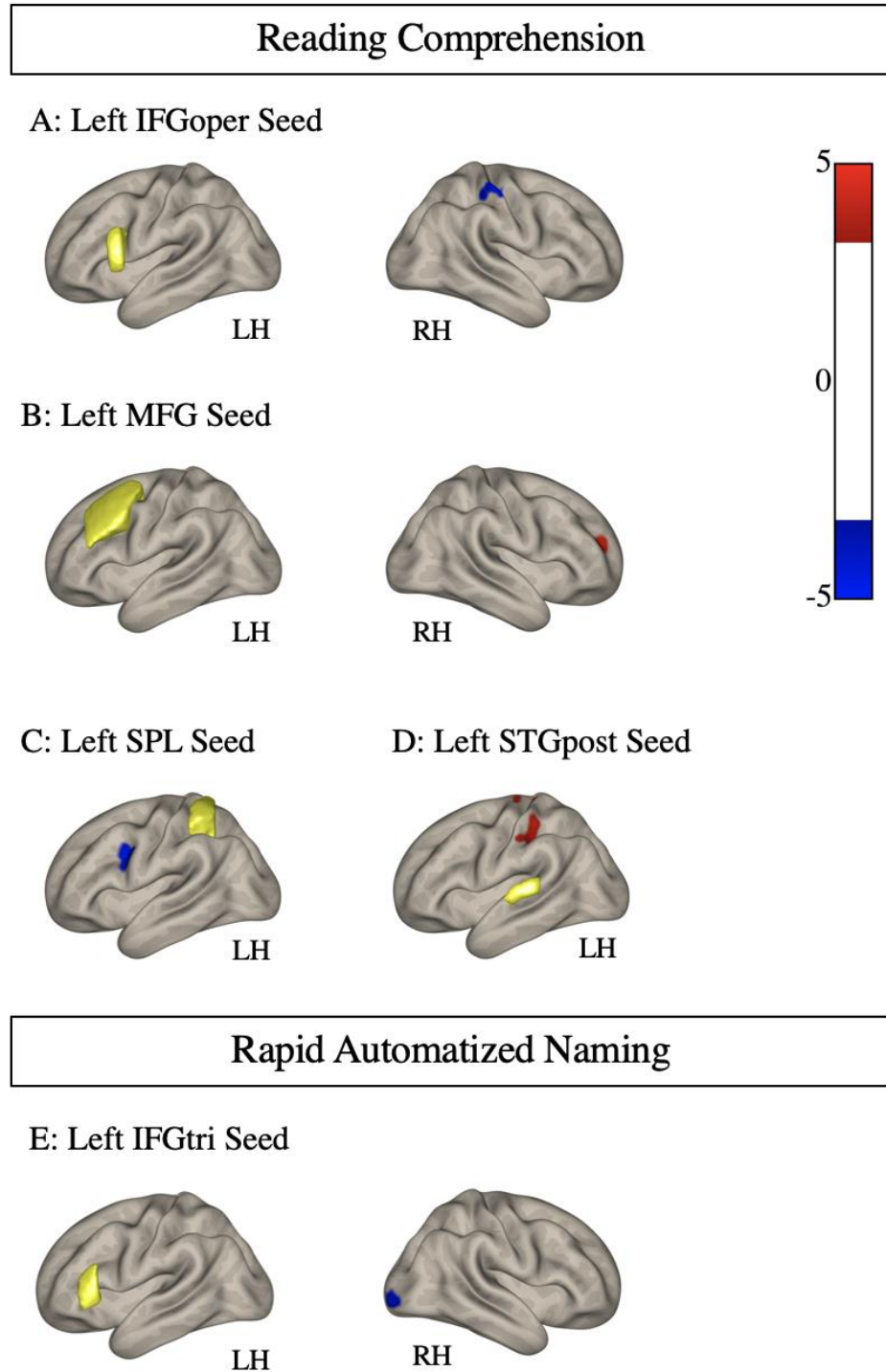
Performance on the reading comprehension task was negatively related to connectivity from the left IFGoper seed to a cluster of voxels on the right postcentral gyrus ( $p \text{ corr} < .01$ ; Figure 2.3A), as well as from the left SPL seed to a left hemisphere cluster including the left PreCG, MFG, and IFGoper ( $p \text{ corr} < .01$ ; Figure 2.3C). Positive associations between reading comprehension scores and connectivity from the left MFG seed were observed for three clusters of voxels: one cluster located in the right frontal pole ( $p \text{ corr} < .01$ ; Figure 2.3B), as well as bilateral clusters including voxels from the putamen and caudate ( $p \text{ corr} < .01$ ). Connectivity from the left STGpost seed was also positively related to reading comprehension for a cluster of voxels in the left postcentral gyrus, left anterior supramarginal gyrus, and left superior parietal lobule ( $p \text{ corr} < .01$ ; Figure 2.3D) and a second cluster of voxels in the left precentral and postcentral gyrus ( $p \text{ corr} < .01$ ; Figure 2.3D).

Both positive and negative relationships between RAN performance and connectivity were observed for RSFC from the left IFGtri seed. Positive relationships were observed for two similar bilateral clusters: one right hemisphere cluster including voxels from the hippocampus, parahippocampal gyrus, and temporal fusiform cortex ( $p \text{ corr} < .01$ ); and a left hemisphere cluster including voxels from the contralateral regions and also extending to voxels in the cerebellum and thalamus ( $p \text{ corr} < .01$ ). The relationship between RAN and connectivity was negative for connections from the left IFGtri seed to a cluster located in the right occipital pole ( $p \text{ corr} < .01$ ; Figure 2.3E).





**Figure 2.2** Significant seed-to-voxel clusters for the decoding efficiency task (A and B) and sight word reading efficiency task (C and D) by seed region. Seeds are shown in yellow and cluster colour represents significant positive (red) and negative (blue)  $t$ -values.

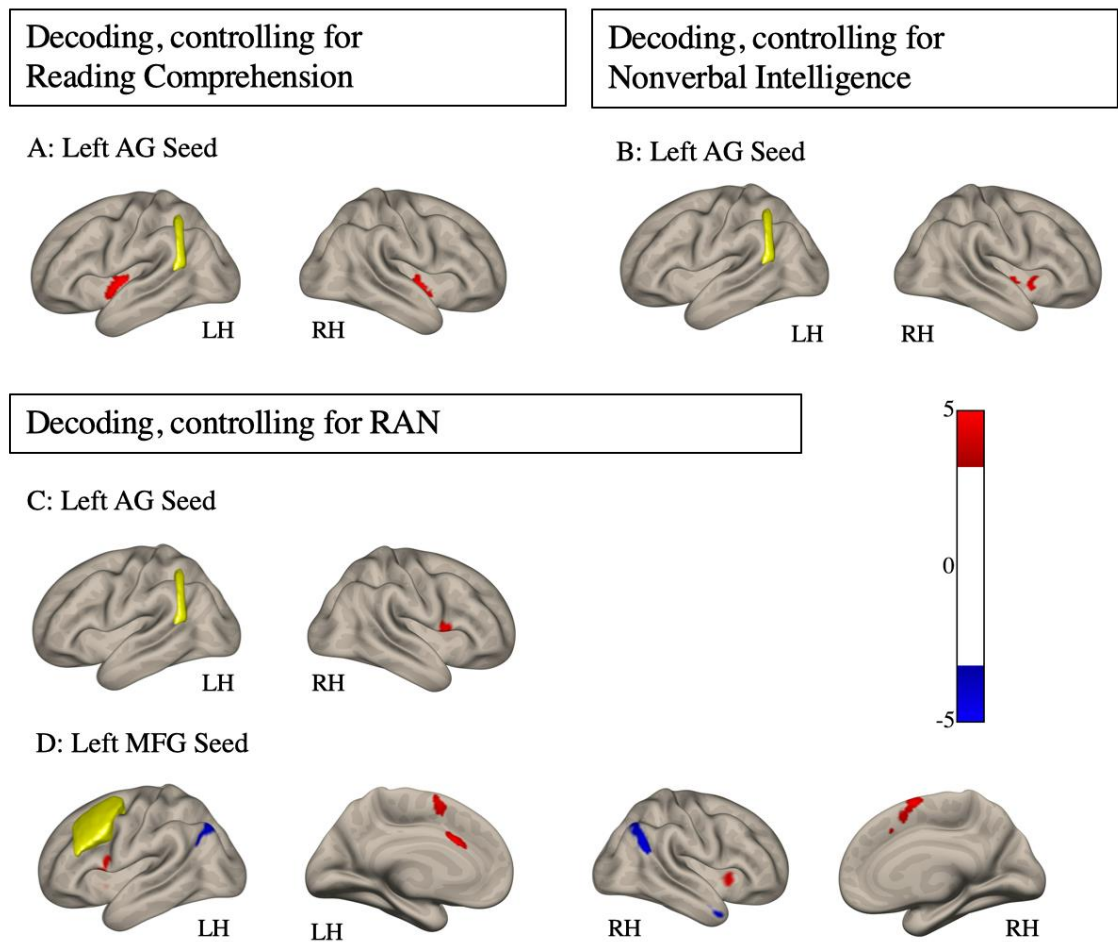


**Figure 2.3** Significant seed-to-voxel clusters for the reading comprehension task (A, B, C, and D) and RAN task (E) by seed region. Seeds are shown in yellow and cluster colour represents significant positive (red) and negative (blue)  $t$ -values.

Given that these subskills are known to be related to one another and scores on most tasks were significantly correlated, multiple regressions were next conducted to examine the unique contributions of specific subskills to each of the findings. Specifically, we conducted additional multiple regression analyses in the seed regions implicated in the first analyses, while controlling for each of the other reading subskills. Importantly, data for the behavioural tasks met the assumptions of multi-collinearity required for multiple regression analyses.

First, we examined unique effects of decoding efficiency when controlling for each of the other subskills in the AG seed and the MFG seed. When controlling for each of RAN, reading comprehension, and nonverbal intelligence, decoding efficiency was a unique predictor of connectivity from the AG seed to a voxel cluster located around the right frontal and central opercular cortex, IFGoper, precentral gyrus, and insular cortex ( $p \text{ corr} < .01$ ; Figure 2.4A-C). Controlling for reading comprehension also revealed that decoding efficiency was uniquely related to connectivity from the AG seed to a similar voxel cluster in the left hemisphere, located in the left insular cortex and frontal and central opercular cortex ( $p \text{ corr} < .01$ ; Figure 2.4A). However, when accounting for sight word reading efficiency, decoding efficiency was not uniquely related to connectivity from the AG seed. Connectivity from the MFG seed to seven clusters of voxels was significantly predicted by decoding efficiency when controlling for RAN scores ( $p \text{ corr} < .01$ ; Figure 2.4D). Specifically, performance was negatively related to connectivity between the MFG and three clusters: one on the right temporal pole and anterior middle temporal gyrus, and two located bilaterally on the lateral occipital cortex and AG. Decoding efficiency was also positively related to connectivity between the MFG and

four clusters: one cluster on the left and right SMA and superior frontal gyrus, a second located on the left IFGoper, frontal opercular cortex, and insular cortex, a third on the right and left paracingulate gyrus and anterior cingulate gyrus, and a fourth on the right frontal opercular cortex, insular cortex, and frontal orbital cortex. Decoding efficiency was not uniquely related to connectivity from the MFG seed when controlling for sight word reading efficiency, reading comprehension, or nonverbal intelligence.



**Figure 2.4** Significant seed-to-voxel clusters for the decoding efficiency task when controlling for sight word reading efficiency (A), nonverbal intelligence (B), and RAN (C&D). Seeds are shown in yellow. Cluster colour represents significant positive (red) and negative (blue)  $t$ -values.

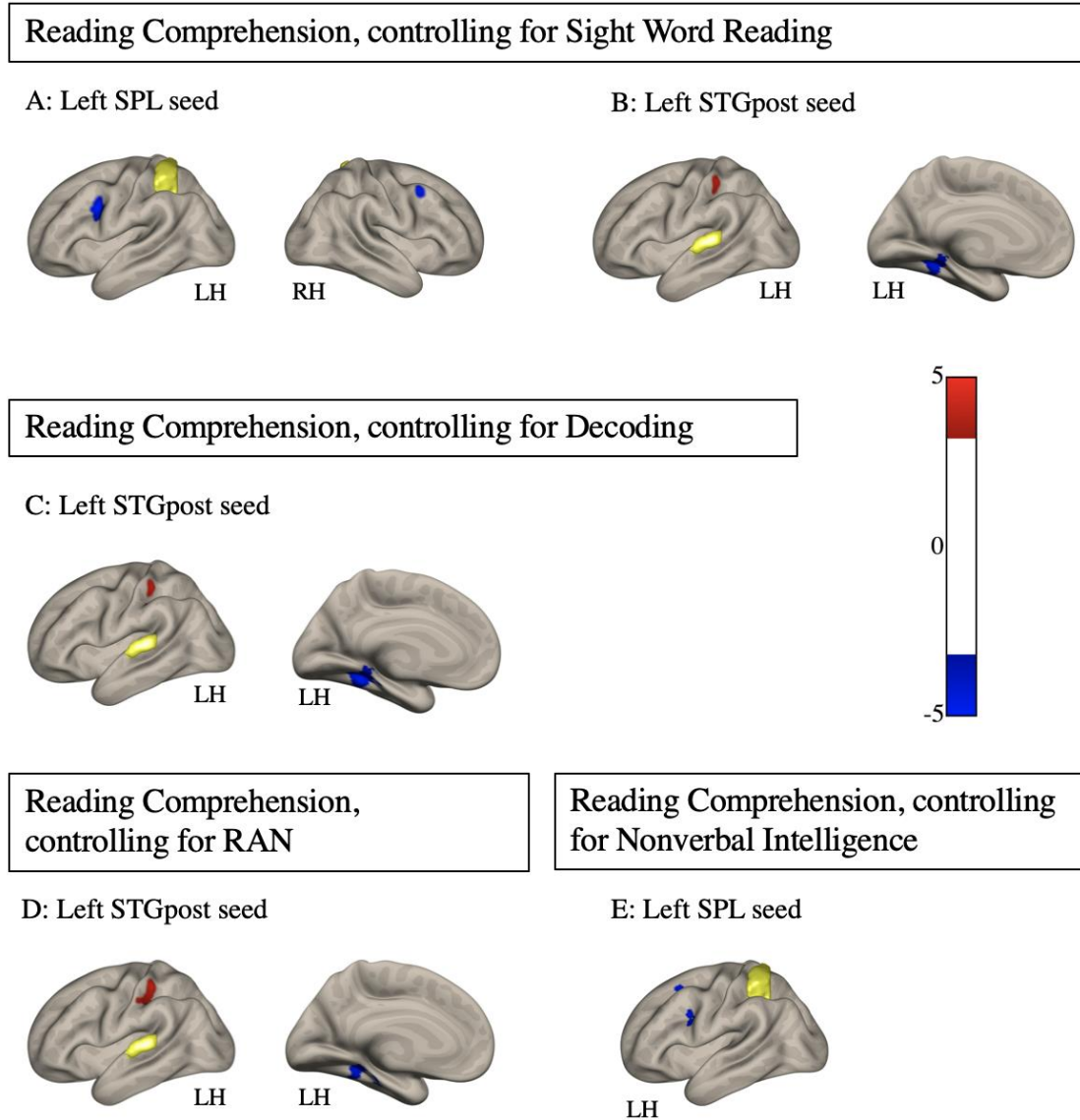
To investigate whether the patterns of connectivity observed for the reading comprehension task were uniquely related to reading comprehension ability or whether they were related to other underlying skills that could contribute to better performance on a reading comprehension task, sight word reading efficiency, decoding efficiency, RAN, and nonverbal intelligence scores were each entered simultaneously with reading comprehension into regression models for the IFGoper, SPL, MFG, and STGpost seeds. Reading comprehension was not a significant predictor of unique variance in connectivity from the MFG or the IFGoper seeds when accounting for decoding efficiency, sight word reading efficiency, RAN, or nonverbal intelligence scores. Reading comprehension also did not significantly predict connectivity from the SPL seed when controlling for decoding efficiency and RAN scores, and from the STG seed when controlling for nonverbal intelligence. When accounting for sight word reading efficiency, better reading comprehension performance uniquely predicted weaker connectivity from the SPL seed to a cluster of voxels in the left PreCG, MFG, IFGoper and to a second cluster in the right MFG and superior frontal gyrus ( $p \text{ corr} < .01$ ; Figure 2.5A). Controlling for nonverbal intelligence in the SPL seed showed that reading comprehension uniquely predicted weaker connectivity to a cluster of voxels in the left PreCG, MFG, and superior frontal gyrus ( $p \text{ corr} < .01$ ; Figure 2.5E). The relationship between reading comprehension and connectivity from the STGpost seed was next examined in a similar manner. When controlling for sight word reading efficiency, reading comprehension performance was uniquely and positively related to connectivity from the STGpost seed to a cluster of voxels on the left postcentral gyrus, SPL, and anterior supramarginal gyrus, and negatively related to connectivity to a cluster of voxels located in the left FFG, lingual

gyrus, a parahippocampal gyrus ( $p \text{ corr} < .01$ ; Figure 2.5B). When accounting for decoding efficiency and for RAN, similar findings were observed for the STGpost seed, such that performance on the passage comprehension task uniquely predicted connectivity to a cluster in the left postcentral gyrus, SPL, and anterior supramarginal gyrus, and a second cluster in the left FFG, lingual gyrus, and parahippocampal gyrus ( $p \text{ corr} < .01$ ; Figure 2.5C-D). No significant relationships between reading comprehension and connectivity from the left STGpost were observed when accounting for nonverbal intelligence scores.

When controlling for each of reading comprehension, sight word reading efficiency, and nonverbal intelligence, RAN was positively associated with connectivity between the IFGtri seed and a cluster located in the right posterior FFG, posterior parahippocampal gyrus, and hippocampus ( $p \text{ corr} < .01$ ; Figure 2.6A,C,D). Controlling for each of reading comprehension and sight word reading efficiency also revealed two clusters in which connectivity from the IFGtri was uniquely related to RAN, one located in the left posterior FFG, posterior parahippocampal gyrus, and hippocampus and a second in the left lingual gyrus, precuneus, and left and right intra- and supra-calcarine cortex ( $p \text{ corr} < .01$ ; Figure 2.6A,C). When accounting for each of sight word reading efficiency and decoding efficiency, a significant cluster of unique negative association between RAN and connectivity was found between the IFGtri seed and the right insula, IFGoper, and frontal opercular cortex ( $p \text{ corr} < .01$ ; Figure 2.6A-B). Finally, controlling for decoding efficiency also revealed two significant clusters of unique associations with RAN from the IFGtri seed, a cluster of positive association in the right supra- and intra-

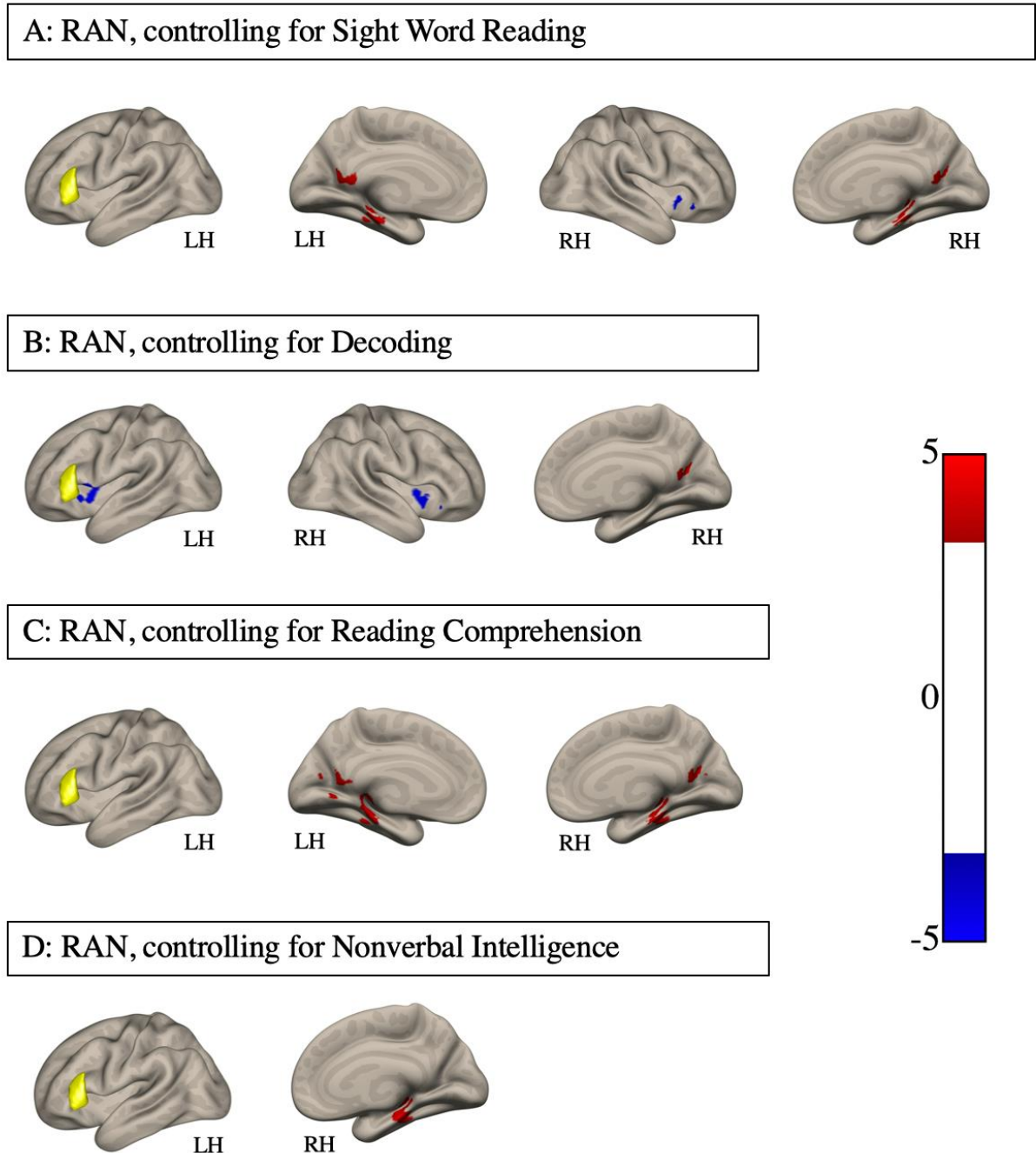
calcarine cortices and precuneus, and a cluster of negative association in the left insula, IFGoper, and central and frontal opercular cortices ( $p_{corr} < .01$ ; Figure 2.6B).

The significant relationships observed for sight word reading efficiency within the left MFG and left SMA seeds were also investigated in a similar manner, controlling for each of the other reading subskills. When controlling for each of decoding efficiency, reading comprehension, RAN, and nonverbal intelligence, sight word reading efficiency was not significantly related to connectivity from the left MFG seed or the left SMA seed.



**Figure 2.5** Significant seed-to-voxel clusters for the reading comprehension task when controlling for sight word reading efficiency (A&B), decoding efficiency (C), RAN (D), and nonverbal intelligence (E). Seeds are shown in yellow. Cluster colour represents significant positive (red) and negative (blue)  $t$ -values.





**Figure 2.6** Significant seed-to-voxel clusters for connectivity from the IFGtri seed for the RAN task when controlling for sight word reading efficiency (A), decoding efficiency (B), reading comprehension (C), and nonverbal intelligence (D). The IFGtri seed is shown in yellow. Cluster colour represents significant positive (red) and negative (blue)  $t$ -values.

## 2.4 Discussion

The aim of the present study was to examine how relationships between RSFC and behaviour vary across different reading subskills. The results demonstrate both common and dissociable RSFC-behaviour relationships for decoding efficiency, sight word reading efficiency, reading comprehension, rapid naming, and, more generally, nonverbal intelligence. Interestingly, while many positive RSFC-behaviour relationships were present indicating stronger functional connectivity in more proficient readers, a number of the RSFC-behaviour relationships observed were negative, suggesting that poorer readers exhibited stronger functional connectivity between some brain regions. These negative associations may represent a pattern of atypical functional connectivity in struggling readers, and a shift towards reduced dependence on these networks in proficient readers. Alternately, negative associations may represent anticorrelation of functional activity in stronger readers, possibly related to inhibition of particular brain regions or networks for more efficient reading. Including other reading subskills as covariates showed that many relationships between RSFC and behavioural scores diverged across the different subskills, suggesting that although these subskills are related, different component skills of reading rely on unique functional connections.

### 2.4.1 Positive RSFC-behaviour relationships

Positive RSFC-reading relationships diverged across the different subskills, suggesting that the functional connections supporting reading differ for various types of reading subskills. Better performance on the decoding efficiency task was uniquely characterized by stronger RSFC from the left AG seed to right temporal and frontal regions when accounting for reading comprehension, RAN, and nonverbal intelligence,

as well as from the left MFG to a number of clusters in the bilateral parietal and frontal lobes when accounting for individual differences in RAN. Interestingly, the cluster of significant association between decoding efficiency and RSFC from the left AG seed did not persist when controlling for sight word reading efficiency, suggesting this may be related to single word reading more generally. Better sight word reading efficiency was associated with strong RSFC from the left SMA to the right AG and right occipital regions, however this relationship did not persist when controlling for each of decoding efficiency, reading comprehension, RAN, and nonverbal intelligence, suggesting that RSFC between these regions may be accounted for by reading or cognitive abilities more generally. The regions implicated here are consistent with previous models of single word reading suggesting that a ventral circuit including occipital regions is associated with sight word reading efficiency, while dorsal circuit including the angular gyrus and other temporo-parietal regions is associated with mapping orthography to phonology when decoding efficiency and a more anterior circuit centered around the IFG is related to articulatory recoding while reading aloud (for a review see Pugh, Mencl, Jenner, et al., 2000 and Sandak, Mencl, Frost, & Pugh, 2004). However, the implication of interhemispheric connections in positive relationships with these reading subskills is of particular interest, given that previous research has tended to focus on left hemisphere connectivity. Studies of reading taking a developmental approach suggest an initial reliance on both hemispheres for reading with a shift towards more left lateralized reading function with maturation or reading experience. For example, fMRI studies of subjects ranging in age from school aged to adulthood have observed decreased activation of right hemisphere regions with increased age, including right superior and

middle frontal regions (Shaywitz et al., 2007) and right inferior temporal regions (Turkeltaub, Gareau, Flowers, Zeffiro, & Eden, 2003). In line with this, our findings suggest that coordinated activation between the left hemisphere reading network and right hemisphere regions play a role in successful reading in school-aged readers.

Reading comprehension scores were positively related to RSFC from the left MFG to the right frontal pole and bilateral dorsal striatum, although analyses controlling for decoding efficiency, sight word reading efficiency, and RAN suggested that this relationship was not unique to comprehension. Although the dorsal striatum has not been previously implicated in RSFC studies of reading, previous fMRI research has shown overactivation of the dorsal striatum, particularly the caudate, in adolescents and adults with RD (Hoeft et al., 2007; Kronbichler et al., 2006; Richlan et al., 2009a, 2011). This has generally been attributed to increased attentional or working memory demands in poor adolescent or adult readers and overintegration of the dorsal striatum into fronto-parietal attention networks (Achal, Hoeft, & Bray, 2016; Hoeft et al., 2007). In early readers, the dorsal striatum has been hypothesized to play an important role in learning of phonological and orthographic rules (Hancock, Richlan, & Hoeft, 2017). Hyperactivation of the dorsal striatum is not consistently observed in children with RD (Richlan et al., 2011), and a study of school-age children showed that activity in the left caudate was positively correlated with later reading ability, but this pattern was not observed in older children (McNorgan, Alvarez, Bhullar, Gayda, & Booth, 2011). In line with this, our RSFC findings indicated that the dorsal striatum and associated networks may contribute to reading success in developing readers, suggesting there may be a developmental shift towards less reliance on these networks as reading becomes more automatized in

adolescents and adults. We also observed unique positive correlations between reading comprehension and RSFC from the left STG to left parietal regions, consistent with regions of the ventral attention network. This network has previously been implicated in reading fluency (Freedman, Zivan, Farah, & Horowitz-Kraus, 2020; Horowitz-Kraus, Toro-Serey, & DiFrancesco, 2015) and narrative processing (Farah & Horowitz-Kraus, 2019), suggesting the ventral attention network may contribute to comprehension and fluency during both reading and oral language processing. Together, our findings suggest an important role for striatal and attentional networks in reading success in developing readers, particularly with respect to reading comprehension abilities.

The final positive RSFC-behaviour relationship observed in the present study showed that children who performed better on the letter RAN task exhibited stronger RSFC from the left IFGtri to the bilateral hippocampi and FFG, when individual differences in other subskills were accounted for. Although the hippocampus is more commonly associated with language learning (Breitenstein et al., 2005; M. H. Davis, Di Betta, Macdonald, & Gaskell, 2009) and memory (Eldridge, Knowlton, Furmanski, Bookheimer, & Engel, 2000; Greicius, Krasnow, Boyett-Anderson, et al., 2003; Schacter & Wagner, 1999; Zeineh, Engel, Thompson, & Bookheimer, 2003), studies of reading have observed that gray matter volume of the hippocampus is associated with form-sound mapping (He et al., 2013) and improvement in general reading skills following intervention (Krafnick, Flowers, Napoliello, & Eden, 2011). RAN performance has been more directly linked to structure and function of the left IFGtri (Cummine, Chouinard, Szepesvari, & Georgiou, 2015; Misra, Katzir, Wolf, & Poldrack, 2004; Rollans, Cheema, Georgiou, & Cummine, 2017) and FFG (Cummine et al., 2015; Cummine, Szepesvari,

Chouinard, Hanif, & Georgiou, 2014; Misra et al., 2004; Raschle, Chang, & Gaab, 2011), although FFG activation has been found to be greater for object RAN tasks relative to letter RAN tasks (Cummine et al., 2014; Misra et al., 2004). Nonetheless, our finding suggests that RSFC from the left IFG to the bilateral hippocampi and FFG may be important for fluency of retrieval and articulation of letter names during rapid letter naming tasks.

#### **2.4.2 Negative RSFC-behaviour relationships**

In contrast, a number of negative RSFC-behaviour relationships were observed, indicating that poorer readers exhibited stronger RSFC between particular brain regions. These negative associations may represent an over-reliance on atypical functional connections in struggling readers, and a shift towards reduced dependence on these areas in strong readers. Alternately, these could represent inhibition of function between regions or functional segregation of different networks in stronger readers, resulting in patterns of anticorrelation in RSFC.

Specifically, children who performed poorly on both the decoding efficiency and sight word reading efficiency tasks had stronger RSFC from the left MFG to the bilateral AG and occipital cortex. When controlling for RAN, this correlation persisted for decoding efficiency but not for sight word reading efficiency, suggesting some unique contributions of decoding efficiency to RSFC between these regions when accounting for individual differences in rapid naming skills. Previous task-based functional connectivity research has suggested that individuals with RD exhibit increased functional connectivity from the right angular gyrus during word and nonword reading tasks, possibly as a form of compensation (Pugh, Mencl, Shaywitz, et al., 2000). Our results raise the possibility of

compensatory reliance on both connectivity from both the left and right angular gyrus to the left MFG in struggling readers. Our findings that RAN was negatively associated with stronger RSFC from the left IFGtri to the right occipital pole further suggest an atypical reliance on functional networks between the left frontal and right occipital lobes for recognizing and rapidly naming letters and unfamiliar words.

Reading comprehension was uniquely related to RSFC between the left STGpost seed and areas of the left fusiform and lingual gyri when controlling for other reading subskills. This relationship did not persist when controlling for nonverbal intelligence, suggesting more general cognitive abilities may be contributing to this effect. Many previous neuroimaging studies have documented activity in the FFG in response to visual forms of words, related to experience with visual word recognition (Glezer, Jiang, & Riesenhuber, 2009; Vinckier et al., 2007). Koyama et al.'s (2011) findings in children included similar negative correlations for RSFC to the FFG and single word reading performance, which they suggest may reflect a lack of dependence on the FFG in developing readers as reading becomes more efficient and automatized. The present study builds on this to suggest that connections from the left FFG to superior temporal regions associated with language comprehension may have a reduced role in reading comprehension in children who are proficient readers, relative to struggling readers.

Finally, when controlling for sight word reading efficiency and nonverbal intelligence, poor reading comprehension was uniquely characterized by stronger RSFC from the left SPL to left frontal areas including the PreCG, MFG, and IFGoper. This is consistent with previous studies finding increased engagement of the inferior frontal gyrus and prefrontal cortex in individuals with RD (Brunswick, McCrory, Price, Frith, &

Frith, 1999; Richards et al., 1999; Rumsey et al., 1997; Salmelin, Service, Kiesilä, Uutela, & Salonen, 1996; Shaywitz et al., 1998), proposed to reflect an atypical reliance on articulatory recoding (Pugh, Mencl, Jenner, et al., 2000). Our findings suggest that children struggling with reading comprehension may rely increasingly on functional networks between the parietal lobe and frontal regions associated with articulatory recoding.

This study is the first investigation of resting-state functional connectivity and reading to consider multiple subskills underlying reading in children, and clearly demonstrates that RSFC-reading relationships diverge across different types of reading subskills. However, a number of other cognitive measures are known to be related to reading and were not included in the current study. Reading competence is also related to skills such as phonological awareness (Gathercole, Alloway, Willis, & Adams, 2006), listening comprehension (Catts et al., 2005, 2003; Hoover & Gough, 1990), oral language (Catts, Fey, Tomblin, & Zhang, 2002), and working memory (Gathercole et al., 2006). Given the divergent RSFC-behaviour relationships observed in the present study, it is likely that these other cognitive measures may also differ in their relationships with RSFC. Nonverbal intelligence was included as a covariate in the present study as it is known to be correlated with reading ability (Ferrer, Shaywitz, Holahan, Marchione, & Shaywitz, 2010; Hulslander et al., 2004), although the magnitude of this correlation varies greatly across studies (Cotton & Crewther, 2009). The findings of the present study suggest that although some RSFC-reading relationships may be partially accounted for by nonverbal intelligence, many of these effects persisted when controlling for



nonverbal intelligence, suggesting effects that are specific to reading-related subskills and are not simply associated with general cognitive processes.

The school age years are periods in which the functional networks of the brain undergo dynamic development (Dosenbach et al., 2010). Importantly, although the present study included children ranging from 8 to 14 years of age, the analyses in the present study included age as a covariate to account for any maturational differences in functional connectivity. This suggests that our findings represent individual differences in functional connectivity that are specifically linked to performance on reading subskills across a wide range of school-aged years. Comparisons of RSFC between children and adults have demonstrated that patterns of RSFC and single word reading competence differ (Koyama et al., 2011), however it is unclear how other component reading skills such as decoding efficiency, comprehension, or rapid naming may be related to RSFC in adults or in pre-reading children. The developmental trajectory of RSFC and its role in reading is of particular interest given previous findings that hyperactivation of brain structures is more frequently reported in adults with RD relative to children with RD, suggesting increasing reliance on compensatory processes with age (Richlan et al., 2011). Future research including a more comprehensive battery of behavioural measures related to reading and investigating both children and adults would shed light on the dynamic nature of RSFC-reading competence relationships throughout reading development.

One additional limitation of this study is that we examined patterns of functional connectivity at the group level. Recent evidence suggests that when functional connectivity is examined at the individual level, some unique network features and topologies are revealed because of individual variability in the functional regions

encompassed by group-averaged ROIs (Gordon et al., 2017). Future research using an individual connectome approach could more precisely characterize the brain networks underlying reading.

### **2.4.3 Conclusions**

We examined how functional connectivity at rest relates to individual differences in reading subskills in school-aged children. The results suggest that distinct functional networks in both hemispheres of the brain support different components of reading ability in children. While our findings were consistent with previous models of reading, they highlight the importance of interhemispheric connectivity in reading, showing that stronger sight word readers exhibited increased RSFC within bilateral ventral networks while stronger decoders exhibited increased RSFC within bilateral dorsal and anterior regions. Better rapid naming skills were related to stronger RSFC between IFG and hippocampal and fusiform areas associated with form-sound mapping. Strong reading comprehension skills were associated with stronger RSFC within striatal networks and ventral attentional networks, demonstrating the importance of these networks in contributing to reading success in early readers. Negative RSFC-behaviour relationships were also observed, suggesting that poor readers exhibit increased dependence on functional connections from the IFG to occipital regions supporting basic visual processing and rapid naming, as well as on functional connections between the FFG and superior temporal regions and between the SPL and prefrontal/inferior frontal regions in children struggling with reading comprehension. These findings further our understanding of the role of functional connectivity in supporting discrete reading

processes involved in reading development in children, and highlight the importance of considering multiple components of reading.

## References

- Achal, S., Hoefl, F., & Bray, S. (2016). Individual differences in adult reading are associated with left temporo-parietal to dorsal striatal functional connectivity. *Cerebral Cortex*, *26*(10), 4069–4081. <https://doi.org/10.1093/cercor/bhv214>
- Arnell, K. M., Klein, R. M., Joanisse, M. F., Bussen, M. A., & Tannock, R. (2009). Decomposing the relation between rapid automatized naming (RAN) and reading ability. *Canadian Journal of Experimental Psychology*, *63*(3), 173–184. <https://doi.org/10.1037/a0015721>
- Behzadi, Y., Restom, K., Liao, J., & Liu, T. T. (2007). A component based noise correction method (CompCor) for BOLD and perfusion based fMRI. *NeuroImage*, *37*(1), 90–101. <https://doi.org/10.1016/j.neuroimage.2007.04.042>
- Biswal, B., Zerrin Yetkin, F., Haughton, V. M., & Hyde, J. S. (1995). Functional connectivity in the motor cortex of resting human brain using echo-planar mri. *Magnetic Resonance in Medicine*, *34*(4), 537–541. <https://doi.org/10.1002/mrm.1910340409>
- Bolger, D. J., Perfetti, C. A., & Schneider, W. (2005). Cross-cultural effect on the brain revisited: Universal structures plus writing system variation. *Human Brain Mapping*, *25*(1), 92–104. <https://doi.org/10.1002/hbm.20124>
- Bowers, P. G., & Wolf, M. (1993). Theoretical links among naming speed, precise timing mechanisms and orthographic skill in dyslexia. *Reading and Writing*, *5*(1), 69–85. <https://doi.org/10.1007/BF01026919>
- Breitenstein, C., Jansen, A., Deppe, M., Foerster, A. F., Sommer, J., Wolbers, T., & Knecht, S. (2005). Hippocampus activity differentiates good from poor learners of a novel lexicon. *NeuroImage*, *25*(3), 958–968. <https://doi.org/10.1016/j.neuroimage.2004.12.019>
- Brunswick, N., McCrory, E., Price, C. J., Frith, C. D., & Frith, U. (1999). Explicit and implicit processing of words and pseudowords by adult developmental dyslexics. A search for Wernicke's Wortschatz? *Brain*, *122*(10), 1901–1917. <https://doi.org/10.1093/brain/122.10.1901>
- Catts, H. W., Fey, M. E., Tomblin, J. B., & Zhang, X. (2002). A longitudinal investigation of reading outcomes in children with language impairments. *Journal of Speech, Language, and Hearing Research*, *45*(6), 1142–1157. [https://doi.org/10.1044/1092-4388\(2002/093\)](https://doi.org/10.1044/1092-4388(2002/093))
- Catts, H. W., Hogan, T. P., & Adlof, S. M. (2005). Developmental changes in reading and reading disabilities. In *The Connections Between Language and Reading Disabilities*. <https://doi.org/10.4324/9781410612052>
- Catts, H. W., Hogan, T. P., & Fey, M. E. (2003). Subgrouping poor readers on the basis of individual differences in reading-related abilities. *Journal of Learning Disabilities*, *36*(2), 151–164. <https://doi.org/10.1177/002221940303600208>
- Cazalis, F., Valabrègue, R., Péligrini-Issac, M., Asloun, S., Robbins, T. W., & Granon, S. (2003). Individual differences in prefrontal cortical activation on the Tower of London planning task: Implication for effortful processing. *European Journal of Neuroscience*, *17*(10), 2219–2225. <https://doi.org/10.1046/j.1460-9568.2003.02633.x>
- Cotton, S. M., & Crewther, S. G. (2009). The relationship between reading and intelligence in primary school aged children: Implications for definitional models of

- dyslexia. *The Open Education Journal*, 2(1), 42–50.  
<https://doi.org/10.2174/1874920800902010042>
- Cummine, J., Chouinard, B., Szepesvari, E., & Georgiou, G. K. (2015). An examination of the rapid automatized naming-reading relationship using functional magnetic resonance imaging. *Neuroscience*, 305, 49–66.  
<https://doi.org/10.1016/j.neuroscience.2015.07.071>
- Cummine, J., Szepesvari, E., Chouinard, B., Hanif, W., & Georgiou, G. K. (2014). A functional investigation of RAN letters, digits, and objects: How similar are they? *Behavioural Brain Research*, 275, 157–165.  
<https://doi.org/10.1016/j.bbr.2014.08.038>
- Davis, M. H., Di Betta, A. M., Macdonald, M. J. E., & Gaskell, M. G. (2009). Learning and consolidation of novel spoken words. *Journal of Cognitive Neuroscience*, 21(4), 803–820. <https://doi.org/10.1162/jocn.2009.21059>
- Denckla, M. B., & Rudel, R. G. (1976). Rapid “automatized” naming (RAN): Dyslexia differentiated from other learning disabilities. *Neuropsychologia*, 14(4), 471–479.  
[https://doi.org/10.1016/0028-3932\(76\)90075-0](https://doi.org/10.1016/0028-3932(76)90075-0)
- Desikan, R. S., Ségonne, F., Fischl, B., Quinn, B. T., Dickerson, B. C., Blacker, D., ... Killiany, R. J. (2006). An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *NeuroImage*, 31(3), 968–980. <https://doi.org/10.1016/j.neuroimage.2006.01.021>
- Dosenbach, N. U. F., Nardos, B., Cohen, A. L., Fair, D. A., Power, J. D., Church, J. A., ... Schlaggar, B. L. (2010). Prediction of individual brain maturity using fMRI. *Science*, 329(5997), 1358–1361. <https://doi.org/10.1126/science.1194144>
- Eldridge, L. L., Knowlton, B. J., Furmanski, C. S., Bookheimer, S. Y., & Engel, S. A. (2000). Remembering episodes: A selective role for the hippocampus during retrieval. *Nature Neuroscience*, 3(11), 1149–1152. <https://doi.org/10.1038/80671>
- Farah, R., & Horowitz-Kraus, T. (2019). Increased functional connectivity within and between cognitive-control networks from early infancy to nine years during story listening. *Brain Connectivity*, 9(3), 285–295.  
<https://doi.org/10.1089/brain.2018.0625>
- Farris, E. A., Odegard, T. N., Miller, H. L., Ring, J., Allen, G., & Black, J. (2011). Functional connectivity between the left and right inferior frontal lobes in a small sample of children with and without reading difficulties. *Neurocase*, 17(5), 425–439.  
<https://doi.org/10.1080/13554794.2010.532141>
- Ferrer, E., Shaywitz, B. A., Holahan, J. M., Marchione, K., & Shaywitz, S. E. (2010). Uncoupling of reading and IQ over time: Empirical evidence for a definition of dyslexia. *Psychological Science*, 21(1), 93–101.  
<https://doi.org/10.1177/0956797609354084>
- Fox, M. D., & Raichle, M. E. (2007). Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nature Reviews Neuroscience*.  
<https://doi.org/10.1038/nrn2201>
- Frazier, J. A., Chiu, S., Breeze, J. L., Makris, N., Lange, N., Kennedy, D. N., ... Biederman, J. (2005). Structural brain magnetic resonance imaging of limbic and thalamic volumes in pediatric bipolar disorder. *American Journal of Psychiatry*, 162(7), 1256–1265. <https://doi.org/10.1176/appi.ajp.162.7.1256>
- Freedman, L., Zivan, M., Farah, R., & Horowitz-Kraus, T. (2020). Greater functional

- connectivity within the cingulo-opercular and ventral attention networks is related to better fluent reading: A resting-state functional connectivity study. *NeuroImage: Clinical*, 26. <https://doi.org/10.1016/j.nicl.2020.102214>
- Gathercole, S. E., Alloway, T. P., Willis, C., & Adams, A. M. (2006). Working memory in children with reading disabilities. *Journal of Experimental Child Psychology*, 93(3), 265–281. <https://doi.org/10.1016/j.jecp.2005.08.003>
- Genovese, C. R., Lazar, N. A., & Nichols, T. (2002). Thresholding of statistical maps in functional neuroimaging using the false discovery rate. *NeuroImage*, 15(4), 870–878. <https://doi.org/10.1006/nimg.2001.1037>
- Glezer, L. S., Jiang, X., & Riesenhuber, M. (2009). Evidence for highly selective neuronal tuning to whole words in the “visual word form area.” *Neuron*, 62(2), 199–204. <https://doi.org/10.1016/j.neuron.2009.03.017>
- Goldstein, J. M., Seidman, L. J., Makris, N., Ahern, T., O’Brien, L. M., Caviness, V. S., ... Tsuang, M. T. (2007). Hypothalamic abnormalities in schizophrenia: Sex effects and genetic vulnerability. *Biological Psychiatry*, 61(8), 935–945. <https://doi.org/10.1016/j.biopsych.2006.06.027>
- Gordon, E. M., Laumann, T. O., Gilmore, A. W., Newbold, D. J., Greene, D. J., Berg, J. J., ... & Hampton, J. M. (2017). Precision functional mapping of individual human brains. *Neuron*, 95(4), 791–807. <https://doi.org/10.1016/j.neuron.2017.07.011>
- Greicius, M. D., Krasnow, B., Boyett-Anderson, J. M., Eliez, S., Schatzberg, A. F., Reiss, A. L., & Menon, V. (2003). Regional analysis of hippocampal activation during memory encoding and retrieval: fMRI study. *Hippocampus*. <https://doi.org/10.1002/hipo.10064>
- Hajnal, J. V., Myers, R., Oatridge, A., Schwieso, J. E., Young, I. R., & Bydder, G. M. (1994). Artifacts due to stimulus correlated motion in functional imaging of the brain. *Magnetic Resonance in Medicine*, 31(3), 283–291. <https://doi.org/10.1002/mrm.1910310307>
- Hampson, M., Tokoglu, F., Sun, Z., Schafer, R. J., Skudlarski, P., Gore, J. C., & Constable, R. T. (2006). Connectivity-behavior analysis reveals that functional connectivity between left BA39 and Broca’s area varies with reading ability. *NeuroImage*, 31(2), 513–519. <https://doi.org/10.1016/j.neuroimage.2005.12.040>
- Hancock, R., Richlan, F., & Hoefft, F. (2017). Possible roles for fronto-striatal circuits in reading disorder. *Neuroscience and Biobehavioral Reviews*. <https://doi.org/10.1016/j.neubiorev.2016.10.025>
- He, Q., Xue, G., Chen, C., Chen, C., Lu, Z. L., & Dong, Q. (2013). Decoding the neuroanatomical basis of reading ability: A multivoxel morphometric study. *Journal of Neuroscience*, 33(31), 12835–12843. <https://doi.org/10.1523/JNEUROSCI.0449-13.2013>
- Hoefft, F., Meyler, A., Hernandez, A., Juel, C., Taylor-Hill, H., Martindale, J. L., ... Gabrieli, J. D. E. (2007). Functional and morphometric brain dissociation between dyslexia and reading ability. *Proceedings of the National Academy of Sciences of the United States of America*, 104(10), 4234–4239. <https://doi.org/10.1073/pnas.0609399104>
- Hoover, W. A., & Gough, P. B. (1990). The simple view of reading. *Reading and Writing*, 2(2), 127–160. <https://doi.org/10.1007/BF00401799>
- Horowitz-Kraus, T., Toro-Serey, C., & Difrancesco, M. (2015). Increased resting-state

- functional connectivity in the cingulo-opercular cognitive-control network after intervention in children with reading difficulties. *PLoS ONE*, *10*(7).  
<https://doi.org/10.1371/journal.pone.0133762>
- Horwitz, B., Rumsey, J. M., & Donohue, B. C. (1998). Functional connectivity of the angular gyrus in normal reading and dyslexia. *Proceedings of the National Academy of Sciences of the United States of America*, *95*(15), 8939–8944.  
<https://doi.org/10.1073/pnas.95.15.8939>
- Houdé, O., Rossi, S., Lubin, A., & Joliot, M. (2010). Mapping numerical processing, reading, and executive functions in the developing brain: An fMRI meta-analysis of 52 studies including 842 children. *Developmental Science*, *13*(6), 876–885.  
<https://doi.org/10.1111/j.1467-7687.2009.00938.x>
- Howe, A. E., Arnell, K. M., Klein, R. M., Joanisse, M. F., & Tannock, R. (2006). The ABCs of computerized naming: Equivalency, reliability, and predictive validity of a computerized rapid automatized naming (RAN) task. *Journal of Neuroscience Methods*, *151*(1), 30–37. <https://doi.org/10.1016/j.jneumeth.2005.07.014>
- Hulslander, J., Talcott, J., Witton, C., DeFries, J., Pennington, B., Wadsworth, S., ... Olson, R. (2004). Sensory processing, reading, IQ, and attention. *Journal of Experimental Child Psychology*, *88*(3), 274–295.  
<https://doi.org/10.1016/j.jecp.2004.03.006>
- Kirby, J. R., Georgiou, G. K., Martinussen, R., Parrila, R., Bowers, P., & Landerl, K. (2010). Naming speed and reading: From prediction to instruction. *Reading Research Quarterly*, *45*(3), 341–362. <https://doi.org/10.1598/rrq.45.3.4>
- Koyama, M. S., Di Martino, A., Kelly, C., Jutagir, D. R., Sunshine, J., Schwartz, S. J., ... Milham, M. P. (2013). Cortical signatures of dyslexia and remediation: An intrinsic functional connectivity approach. *PLoS ONE*, *8*(2).  
<https://doi.org/10.1371/journal.pone.0055454>
- Koyama, M. S., di Martino, A., Zuo, X. N., Kelly, C., Mennes, M., Jutagir, D. R., ... Milham, M. P. (2011). Resting-state functional connectivity indexes reading competence in children and adults. *Journal of Neuroscience*, *31*(23), 8617–8624.  
<https://doi.org/10.1523/JNEUROSCI.4865-10.2011>
- Koyama, M. S., Kelly, C., Shehzad, Z., Penesetti, D., Castellanos, F. X., & Milham, M. P. (2010). Reading networks at rest. *Cerebral Cortex*, *20*(11), 2549–2559.  
<https://doi.org/10.1093/cercor/bhq005>
- Krafnick, A. J., Flowers, D. L., Napoliello, E. M., & Eden, G. F. (2011). Gray matter volume changes following reading intervention in dyslexic children. *NeuroImage*, *57*(3), 733–741. <https://doi.org/10.1016/j.neuroimage.2010.10.062>
- Kronbichler, M., Hutzler, F., Staffen, W., Mair, A., Ladurner, G., & Wimmer, H. (2006). Evidence for a dysfunction of left posterior reading areas in German dyslexic readers. *Neuropsychologia*, *44*(10), 1822–1832.  
<https://doi.org/10.1016/j.neuropsychologia.2006.03.010>
- MacDonald, K. B. (2008). Effortful control, explicit processing, and the regulation of human evolved predispositions. *Psychological Review*, *115*(4), 1012–1031.  
<https://doi.org/10.1037/a0013327>
- Makris, N., Goldstein, J. M., Kennedy, D., Hodge, S. M., Caviness, V. S., Faraone, S. V., ... Seidman, L. J. (2006). Decreased volume of left and total anterior insular lobule in schizophrenia. *Schizophrenia Research*, *83*(2–3), 155–171.

- <https://doi.org/10.1016/j.schres.2005.11.020>
- Marklund, P., Fransson, P., Cabeza, R., Larsson, A., Ingvar, M., & Nyberg, L. (2007). Unity and diversity of tonic and phasic executive control components in episodic and working memory. *NeuroImage*, *36*(4), 1361–1373. <https://doi.org/10.1016/j.neuroimage.2007.03.058>
- McNorgan, C., Alvarez, A., Bhullar, A., Gayda, J., & Booth, J. R. (2011). Prediction of reading skill several years later depends on age and brain region: Implications for developmental models of reading. *Journal of Neuroscience*, *31*(26), 9641–9648. <https://doi.org/10.1523/JNEUROSCI.0334-11.2011>
- Mechelli, A., Crinion, J. T., Long, S., Friston, K. J., Lambon Ralph, M. A., Patterson, K., ... Price, C. J. (2005). Dissociating reading processes on the basis of neuronal interactions. *Journal of Cognitive Neuroscience*, *17*(11), 1753–1765. <https://doi.org/10.1162/089892905774589190>
- Meyer, M. S., Wood, F. B., Hart, L. A., & Felton, R. H. (1998). Selective predictive value of rapid automatized naming in poor readers. *Journal of Learning Disabilities*, *31*(2), 106–117. <https://doi.org/10.1177/002221949803100201>
- Misra, M., Katzir, T., Wolf, M., & Poldrack, R. A. (2004). Neural systems for rapid automatized naming in skilled readers: Unraveling the RAN-reading relationship. *Scientific Studies of Reading*, *8*(3), 241–256. [https://doi.org/10.1207/s1532799xssr0803\\_4](https://doi.org/10.1207/s1532799xssr0803_4)
- Nakamura, K., Dehaene, S., Jobert, A., Le Bihan, D., & Kouider, S. (2007). Task-specific change of unconscious neural priming in the cerebral language network. *Proceedings of the National Academy of Sciences of the United States of America*, *104*(49), 19643–19648. <https://doi.org/10.1073/pnas.0704487104>
- Norton, E. S., Black, J. M., Stanley, L. M., Tanaka, H., Gabrieli, J. D., Sawyer, C., & Hoefft, F. (2014). Functional neuroanatomical evidence for the double-deficit hypothesis of developmental dyslexia. *Neuropsychologia*, *61*, 235–246. <https://doi.org/10.1016/j.neuropsychologia.2014.06.015>
- Norton, E. S., & Wolf, M. (2012). Rapid automatized naming (RAN) and reading fluency: Implications for understanding and treatment of reading disabilities. *Annual Review of Psychology*, *63*(1), 427–452. <https://doi.org/10.1146/annurev-psych-120710-100431>
- Pennington, B. F., & Lefly, D. L. (2001). Early reading development in children at family risk for dyslexia. *Child Development*, *72*(3), 816–833. <https://doi.org/10.1111/1467-8624.00317>
- Price, C. J. (2012). A review and synthesis of the first 20 years of PET and fMRI studies of heard speech, spoken language and reading. *NeuroImage*, *62*(2), 816–847. <https://doi.org/10.1016/j.neuroimage.2012.04.062>
- Pugh, K. R., Einar Mencl, W., Jenner, A. R., Katz, L., Frost, S. J., Lee Ren, J., ... Laboratories, H. (2000). Functional neuroimaging studies of reading and reading disability (developmental dyslexia). *Mental Retardation and Developmental Disabilities Research Reviews*, *6*(3), 207–213. [https://doi.org/10.1002/1098-2779\(2000\)6:3<207::AID-MRDD8>3.0.CO;2-P](https://doi.org/10.1002/1098-2779(2000)6:3<207::AID-MRDD8>3.0.CO;2-P)
- Pugh, K. R., Mencl, W. E., Shaywitz, B. A., Shaywitz, S. E., Fulbright, R. K., Constable, R. T., ... Gore, J. C. (2000). The angular gyrus in developmental dyslexia: Task-specific differences in functional connectivity within posterior cortex. *Psychological*



- Science*, 11(1), 51–56. <https://doi.org/10.1111/1467-9280.00214>
- Raichle, M. E. (2015). The brain's default mode network. *Annual Review of Neuroscience*, 38(1), 433–447. <https://doi.org/10.1146/annurev-neuro-071013-014030>
- Raschle, N. M., Chang, M., & Gaab, N. (2011). Structural brain alterations associated with dyslexia predate reading onset. *NeuroImage*, 57(3), 742–749. <https://doi.org/10.1016/j.neuroimage.2010.09.055>
- Richards, T. L., Dager, S. R., Corina, D., Serafini, S., Heide, A. C., Steury, K., ... Berninger, V. W. (1999). Dyslexic children have abnormal brain lactate response to reading-related language tasks. *American Journal of Neuroradiology*, 20(8), 1393–1398.
- Richlan, F., Kronbichler, M., & Wimmer, H. (2009). Functional abnormalities in the dyslexic brain: A quantitative meta-analysis of neuroimaging studies. *Human Brain Mapping*, 30(10), 3299–3308. <https://doi.org/10.1002/hbm.20752>
- Richlan, F., Kronbichler, M., & Wimmer, H. (2011). Meta-analyzing brain dysfunctions in dyslexic children and adults. *NeuroImage*, 56(3), 1735–1742. <https://doi.org/10.1016/j.neuroimage.2011.02.040>
- Rollans, C., Cheema, K., Georgiou, G. K., & Cummine, J. (2017). Pathways of the inferior frontal occipital fasciculus in overt speech and reading. *Neuroscience*, 364, 93–106. <https://doi.org/10.1016/j.neuroscience.2017.09.011>
- Rumsey, J. M., Horwitz, B., Donohue, B. C., Nace, K., Maisog, J. M., & Andreason, P. (1997). Phonological and orthographic components of word recognition. A PET-rCBF study. *Brain*, 120(5), 739–759. <https://doi.org/10.1093/brain/120.5.739>
- Salmelin, R., Service, E., Kiesilä, P., Uutela, K., & Salonen, O. (1996). Impaired visual word processing in dyslexia revealed with magnetoencephalography. *Annals of Neurology*, 40(2), 157–162. <https://doi.org/10.1002/ana.410400206>
- Sandak, R., Mencl, W. E., Frost, S. J., & Pugh, K. R. (2004). The neurobiological basis of skilled and impaired reading: Recent findings and new directions. *Scientific Studies of Reading*, 8(3), 273–292. [https://doi.org/10.1207/s1532799xssr0803\\_6](https://doi.org/10.1207/s1532799xssr0803_6)
- Scarborough, H. S. (1998). Predicting the future achievement of second graders with reading disabilities: Contributions of phonemic awareness, verbal memory, rapid naming, and IQ. *Annals of Dyslexia*, 48, 115–136. <https://doi.org/10.1007/s11881-998-0006-5>
- Schacter, D. L., & Wagner, A. D. (1999). Medial temporal lobe activations in fMRI and PET studies of episodic encoding and retrieval. *Hippocampus*, 9(1), 7–24. [https://doi.org/10.1002/\(SICI\)1098-1063\(1999\)9:1<7::AID-HIPO2>3.0.CO;2-K](https://doi.org/10.1002/(SICI)1098-1063(1999)9:1<7::AID-HIPO2>3.0.CO;2-K)
- Schatschneider, C., Fletcher, J. M., Francis, D. J., Carlson, C. D., & Foorman, B. R. (2004). Kindergarten prediction of reading skills: A longitudinal comparative analysis. *Journal of Educational Psychology*, 96(2), 265–282. <https://doi.org/10.1037/0022-0663.96.2.265>
- Schurz, M., Wimmer, H., Richlan, F., Ludersdorfer, P., Klackl, J., & Kronbichler, M. (2015). Resting-state and task-based functional brain connectivity in developmental dyslexia. *Cerebral Cortex*, 25(10), 3502–3514. <https://doi.org/10.1093/cercor/bhu184>
- Semrud-Clikeman, M., Biederman, J., Sprich-Buckminster, S., Lehman, B. K., Faraone, S. V., & Norman, D. (1992). Comorbidity between ADHD and learning disability: A

- review and report in a clinically referred sample. *Journal of the American Academy of Child and Adolescent Psychiatry*, 31(3), 439–448.  
<https://doi.org/10.1097/00004583-199205000-00009>
- Shaywitz, B. A., Skudlarski, P., Holahan, J. M., Marchione, K. E., Constable, R. T., Fulbright, R. K., ... Shaywitz, S. E. (2007). Age-related changes in reading systems of dyslexic children. *Annals of Neurology*, 61(4), 363–370.  
<https://doi.org/10.1002/ana.21093>
- Shaywitz, S. E., Shaywitz, B. A., Pugh, K. R., Fulbright, R. K., Constable, R. T., Mencl, W. E., ... Gore, J. C. (1998). Functional disruption in the organization of the brain for reading in dyslexia. *Proceedings of the National Academy of Sciences of the United States of America*, 95(5), 2636–2641. <https://doi.org/10.1073/pnas.95.5.2636>
- Torgesen, J. K., Wagner, R. K., & Rashotte, C. A. (2012). *Test of Word Reading Efficiency* (2<sup>nd</sup> ed.). Austin, TX: Pro-Ed.
- Turkeltaub, P. E., Gareau, L., Flowers, D. L., Zeffiro, T. A., & Eden, G. F. (2003). Development of neural mechanisms for reading. *Nature Neuroscience*, 6(7), 767–773. <https://doi.org/10.1038/nn1065>
- Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., ... Joliot, M. (2002). Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *NeuroImage*, 15(1), 273–289. <https://doi.org/10.1006/nimg.2001.0978>
- van der Mark, S., Klaver, P., Bucher, K., Maurer, U., Schulz, E., Brem, S., ... Brandeis, D. (2011). The left occipitotemporal system in reading: Disruption of focal fMRI connectivity to left inferior frontal and inferior parietal language areas in children with dyslexia. *NeuroImage*, 54(3), 2426–2436.  
<https://doi.org/10.1016/j.neuroimage.2010.10.002>
- Vinckier, F., Dehaene, S., Jobert, A., Dubus, J. P., Sigman, M., & Cohen, L. (2007). Hierarchical coding of letter strings in the ventral stream: Dissecting the inner organization of the visual word-form system. *Neuron*, 55(1), 143–156.  
<https://doi.org/10.1016/j.neuron.2007.05.031>
- Vogel, A. C., Miezin, F. M., Petersen, S. E., & Schlaggar, B. L. (2012). The putative visual word form area is functionally connected to the dorsal attention network. *Cerebral Cortex*, 22(3), 537–549. <https://doi.org/10.1093/cercor/bhr100>
- Wendelken, C., Bunge, S. A., & Carter, C. S. (2008). Maintaining structured information: An investigation into functions of parietal and lateral prefrontal cortices. *Neuropsychologia*, 46(2), 665–678.  
<https://doi.org/10.1016/j.neuropsychologia.2007.09.015>
- Wechsler, D. (1999). *Wechsler Abbreviated Scale of Intelligence*. San Antonio, TX: The Psychological Corporation.
- Whitfield-Gabrieli, S., & Nieto-Castanon, A. (2012). Conn: A functional connectivity toolbox for correlated and anticorrelated brain networks. *Brain Connectivity*, 2(3), 125–141. <https://doi.org/10.1089/brain.2012.0073>
- Wolf, M. (1986). Rapid alternating stimulus naming in the developmental dyslexias. *Brain and Language*, 27(2), 360–379. [https://doi.org/10.1016/0093-934X\(86\)90025-8](https://doi.org/10.1016/0093-934X(86)90025-8)
- Woodcock, R. W., McGrew, K. S., & Mather, N. (2001). *Woodcock-Johnson III*. Itasca, IL: Riverside Publishing.

Zeineh, M. M., Engel, S. A., Thompson, P. M., & Bookheimer, S. Y. (2003). Dynamics of the hippocampus during encoding and retrieval of face-name pairs. *Science*, 299(5606), 577–580. <https://doi.org/10.1126/science.1077775>

## Chapter 3: DTI Connectivity Correlates of Reading Subskills in Children

### 3.1 Introduction

Reading is a complex skill involving multiple cognitive processes and types of representations. Efficient reading is associated with a number of subskills, including *decoding*, in which readers read unfamiliar words by mapping orthographic representations onto phonological and later semantic knowledge; *sight word reading*, in which readers recognize familiar words by mapping orthographic representations directly onto semantic knowledge; and *comprehension*, in which orthographic and phonological information is linked to semantic knowledge in order for a reader to understand a word or a written text. *Rapid automatized naming* (RAN) is also known to be an important predictor of fluent reading in both developing readers and adults (for a review see Norton & Wolf, 2012), and is thought to index the fluent perceptual, attentional, and motoric processes involved in reading aloud (Arnell et al., 2009). Neuroimaging research has identified specific regions of the brain distributed widely across the cortex that support reading and its associated subskills (see Price, 2012), and a growing body of research has also highlighted the importance of white matter tracts to support coordination of among these cortical regions and facilitate efficient reading (see Vandermosten, Boets, Wouters, & Ghesquière, 2012). However, questions still remain regarding how the discrete subskills supporting reading may be differentially related to the microstructure of these white matter tracts.

Recent research on structural connectivity in the brain has utilized diffusion tensor imaging (DTI), a structural MRI technique which measures diffusion of water molecules in the brain to characterize white matter tracts connecting grey matter regions

of the brain (Le Bihan et al., 2001). A common measure of DTI connectivity is fractional anisotropy (FA), which quantifies the directionality of water diffusion in white matter tracts. FA values range between 0 and 1 and characterize fiber density, axon diameter, and myelination (Basser & Pierpaoli, 1996). This technique allows for examination of the relationship between behavioural measures and white matter integrity to characterize the roles that various white matter pathways may have in reading.

A number of white matter tracts have been linked to reading, many through DTI studies examining differences in white matter between individuals with reading disability (RD) and typical readers. RD, sometimes known as dyslexia, is characterized by difficulty recognizing familiar words and decoding words fluently and accurately (Lyon et al., 2003) and is generally associated with difficulties processing phonological information (Ramus, 2003; Snowling, Gooch, & Henderson, 2012; Wagner, Torgesen, Laughon, Simmons, & Rashotte, 1993). The first and seminal study of white matter microstructure in individuals with RD documented reduced FA in bilateral temporo-parietal regions compared to typical readers (Klingberg et al., 2000). The finding of reduced FA in left temporo-parietal regions has been replicated in numerous studies of both adults with RD (Gold, Powell, Xuan, Jiang, & Hardy, 2007; Klingberg et al., 2000; Richards et al., 2008; Steinbrink et al., 2008), illiterate adults (Thiebaut de Schotten et al., 2014), and children with RD (Carter et al., 2009; Christodoulou, Murtagh, et al., 2017; Deutsch et al., 2005; Niogi & McCandliss, 2006; Rimrodt, Peterson, Denckla, Kaufmann, & Cutting, 2010; Vandermosten, Boets, Poelmans, et al., 2012). In many of these studies, these temporo-parietal regions were hypothesized to correspond with left arcuate fasciculus (Deutsch et al., 2005; Gold et al., 2007; Klingberg et al., 2000; Steinbrink et

al., 2008), and more recent methodology using atlas-based or region-of-interest localization or using tractography has confirmed this (Carter et al., 2009; Christodoulou, Murtagh, et al., 2017; Richards et al., 2008; Rimrodt et al., 2010; Vandermosten, Boets, Poelmans, et al., 2012). The arcuate fasciculus is a dorsal tract that connects superior/middle temporal regions to inferior frontal regions and is frequently linked to spoken and written language processing. Evidence from pre-reading children who went on to later develop RD suggest that group differences in the white matter of the left and right arcuate fasciculus are present even before the start of literacy acquisition (Vanderauwera, Wouters, Vandermosten, & Ghesquière, 2017). As a whole, the literature clearly demonstrates that the bilateral arcuate fasciculi play an important role in reading ability in both children and adults.

Studies of individuals with RD and individuals with reading impairments following brain lesions suggest that other white matter tracts support written language processing, in addition to the arcuate fasciculus. Steinbrink et al. (2008) observed reduced FA in left temporo-parietal and bilateral fronto-temporal regions in adults with a history of reading difficulties and suggested that these regions of reduced FA corresponded with the arcuate fasciculus as well as posterior parts of either the inferior fronto-occipital fasciculus (IFOF) or the inferior longitudinal fasciculus (ILF). The IFOF is a ventral tract connecting temporal, occipital, and frontal areas, while the ILF travels between anterior temporal and occipital brain regions. Studies of individuals with lesions to these areas suggest they have a role in linking orthographic representations to lexical representations (Epelbaum et al., 2008) and in semantic language processing (Mandonnet, Nouet, Gatignol, Capelle, & Duffau, 2007). The uncinate fasciculus, which

connects anterior temporal and ventral frontal regions, has also been implicated in reading via lesion studies highlighting its importance in processing lexical stimuli and semantic associations (Grossman et al., 2004; Lu et al., 2002; Marchina et al., 2011; Wilson et al., 2011). Together, these studies suggest a role for both the arcuate fasciculus and ventral tracts, including the IFOF, ILF, and uncinate fasciculus, in supporting reading-related processes.

Differences between groups with and without RD also appear to extend to both hemispheres of the brain. For example, Richards et al. (2008) observed that adults with RD had differences in FA across multiple regions distributed bilaterally across the cortex, including regions of reduced FA as well as regions with increased FA. Additionally, evidence of increased FA in the corpus callosum (Frye et al., 2009), right cingulum (Banfi et al., 2018), right inferior longitudinal fasciculus (Banfi et al., 2018), and right superior longitudinal fasciculus (Banfi et al., 2018), and results showing reduced white matter lateralization in the posterior superior temporal gyrus and arcuate fasciculus (Vandermosten, Poelmans, Sunaert, Ghesquière, & Wouters, 2013) suggest that left hemisphere lateralization may be reduced in individuals with RD. A recent study using a whole-brain network-based statistics approach found reduced FA in a left occipito-temporal and temporo-parietal network in children with RD, and observed that reading abilities were correlated with the network's efficiency of communication among distributed cortical regions and the network's capacity for specialized processing within more localized area (Lou et al., 2019). Taken together, the current evidence suggests that individuals with RD exhibit widespread, bilateral differences in white matter

microstructure, and these likely contribute to reduced efficiency of both distributed and localized processing in regions of the brain associated with reading.

Although the studies discussed above have demonstrated clear differences in white matter microstructure between individuals with and without RD, reading performance is not distributed categorically, but rather, along a continuum. Thresholds for determining how to divide individuals into typically-developing and RD groups tend to be arbitrary (Lyon et al., 2003) and variable across different studies (Siegel, 2006). In line with this, DTI studies examining individual differences in reading ability have suggested that previous evidence of atypical white matter in individuals with RD do not reflect categorical differences in brain structure, but rather, represent the tail end of the distribution. For example, in children and adults, individual differences in behavioural measures of single word reading, spelling, and rapid naming are correlated with FA in left temporo-parietal regions (Beaulieu et al., 2005; Deutsch et al., 2005; Nagy et al., 2004; Thiebaut de Schotten, 2014). Reaction time when reading exception words is negatively associated with FA of the left uncinate fasciculus, suggesting a role for this tract in individual differences in orthographic lexical processing (Cummine et al., 2013). Correlations between reading and white matter microstructure also extend to the right hemisphere: for example, a study of word reading, decoding, and reading fluency found that correlations were bilaterally distributed, implicating both left and right hemisphere tracts (Lebel et al., 2013). Similarly, Odegard et al. (2009) found implications for both left and right hemisphere tracts in children's decoding skill, showing that decoding was positively correlated with FA in areas of the bilateral IFOF, right uncinate fasciculus, and a region located either in the right IFOF or right ILF, and negatively correlated with FA



in the corpus callosum. Characteristics of the microstructure of the left arcuate fasciculus and of the corpus callosum have also been associated with pre-reading skills such as phonological awareness and phonological memory abilities (Dougherty et al., 2007; Saygin et al., 2013; Yeatman et al., 2011), suggesting that differences in white matter structure related to reading skill may be present prior to reading instruction.

As a whole, the current literature implicates many different white matter structures in both the right and left hemispheres in supporting reading. One reason for these widespread findings may be that many previous studies of reading have measured reading as a single construct. However, reading performance relies on integration of multiple cognitive subskills (Sandak et al., 2012), and therefore examining a more comprehensive battery of reading-related skills may help to elucidate the discrete roles of bilateral white matter tracts in reading. Indeed, the relationship between FA and reading has been found to differ across decoding and sight word reading in children and adults (Niogi & McCandliss, 2006; Welcome & Joanisse, 2014). Specifically, Niogi and McCandliss (2006) found that in children with and without RD, FA in left temporo-parietal regions was strongly correlated with word identification skills but not decoding skills. In adults, Welcome and Joanisse (2014) demonstrated that decoding skills in adults were correlated with white matter structure in the IFOF and uncinate fasciculus, whereas reliable associations between white matter structure in this region and sight word reading skills were not observed. Additionally, reading comprehension has been associated with FA in both the left and right arcuate fasciculus, while sight word reading has similarly been associated with FA the inferior longitudinal fasciculus bilaterally (Horowitz-Kraus et al., 2014). These studies demonstrate the importance of studying discrete subskills in

order to characterize the roles that that different neural pathways play in reading.

However, questions remain about how individual differences in a more comprehensive battery of reading subskills, such as decoding, sight word reading, comprehension, and rapid naming, may be linked to white matter structure in children. Importantly, the link between white matter and reading may be multifactorial, with reading subskills showing both overlapping and discrete relationships with white matter microstructure.

The present study aimed to examine how reading subskills in children with a wide range of reading abilities relate to differences in microstructure along the length of the arcuate fasciculus, uncinate fasciculus, IFOF, and ILF. We examined all tracts bilaterally given previous evidence implicating both left and right hemisphere tracts in reading. Additionally, previous DTI studies of reading have tended to measure connectivity based on averages of FA across the entire tract of interest, which may not fully capture microstructure at different points along the tract (Yeatman et al., 2011). For example, a study examining the arcuate fasciculus in three distinct sections rather than as a single tract found that reading skills were related to FA in only the direct segment, but not in the shorter anterior and posterior segments (Gullick & Booth, 2015). Our approach therefore focused on distinct tract segments in order to examine the role of discrete areas of each white matter tract in reading subskills.

Of note, we recruited children with a wide range of reading abilities, including children identified as struggling readers, and examined brain-behavior relationships for multiple behavioural measures of sight word reading, decoding, reading comprehension, and rapid naming. Performance was then correlated with white matter microstructure within white matter tracts subserving reading processes in the left and right arcuate

fasciculus, IFOF, ILF, and uncinate fasciculus. Nonverbal intelligence was included as a covariate, to assess whether the effects observed were specific to reading-related skills or whether they could be linked to more general cognitive processes. We predicted that, consistent with previous studies, FA would be positively associated with reading in these white matter tracts, suggesting that poor readers exhibit reduced connectivity between these regions. We also predicted that compensation for poor reading skills may result in findings of negative correlations between FA and reading skills, particularly in right hemisphere tracts. Importantly, we hypothesized that some patterns of correlations between white matter connectivity and individual differences in reading would differ across reading subskills, as these skills are related but distinct from one another.

## **3.2 Methods**

### **3.2.1 Participants**

The participants in the present study were a subset of participants in the study described in Chapter 2 of this thesis. Sixty-five children between 8 and 14 years old (35 female; 63 right-handed) were recruited through local schools and social media advertisements in the London, Ontario community. A portion of recruitment was targeted to classrooms of children with reading disabilities, recruited by letters sent home through their school. As a result, eighteen children in the sample had been identified by school professionals as having reading difficulties. Recruitment was not targeted for the remaining forty-seven participants, as such, this portion of the sample drew from school-age children with a wide range of reading abilities. All participants' parents reported via a structured questionnaire that the children had normal or corrected-to-normal vision, no

hearing impairments, and were neurologically healthy. All parents provided informed consent and children provided assent to participate at the beginning of the study.

### 3.2.2 Behavioural measures

Children completed a mock scanner training and a battery of behavioral measures one to two weeks prior to the scanning session, as described below.

***Sight word reading efficiency.*** The *Sight Word Efficiency* subtest of the *Test of Word Reading Efficiency II* (TOWRE-2; Torgesen et al., 2012) assessed sight word reading efficiency ability. Children were given 45 seconds to read as many words as possible from a list of words increasing in length and difficulty.

***Decoding efficiency.*** Decoding efficiency was assessed using the *Phonemic Decoding Efficiency* subtest of the TOWRE-2. Children read as many pronounceable nonwords as possible in 45 seconds.

***Reading comprehension.*** Participants completed the *Woodcock-Johnson III* (WJ-III; Woodcock et al., 2001) *Passage Comprehension subtest* as a measure of reading comprehension skills. Participants were asked to read a sentence or paragraph and supply a word that could go in a blank space.

***Rapid automatized naming (RAN).*** Children completed a RAN task (Howe, Arnell, Klein, Joanisse, & Tannock, 2006; see Appendix A) in which they were given a 5 x 10 grid of letters (*k, r, m, g*) and asked to name each item in the array in order as quickly and accurately as possible. The task was scored based on the number of items named correctly per second.

***Nonverbal intelligence.*** Nonverbal intelligence was assessed using the *Weschler Abbreviated Scale of Intelligence Second Edition* (WASI-II; Weschler, 2011)

Performance IQ measures, which consisted of the *Block Design* and *Matrix Reasoning* subtests. In the *Block Design* subtest, participants viewed a sample model or a picture and were asked to replicate the design as quickly as possible using red and white blocks. The *Matrix Reasoning* task involves looking at an unfinished matrix or series and selecting an item which completes the matrix from an array of five items. The scores on the *Block Design* and *Matrix Reasoning* subtests were combined to provide a standardized Performance IQ score measuring nonverbal intelligence.

***Mock scanner training.*** Children were familiarized with the MRI procedures and environment. They practiced removing all metal from their person, lay on a bed in a simulated scanner, and were asked to lie still for ten minutes while listening to an audiobook and recorded sounds from an MRI scanner. Head movements were monitored via an electromagnetic position tracker (Polhemus FasTrack) during the simulated scan, which provided feedback on the importance of lying still and served as an informal assessment of whether they would be able to remain sufficiently still during the actual MRI scan to acquire good quality MRI images. No participants were excluded from the study based on movement in the simulated scan.

### **3.2.3 MRI acquisition and processing**

Imaging was performed at the University of Western Ontario's Centre for Functional and Metabolic Mapping on a Siemens Magnetom Prisma 3 Tesla scanner with a 32-channel head coil. A high-resolution 3-D T1-weighted anatomical scan was acquired in the sagittal plane (MPRAGE; GRAPPA acceleration factor = 2; TR = 2.3 s; TE = 2.98 ms; field of view = 256 x 256 mm; voxel size = 1 mm<sup>3</sup>; 192 slices). The DTI scans were acquired in the transverse plane using an echo planar imaging sequence (64 slices with

2mm slice thickness; in-plane voxel size = 2.041 x 2.041 mm; matrix = 96 x 96 x 68; field of view = 200 x 200 mm; 64 diffusion directions with  $b = 1000 \text{ s/mm}^2$ ; TR = 3.0 s; TE = 50.6 ms; GRAPPA acceleration factor = 3). A resting-state fMRI scan was also acquired during the same session as part of the studies described in Chapters 2 and 4 of this thesis, yielding a total scan time of approximately 15 minutes. A subset of 22 participants also completed three fMRI tasks as part of a separate study, and total scan time for these participants was approximately 45 minutes.

Images were processed and analyzed using the automatic fiber quantification (AFQ) version 1.2 (Yeatman, Dougherty, Myall, Wandell, & Feldman, 2012) and SPM8 toolboxes in MATLAB. Preprocessing included motion and eddy current correction and alignment of the DTI data to the T1 weighted anatomical image. White matter tractography was then performed using a deterministic streamlined tracking algorithm (Yeatman, Dougherty, Myall, et al., 2012) from each white matter voxel identified with a fractional anisotropy (FA) value greater than 0.3. From these initial seed voxels, tracking continued tracing streamlines along the principal diffusion axes until the estimated FA fell below 0.2. Additionally, to avoid effects of crossing fibers, the algorithm also stopped tracking if the angle between two segments was greater than 30 degrees. Tracts were segmented in MNI standard space and transformed into single-subject space using waypoint ROI masks (Wakana et al., 2007). Tracts of interest were identified using region of interest (ROI) inclusion, exclusion and waypoint masks as detailed in Wakana et al. (2007). Our analyses focused on the arcuate fasciculus, inferior longitudinal fasciculus (ILF), inferior fronto-occipital fasciculus (IFOF), and uncinate fasciculus in both hemispheres, given previous findings that FA in these tracts tends to differentiate

good vs. poor readers. Each tract was defined as the collection of streamlines fitting the prescribed ROI masks, and was subsequently cleaned by removing fibers that were more than four standard deviations above or below the mean fiber length or deviated spatially by more than five standard deviations from the averaged centroid of the fiber tract (Yeatman, Dougherty, Myall, et al., 2012). All tracts of interest were identified in all subjects, with the exception of the right arcuate fasciculus, which was identified in 50 of the 65 subjects. The right arcuate fasciculus tends to be smaller than the left arcuate fasciculus and can sometimes not be identified using a deterministic tracking algorithm such as the one used in the present study (Catani et al., 2007; Yeatman et al., 2011). Independent samples t-tests were conducted to compare age and scores on behavioural measures between the participants in which the right arcuate was identified versus the participants in which it was not identified.

For statistical analyses, each fiber tract was then divided into 100 nodes spaced equally along the length of the tract, and FA was calculated for DTI voxels falling within each node. We then computed partial correlations between raw behavioural scores and FA at each node along the tract, with age added as a covariate. Raw scores were used here for all behavioural tasks for consistency as the RAN measure used in the present study does not have norms available. Age was included as a covariate in analyses to account for maturational differences in white matter and behavioural performance.

To reduce the probability of false positives, a permutation-based correction for family-wise error was used to calculate a cluster threshold at a corrected level of  $p < .05$  for each tract, averaged across the behavioural measures (Nichols & Holmes, 2002). This cluster threshold identified the minimum number of *consecutive* (directly adjacent) nodes

reaching an individual significance level of  $p < .05$  for this cluster to be greater than what is might occur by chance. The cluster thresholds ranged from 12-20 nodes depending on the tract.

Because our behavioural measures were highly correlated with one another, we then used partial correlations to identify the extent to which effects were unique to any one sub-measure of reading. The cluster correction was not used for the partial correlations as these were largely exploratory and examined whether the zero-order correlations were modulated by other tasks.

### **3.3 Results**

#### **3.3.1 Behavioural results**

Descriptive statistics for the behavioural tasks, presented in Table 3.1, show that the sample included a wide range of variability in nonverbal intelligence, sight word reading efficiency, decoding efficiency, reading comprehension, and rapid naming abilities. Thirteen children met criteria for reading disability, defined as standard scores less than 1.5 standard deviations below the mean on at least two of the three normed reading measures. These thirteen children were all part of the subsample previously identified by school professionals as struggling readers.

Pearson's correlations among behavioural measures indicated that all measures were significantly correlated with one another, with the exception of nonverbal intelligence with decoding efficiency, reading comprehension, and RAN, each of which did not pass the Bonferroni correction for multiple comparisons (corrected  $p < .0025$ ; Table 3.2). Pearson's correlations between behavioural measures and motion during the DTI scan were also examined to ensure this was not a confounding variable, given



previous reports that head motion during scanning can bias measurement of diffusion values such as FA (Ling et al., 2012). Maximum translation was measured by summing the three movement parameters of each scan to identify the maximum amount of movement for each participant. Mean movement was calculated by calculating each child's average translation parameters in each dimension. Pearson's correlations were then conducted between the resulting maximum and mean movement and the behavioural scores (corrected  $p < .0025$ ; Table 3.2). Maximum movement and mean movement were not significantly correlated with any behavioural measures, suggesting that motion during the DTI scan was not a significant confound in the present study. The preprocessing steps for all DTI data also included motion correction, to account for the possibility of motion effects that were not completely captured by the Pearson's correlations.

**Table 3.1** Descriptive statistics for behavioural tasks.

	Mean (SD)	Range
Age (years)	10.90 (1.19)	8.83-14.68
Sight word reading efficiency (standard score)	94.18 (20.86)	55-139
Decoding efficiency (standard score)	94.06 (19.65)	56-129
Reading comprehension (standard score)	91.31 (12.64)	46-118
RAN (#correct/second)	1.89 (0.44)	0.90-2.84
Nonverbal intelligence (standard score)	106.83 (18.08)	63-147

### 3.3.2 DTI connectivity results

Partial correlations were performed at each of 100 nodes on each tract, for every reading task, with age added as a covariate. In the left arcuate fasciculus, positive correlations were observed at overlapping nodes in the posterior region of the tract for the decoding efficiency task (19 consecutive nodes, average  $r = 0.29$ ) and the RAN task (20

consecutive nodes, average  $r = 0.37$ ; Figure 3.1A). The partial correlations for the right arcuate fasciculus included only the 50 subjects in which this tract was identified, as 15 subjects failed to show enough streamlines to identify this tract. Positive correlations were observed at overlapping nodes of the right arcuate fasciculus between FA and sight word reading efficiency (21 nodes, average  $r = 0.39$ ) and decoding efficiency (19 nodes, average  $r = 0.38$ ; Figure 3.2A).

**Table 3.2** Pearson's correlations among behavioural measures.

	1.	2.	3.	4.	5.	6.
1. Sight word reading efficiency	-					
2. Decoding efficiency	0.87*	-				
3. Reading comprehension	0.77*	0.74*	-			
4. RAN	0.57*	0.67*	0.38*	-		
5. Nonverbal intelligence	0.40*	0.33	0.34	0.12	-	
6. Maximum movement	-0.02	-0.01	0.01	-0.06	-0.26	-
7. Mean movement	-0.08	-0.11	-0.04	-0.06	-0.30	0.90*

Note: \* denotes  $r$ -value significant at corrected  $p < .0024$ .

Given that most behavioural measures were highly correlated with one another, partial correlations were conducted to examine whether the observed effects in the bilateral arcuate fasciculi persisted when other subskills were controlled for. Specifically, the correlation between decoding efficiency and FA as well as the correlation between RAN and FA in the left arcuate were examined while controlling for each of the other subskills. The posterior cluster of significant correlations with decoding efficiency was no longer significant when controlling for RAN, decreased substantially in cluster size when controlling for sight word reading efficiency (4 nodes, average  $r = 0.26$ ), and

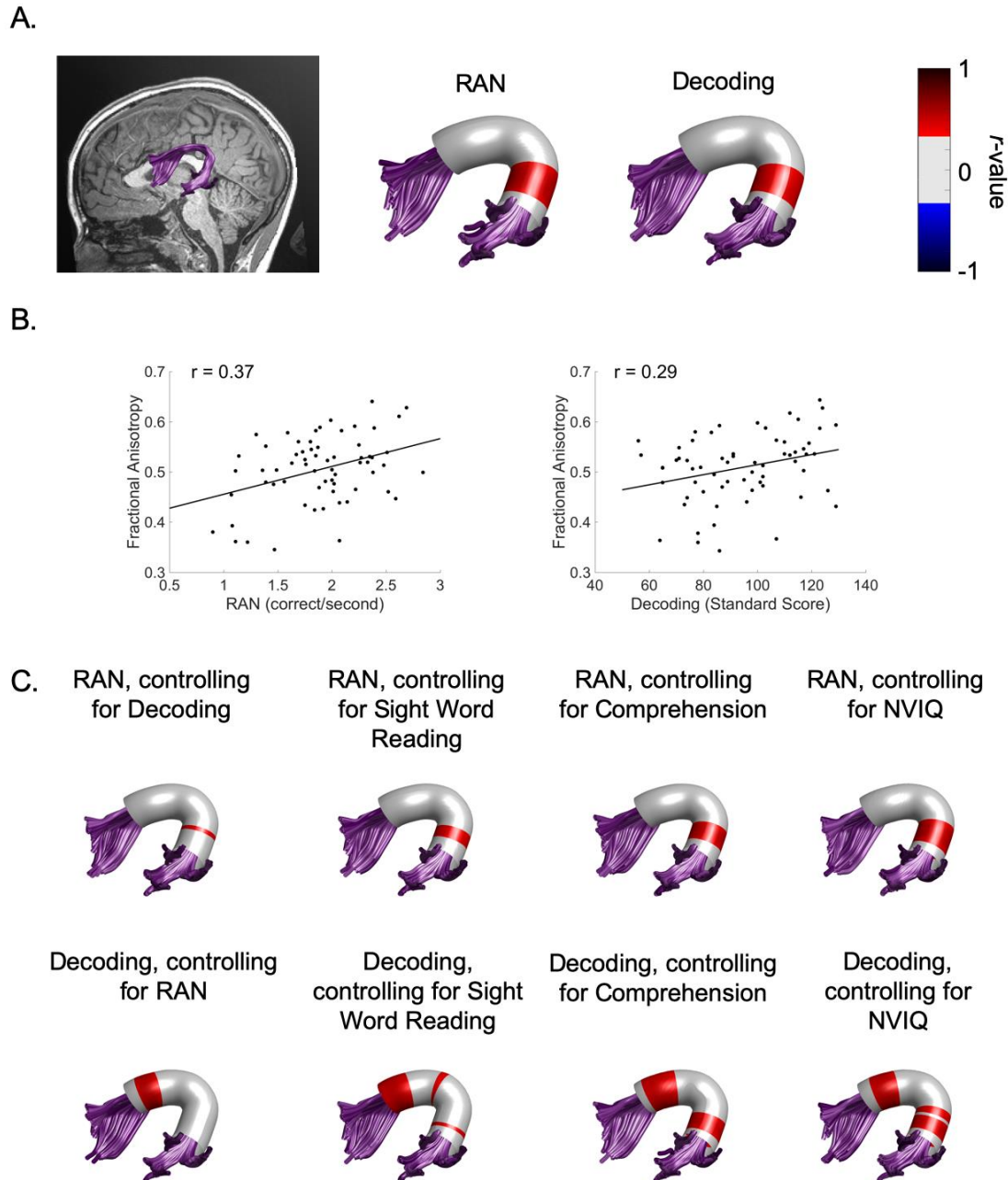
decreased only slightly in cluster size when controlling for comprehension (17 nodes, average  $r = 0.29$ ) and nonverbal intelligence (5 and 13 nodes, average  $r = 0.27$ ; Figure 3.1C). However, a more anterior cluster of correlations between decoding efficiency and FA emerged when controlling for each of the other subskills (RAN: 13 nodes, average  $r = 0.33$ ; sight word reading efficiency: 19 nodes and 4 nodes, average  $r = 0.30$ ; reading comprehension: 23 nodes, average  $r = 0.29$ ; nonverbal intelligence: 17 nodes, average  $r = 0.33$ ; Figure 3.1C). The correlation between RAN and FA persisted in 20 nodes when controlling for nonverbal intelligence (average  $r = 0.33$ ), but decreased to a cluster of 15 nodes when controlling for reading comprehension (average  $r = 0.32$ ), 10 nodes when controlling for sight word reading efficiency (average  $r = 0.26$ ), and only 3 nodes when controlling for decoding efficiency scores (average  $r = 0.26$ ; Figure 3.1C). These findings suggest that FA in this tract strongly reflects decoding efficiency abilities in anterior regions of the tract and rapid naming skill and single word reading skill in posterior regions of the tract, and that FA is largely independent of reading comprehension abilities and nonverbal intelligence.

In the right arcuate fasciculus, partial correlations between sight word reading efficiency and FA and between decoding efficiency and FA were examined while controlling for each of the reading subskills. These showed that the correlation between sight word reading efficiency and FA originally observed in the centre of the tract no longer reached significance when accounting for other subskills, although two small surrounding clusters of positive correlation persisted when controlling for RAN (2 nodes and 5 nodes, average  $r = 0.29$ ; Figure 3.2C). The correlation between sight word reading efficiency and FA only persisted in 3 nodes (average  $r = 0.29$ ) when controlling for

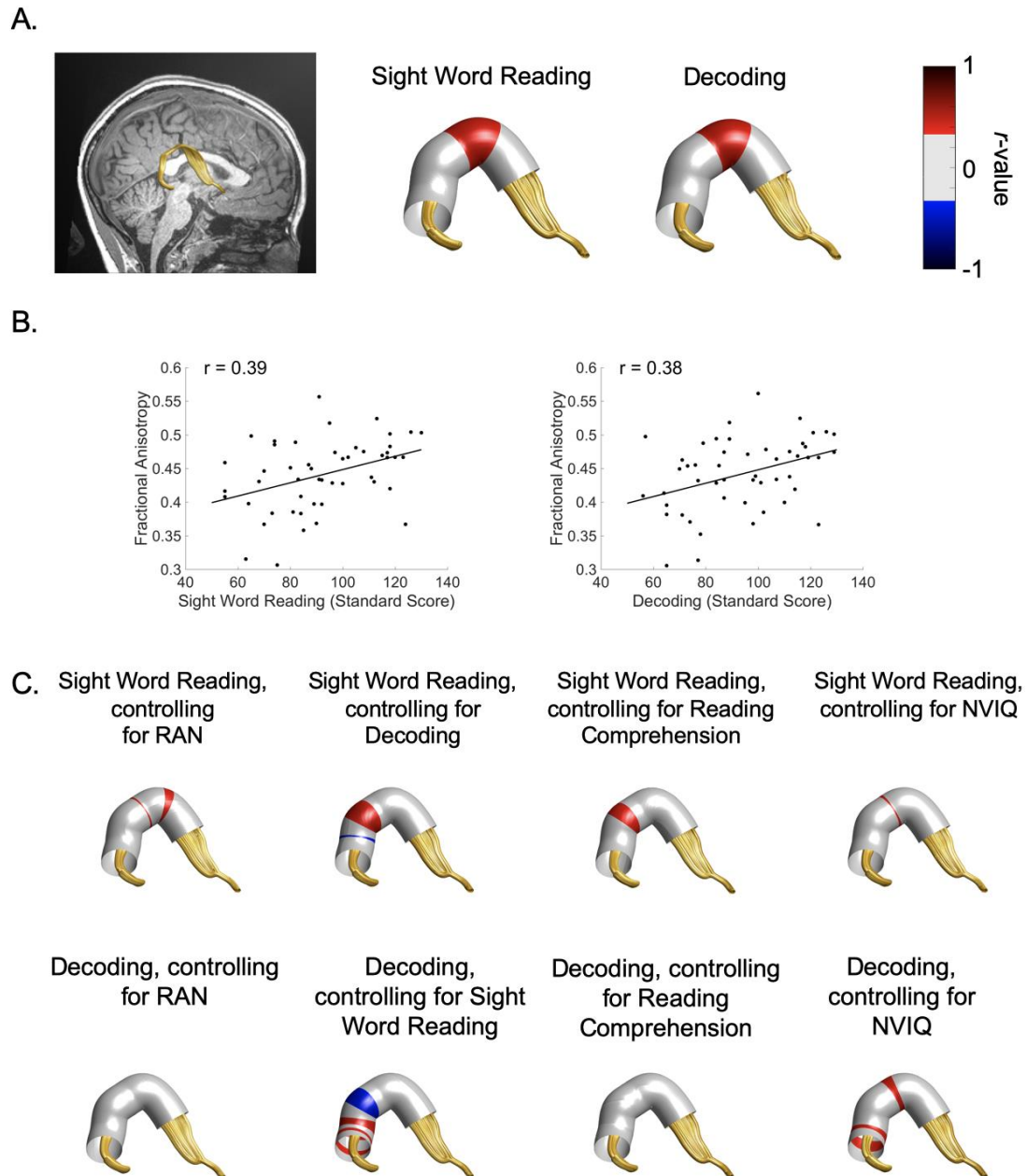
nonverbal intelligence. A more posterior cluster of positive correlation also emerged when controlling for decoding efficiency (12 nodes, average  $r = 0.35$ ) and for reading comprehension (6 nodes, average  $r = 0.30$ ), as well as a small cluster of negative correlation in posterior nodes when controlling for decoding efficiency (2 nodes, average  $r = -0.29$ ; Figure 3.2C). Interestingly, the relationship between decoding efficiency and FA in the right arcuate showed an opposite effect when controlling for sight word reading efficiency, in which the most posterior nodes of the tract exhibited positive correlations (4 nodes (average  $r = 0.28$ ) and 9 nodes (average  $r = 0.34$ )) and a cluster of negative correlation emerged in more central nodes of the tract (7 nodes, average  $r = -0.36$ ; Figure 3.2C). Significant correlations between decoding efficiency and FA were only present in a small number of nodes when controlling for nonverbal intelligence (7 nodes, average  $r = 0.30$ ) and did not persist when controlling for RAN and for reading comprehension. These results indicate that although sight word reading efficiency and decoding efficiency were related to FA in the right arcuate fasciculus, these effects were not entirely unique to single word reading skills, and other reading subskills contributed to this relationship.

Partial correlations were next performed at each of 100 nodes on the left and right uncinate fasciculus, for every reading task, with age added as a covariate. In the left uncinate fasciculus, FA values at inferior nodes were negatively correlated with performance on the sight word reading efficiency (34 nodes, average  $r = -0.48$ ), decoding efficiency (42 nodes, average  $r = -0.43$ ), reading comprehension (43 nodes, average  $r = -0.53$ ), and RAN (31 nodes, average  $r = -0.39$ ) tasks in overlapping posterior regions of the tract (Figure 3.3A). Negative correlations were also observed contralaterally, in which

FA values at posterior nodes of the right uncinate fasciculus were correlated with sight word reading efficiency (26 nodes, average  $r = -0.44$ ), decoding efficiency (31 nodes, average  $r = -0.49$ ), reading comprehension (35 nodes, average  $r = -0.46$ ), and RAN (32 nodes, average  $r = -0.53$ ; Figure 3.4A).



**Figure 3.1** A) White matter correlations of FA and reading subskills in the left arcuate fasciculus, controlling for age. The colourbar shows significant  $r$ -values. B) Scatterplots for reading subskills and FA averaged across significant nodes shown in panel A. C) Partial correlations between FA and reading subskills, while controlling for other subskills.



**Figure 3.2** A) White matter correlations of FA and reading subskills in the right arcuate fasciculus, controlling for age. The colourbar shows significant  $r$ -values. B) Scatterplots for reading subskills and FA averaged across significant nodes shown in panel A. C) Partial correlations between FA and reading subskills, while controlling for other subskills.

Partial correlations were next conducted between each pairing of the reading subskills to examine which made independent contributions to the relationship between reading and FA in the uncinate fasciculi. In the left uncinate fasciculus, partial correlations between sight word reading efficiency and FA showed that the effect persisted when controlling for nonverbal intelligence (37 nodes, average  $r = -0.35$ ), decreased in cluster size when controlling for each of decoding efficiency (13 nodes, average  $r = -0.30$ ) and RAN (24 nodes, average  $r = -0.36$ ), and was no longer significant when controlling for comprehension (Figure 3.3C). Similarly, the effect between decoding efficiency and FA persisted when controlling for nonverbal intelligence (37 nodes, average  $r = -0.35$ ), decreased in cluster size when controlling for RAN (24 nodes, average  $r = -0.39$ ), and was no longer significant when controlling for sight word reading efficiency or reading comprehension (Figure 3.3C). Partial correlations between comprehension and FA persisted when controlling for RAN (35 nodes, average  $r = -0.38$ ) and nonverbal intelligence (38 nodes, average  $r = -0.40$ ) and decreased slightly in cluster size when controlling for sight word reading efficiency (17 nodes, average  $r = -0.29$ ) and decoding efficiency (26 nodes, average  $r = -0.33$ ; Figure 3.3C). Finally, the relationship between RAN and FA was no longer significant when accounting each of the other reading subskills but persisted when accounting for nonverbal intelligence (36 nodes, average  $r = -0.30$ ). Together, these findings suggest that FA in the left uncinate fasciculus is largely accounted for by reading comprehension, although single word reading measures account for this effect to a small degree when rapid naming is controlled for.

In the right uncinate fasciculus, the negative correlation between sight word reading efficiency and FA persisted when accounting for nonverbal intelligence (30

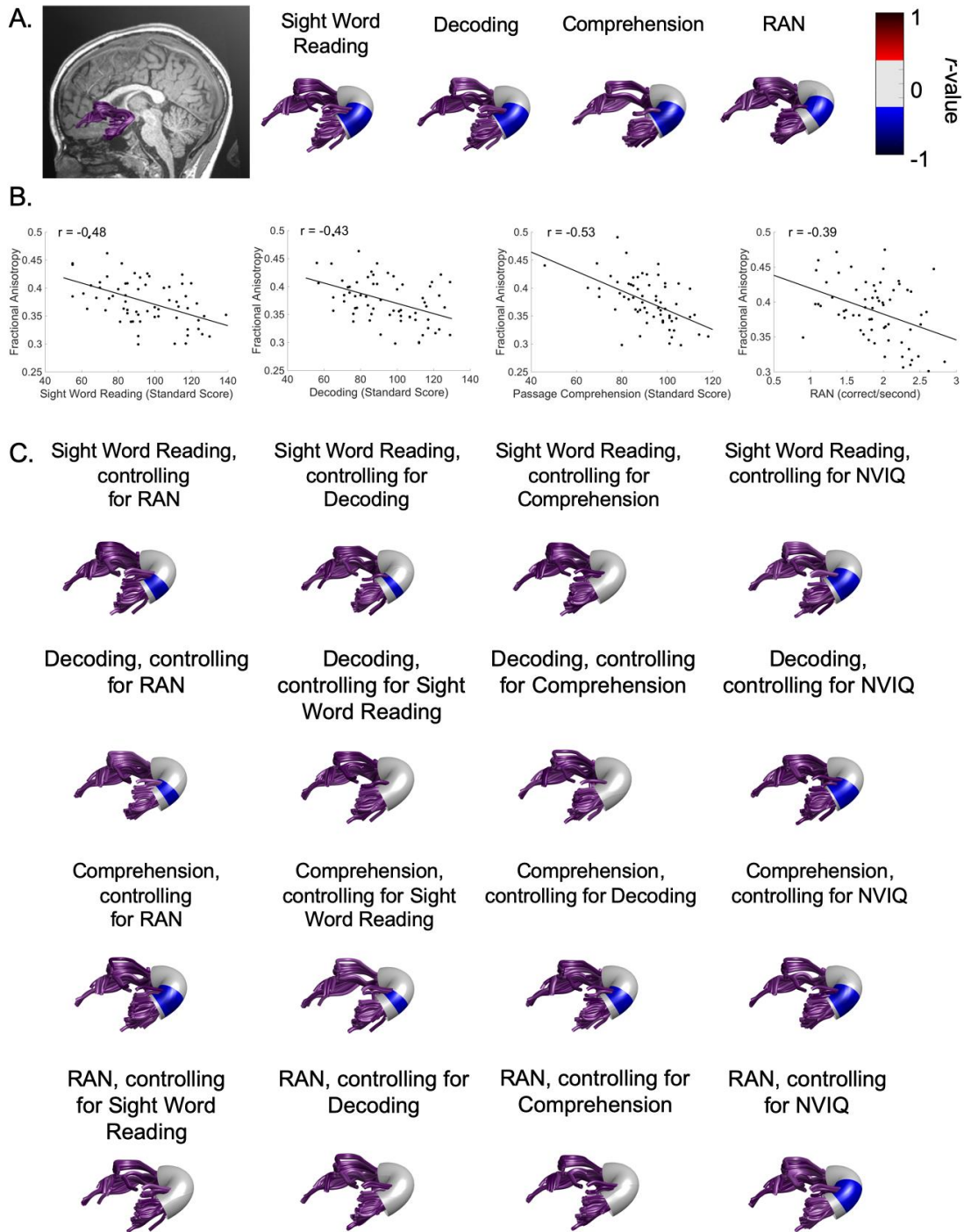


nodes, average  $r = -0.38$ ), but was no longer significant when accounting for other reading subskills (Figure 3.4C). Small clusters of positive correlations between sight word reading efficiency and FA were observed more anteriorly when controlling for RAN (5 nodes, average  $r = 0.25$ ) and decoding efficiency (10 nodes, average  $r = 0.26$ ; Figure 3.4C). The effect observed between decoding efficiency and FA persisted when controlling for nonverbal intelligence (33 nodes, average  $r = -0.41$ ), was reduced in cluster size when controlling for RAN (7 nodes, average  $r = -0.26$ ), and was no longer significant when controlling for sight word reading efficiency and reading comprehension (Figure 3.4C), although a small more anterior cluster of negative correlations between decoding efficiency and FA was observed when controlling for sight word reading efficiency (4 nodes, average  $r = -0.25$ ). Partial correlations between reading comprehension and FA showed that effects persisted when controlling for nonverbal intelligence (32 nodes, average  $r = -0.38$ ) and decreased in cluster size when accounting for RAN (22 nodes, average  $r = -0.30$ ) and for sight word reading efficiency (12 nodes, average  $r = -0.26$ ; Figure 3.4C). A more anterior cluster of positive correlations between FA and reading comprehension emerged when controlling for RAN (15 nodes, average  $r = 0.29$ ) and decoding efficiency (17 nodes, average  $r = 0.31$ ; Figure 3.4C). Finally, the negative relationship between RAN and FA persisted when accounting for nonverbal intelligence (42 nodes, average  $r = -0.40$ ), and was reduced only marginally in cluster size when accounting for sight word reading efficiency (21 nodes, average  $r = -0.32$ ), decoding efficiency (18 nodes, average  $r = -0.29$ ), and reading comprehension (23 nodes, average  $r = -0.36$ ). In general, these partial correlations suggest that RAN contributed strongly to unique variance in FA in the posterior right uncinate fasciculus, although

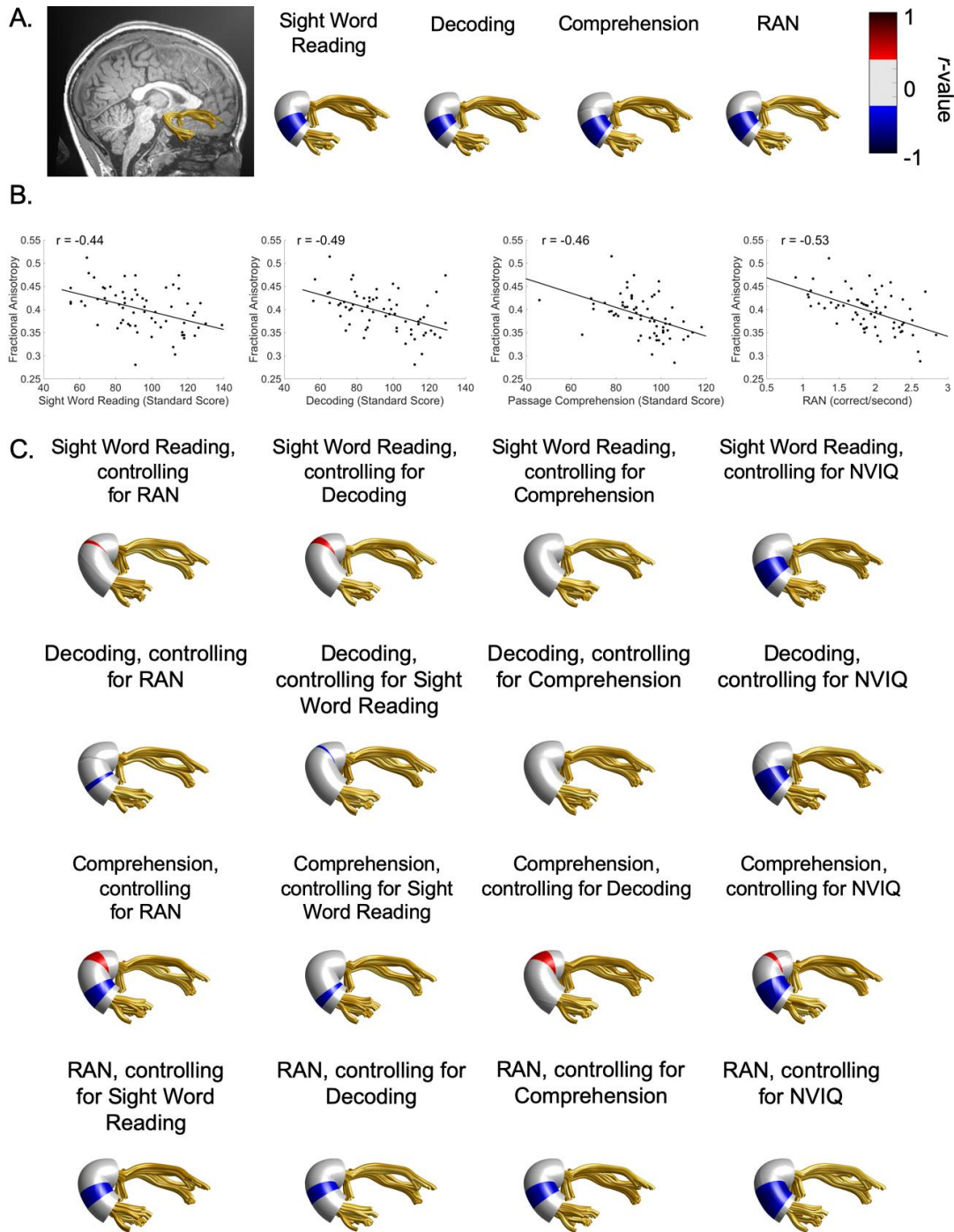
reading comprehension accounted for some unique variance in the more anterior region of the tract.

In the right ILF, significant negative correlations were observed between FA and scores on the reading comprehension task in 23 nodes in the anterior region of the tract (average  $r = -0.43$ ; Figure 3.5A). Partial correlations showed that the negative correlation between reading comprehension and FA persisted when controlling for RAN (20 nodes, average  $r = -0.31$ ) and for nonverbal intelligence (10 nodes, average  $r = -0.40$ ; Figure 3.5C). When controlling for each of decoding efficiency and sight word reading efficiency, some clusters of correlation between comprehension and FA persisted but were fragmented into three smaller clusters (decoding efficiency: 2 nodes (average  $r = -0.26$ ), 6 nodes (average  $r = -0.26$ ), and 6 nodes (average  $r = -0.29$ ); sight word reading efficiency: 5 nodes (average  $r = -0.28$ ), 5 nodes (average  $r = -0.26$ ), and 6 nodes (average  $r = -0.28$ ); Figure 3.5C). These findings suggest that microstructure in this tract strongly reflects reading comprehension, although this effect is modulated somewhat by single word reading skills, which may reflect the general interrelatedness of different reading subskills and overall reading success.

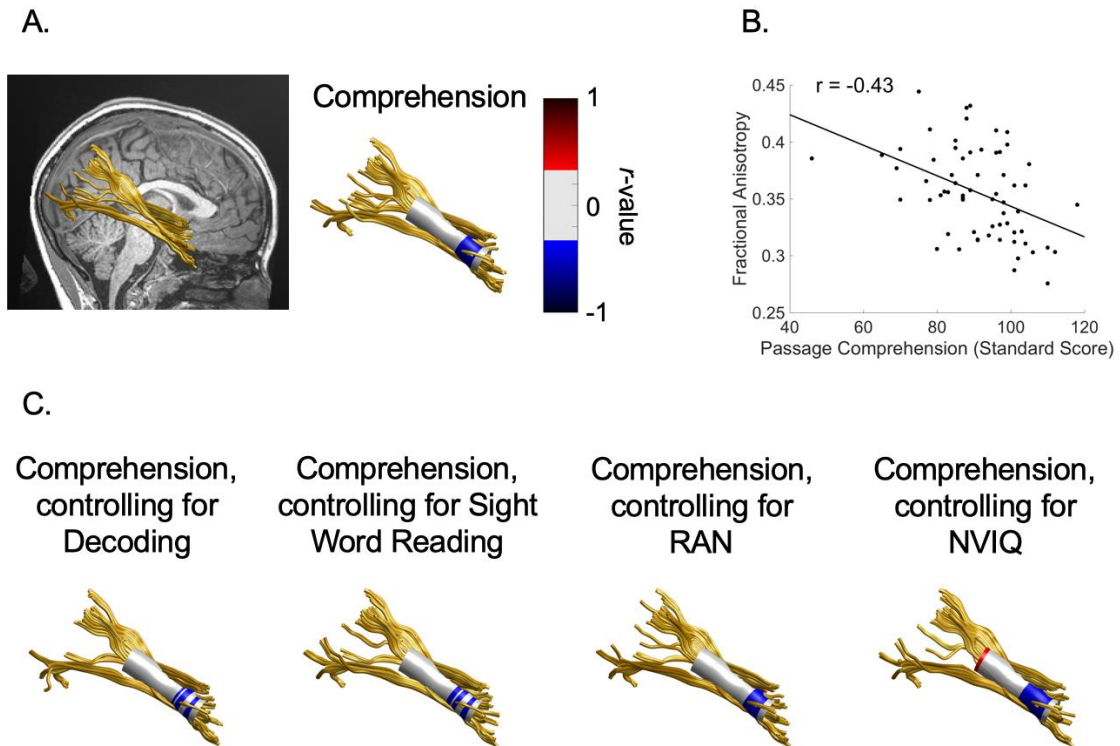
In the left ILF and in the right and left IFOF, no significant correlations were observed in cluster sizes large enough to pass the cluster-size correction.



**Figure 3.3** A) White matter correlations of FA and reading subskills in the left uncinate fasciculus, controlling for age. The colourbar shows significant  $r$ -values. B) Scatterplots for reading subskills and FA averaged across significant nodes shown in panel A. C) Partial correlations between FA and reading subskills, while controlling for other subskills.



**Figure 3.4** A) White matter correlations of FA and reading subskills in the right uncinate fasciculus, controlling for age. The colourbar shows significant  $r$ -values. B) Scatterplots for reading subskills and FA averaged across significant nodes shown in panel A. C) Partial correlations between FA and reading subskills, while controlling for other subskills.



**Figure 3.5** A) White matter correlations of FA and reading comprehension in the right ILF, controlling for age. The colourbar shows significant  $r$ -values. B) Scatterplots for reading comprehension and FA averaged across significant nodes shown in panel A. C) Partial correlations between FA and reading comprehension, while controlling for other subskills.

To examine whether reading subskills and FA were represented by continuous or categorical distributions, scatterplots were also generated within each tract for tasks which showed significant clusters in the zero-order correlations. For these scatterplots, each participant's FA values in the significant nodes for each task were averaged in each tract. As shown in Figures 3.1B, 3.2B, 3.3B, 3.4B, and 3.5B, the scores and FA values show a relatively linear relationship for all tasks and tracts. This suggests that findings in

the present study were not simply driven by poor readers and represent a relationship between FA and reading subskills that applies to the full distribution of reading abilities.

To further examine whether the results reflected maturational differences, Pearson's correlations were conducted between age and FA in each tract of interest. No significant correlations passing the cluster-size correction were observed in any of the tracts, suggesting that the observed correlations between reading subskills and FA are not related to differences in age. An exploratory analysis was conducted examining whether age and FA were correlated across all 10 tracts in both hemispheres, including the bilateral thalamic radiation, corticospinal tract, cingulum, superior longitudinal fasciculus, and callosum forceps major and minor, in addition to the tracts of interest of the present study. Clusters of positive correlations between FA and age were observed in the left and right thalamic radiations, and negative correlations were found in the right corticospinal tract, the branch of the left cingulum extending to the hippocampus, and the callosum forceps minor. This suggests that, as expected, differences in FA related to maturation were present in the sample, although not in the four tracts of interest of the present study.

The deterministic tractography technique we used is known to sometimes fail to identify tracts, particularly in the case of the right arcuate fasciculus which tends to be smaller than the left arcuate fasciculus (Yeatman et al., 2011). To address this, independent samples t-tests were conducted to compare the group of subjects in which a right arcuate could be identified ( $n = 50$ ) to the group of subjects in which a right arcuate could not be identified ( $n = 15$ ), to examine whether these groups differed in terms of age or cognitive abilities. The two groups did not differ significantly in age ( $t(63) = -1.22, p =$

0.23), decoding efficiency ( $t(63) = 0.04, p = 0.96$ ), sight word reading efficiency ( $t(63) = 1.19, p = 0.24$ ), RAN ( $t(63) = -0.98, p = 0.33$ ), reading comprehension ( $t(63) = 0.70, p = 0.48$ ), or nonverbal intelligence ( $t(63) = 0.71, p = 0.48$ ), suggesting that the ability to identify a participant's right arcuate fasciculus was not related to developmental or cognitive differences and that significant findings in this tract cannot be attributed to the exclusion of these individuals.

### 3.4 Discussion

The present study aimed to examine how different components of reading ability, including sight word reading efficiency, decoding efficiency, reading comprehension, and rapid naming, relate to the microstructure of reading-related white matter tracts in children. Previous studies of structural connectivity and reading ability in good and poor readers have tended to measure reading ability using a composite measure or from the perspective of phonological decoding. These studies have identified multiple tracts reflecting individual differences in reading skill. Of note, the present results demonstrate that the relationship between regional white matter integrity and reading ability in children is dissociable between different reading subskills.

One of our main findings was that more coherent white matter microstructure in the dorsal tracts was related to better single word abilities, as well as rapid naming abilities in the left hemisphere. In the left arcuate fasciculus, dissociable relationships were observed for decoding efficiency and RAN, in which better RAN scores were related to greater FA in a small posterior region of the tract while stronger decoding efficiency was uniquely related to greater FA in anterior regions. The significant effects observed posteriorly were also modulated to some degree by sight word reading

efficiency, but reading comprehension and nonverbal intelligence accounted for little variance in FA in this region. The implication of the left arcuate fasciculus in decoding and RAN was consistent with previous studies showing that integrity of the left arcuate is reduced in individuals with RD (Christodoulou, Cyr, et al., 2017; Klingberg et al., 2000; Richards et al., 2008; Steinbrink et al., 2008), who tend to perform poorly on decoding and rapid naming tasks (Denckla & Rudel, 1976; Ziegler, Perry, Ma-Wyatt, Ladner, & Schulte-Körne, 2003). This is also consistent with research relating FA in this dorsal tract to phonological and articulatory processes (Bernal & Ardila, 2009; Dick & Tremblay, 2012; Marchina et al., 2011; Shinoura et al., 2013; Vandermosten et al., 2012; Yeatman et al., 2011), both processes which have key roles in oral letter naming and in linking orthographic representations to phonological representations while decoding words aloud. In contrast with our findings, Saygin et al. (2013) found no relation between mean FA of the left arcuate and RAN despite strong associations between FA and phonological awareness in this tract. One possible reason for this discrepancy is our approach examining FA at 100 nodes along each tract, rather than examining mean FA across a large portion of the tract, as this is likely to have revealed effects in smaller clusters of nodes. However, when we controlled for decoding efficiency, the correlation between FA and RAN only persisted in a small number of posterior nodes, suggesting that this tract plays larger role in the phonological processes involved in decoding with smaller contributions to rapid naming ability.

In the right arcuate fasciculus, FA strongly reflected sight word reading efficiency and decoding efficiency, but these effects were modulated by reading comprehension and nonverbal intelligence. Unique negative correlations with decoding efficiency were also



observed when sight word reading efficiency was controlled for, suggesting opposite relationships for FA with sight word reading efficiency and FA with decoding efficiency in this posterior right arcuate region. In comparison to the left arcuate fasciculus, the right arcuate fasciculus is relatively understudied in reading research, in part because many other previous DTI studies have not successfully identified the right arcuate fasciculus in many subjects. This is likely due to limitations in the DTI fiber-tracking methodologies used, and use of a probabilistic tracking algorithm has suggested that a right arcuate fasciculus may be smaller than the left arcuate but is present in all healthy subjects (Yeatman et al., 2011). In the present study, we identified the right arcuate fasciculus in 50 out of the 65 subjects using deterministic tractography and performed analyses for this tract only on these 50 subjects. Importantly, we found no significant differences in age or cognitive measures between participants in which the right arcuate was and was not identified, suggesting the identifiability of this tract was not related to maturational factors, reading skills, or general intelligence. Our findings of unique negative correlations with decoding efficiency as well as positive correlations with sight word reading efficiency, both modulated to a degree by nonverbal intelligence and reading comprehension, contrast with the results of studies examining the right arcuate fasciculus. Yeatman et al. (2011) found no correlation between single-word reading in children and FA of the right arcuate, while Horowitz-Kraus et al. (2014) found that FA of the right arcuate was related to comprehension but not sight word reading in adolescents and adults. Although both of these studies assessed general intelligence for the purposes of describing their sample, they did not include this measure in their analyses examining relationships between FA and behavioural measures. However, general intelligence is

known to be related to reading abilities in typical readers (Ferrer et al., 2010; Hulslander et al., 2004), which may account for the correlation between reading comprehension and FA in Horowitz-Kraus et al. (2014). The inclusion of nonverbal intelligence in our analyses may in part explain the discrepancy between the findings of the present study and past research, and suggests a role for the right arcuate fasciculus in general cognition as well as in single word reading.

In ventral tracts including the right ILF and bilateral uncinate fasciculi, white matter integrity and reading subskills were negatively correlated, suggesting that poorer readers have greater integrity within these ventral white matter tracts. Previous research suggests that the left hemisphere ventral stream tracts, including the ILF, IFOF, and uncinate fasciculus, are important for processing lexical stimuli (Cummine et al., 2013; Dick & Tremblay, 2012; Shinoura et al., 2013; Wilson et al., 2011), but right hemisphere tracts are less frequently examined in DTI studies of reading. Our primary findings in ventral tracts were that in the bilateral uncinate fasciculi, poorer performance on all reading subskills was related to greater white matter integrity. The white matter-behaviour relationships were shown to be largely related to reading comprehension in the left uncinate fasciculus, while RAN and reading comprehension both contributed in the right uncinate fasciculus. In the right ILF, poor reading comprehension was related to greater FA, and this relationship was partially accounted for by differences in sight word reading efficiency, decoding efficiency, and nonverbal intelligence. These negative correlations suggest an over-reliance on these ventral tracts in struggling readers, and are consistent with findings of Banfi et al. (2018) showing a negative correlation between FA of the right ILF and performance on sight word reading and decoding tasks. In line with

our findings in the right ILF and right uncinate fasciculus, studies of functional connectivity have also observed that school-age children with RD have increased overall functional connectivity in the right hemisphere and tend to attain left-lateralization of language more slowly and to a lesser degree (Finn et al., 2014), suggesting a strong reliance on right hemisphere connectivity in school-aged struggling readers as a form of compensation.

Interestingly, when we controlled for decoding efficiency, RAN, and nonverbal intelligence, small clusters of positive correlations between reading comprehension and FA were revealed in the right uncinate fasciculus. This trend suggests some specific role of the right uncinate in processing semantic information, consistent with previous studies implicating right temporal lobe areas (Plante, Ramage, & Magloire, 2006; Plante, Schmithorst, Holland, & Byars, 2006; Robertson et al., 2000) and right ventral tracts (Horowitz-Kraus et al., 2014) in reading and language comprehension. An alternate interpretation is that reading comprehension performance represents the cumulative effect of all the reading subskills: completing this task necessarily involves single-word reading skills implicated in sight word reading and decoding measures, in addition to language comprehension abilities more generally.

Throughout development, FA of white matter tracts tends to increase, in a way that varies somewhat across tracts (Lebel, Walker, Leemans, Phillips, & Beaulieu, 2008). Given that age and reading skill are highly correlated with one another, the analyses of the present study included age as a covariate to account for any maturational differences in white matter in the school-aged participants. Our subsequent analysis finding no significant correlations between age and FA in the tracts of interest suggests that the

results of the present study do not simply represent age-related differences in white matter. Rather, our findings represent individual differences in focal white matter microstructure that are specifically linked to performance on reading subskills across a wide range of school-aged years.

A key question when considering the developmental trajectory of reading and the brain is whether the individual differences observed in white matter microstructure are a cause or a consequence of individual differences in reading ability. One possibility is that characteristics of white matter early on in childhood influence variation in reading ability and limit the impact of environmental factors on reading. For example, Hoeft et al. (2011) found that organization of white matter in the right superior longitudinal fasciculus predicted later response to intervention in adolescents with RD, suggesting that these white matter characteristics were a limiting factor for gains in reading skill. Alternately, change in white matter microstructure can be a function of experience (Yeatman et al., 2012). Consistent with this are studies showing changes in white matter integrity throughout development following reading intervention in individuals with RD (Gebauer et al., 2012; Keller & Just, 2009). It is likely that a combination of these two views best describes the relationship between white matter and reading: variability in white matter likely stems from both endogenous and environmental factors. The relationship between white matter and particular reading subskills is also likely to vary throughout development, as readers gain experience and some skills become more automatized. Further longitudinal research examining both neuroimaging and behavioural data is needed to better understand the dynamic nature of the relationship between reading subskills and white matter throughout development.

While this study is the first of its kind to examine white matter integrity in children with a wide range of reading abilities through the lens of multiple reading subskills, there are many other cognitive measures that are known to be related to reading and that were not included in the present study, for example phonological awareness (Gathercole et al., 2006), listening comprehension (Catts et al., 2005, 2003; Hoover & Gough, 1990), oral language (Catts et al., 2002), and working memory (Gathercole et al., 2006). Given that the relationships between white matter and reading diverged across the different tracts and subskills included in the present study, future research including other reading-related measures could more fully capture how different cognitive components of reading may be uniquely associated with integrity of these tracts.

### **3.4.1 Conclusion**

Our results provide evidence for multiple components of reading ability that are supported by distinct structural characteristics of the brain. Importantly, we observed both positive and negative correlations between reading ability and white matter integrity, such that arcuate fasciculus microstructure is positively associated with reading-related skills, particularly rapid naming and decoding efficiency in the left hemisphere and sight word reading efficiency in the right hemisphere. Conversely, struggling readers showed increased FA in right ILF and the bilateral uncinate especially with respect to reading comprehension and rapid naming. These findings shed new light on prior studies linking poor reading to white matter integrity and development, by demonstrating the contribution of multiple components of reading skill. Additionally, the present study showed that white matter integrity and reading abilities were related across a wide range of reading abilities, supporting the view that findings of atypical white matter structure in

individuals with RD reflect differences along the tail end of the distribution rather than a categorical difference in reading and brain structure.

## References

- Arnell, K. M., Klein, R. M., Joanisse, M. F., Bussen, M. A., & Tannock, R. (2009). Decomposing the relation between rapid automatized naming (RAN) and reading ability. *Canadian Journal of Experimental Psychology*, *63*(3), 173–184. <https://doi.org/10.1037/a0015721>
- Banfi, C., Koschutnig, K., Moll, K., Schulte-Körne, G., Fink, A. & Landerl, K (2018). White matter alterations and tract lateralization in children with dyslexia and isolated spelling deficits. *Human Brain Mapping* *40*(3), 765-776. <https://doi.org/10.1002/hbm.24410>
- Basser, P. J., & Pierpaoli, C. (1996). Microstructural and physiological features of tissues elucidated by quantitative-diffusion-tensor MRI. *Journal of Magnetic Resonance - Series B*, *111*(3), 209–219. <https://doi.org/10.1006/jmrb.1996.0086>
- Beaulieu, C., Plewes, C., Paulson, L. A., Roy, D., Snook, L., Concha, L., & Phillips, L. (2005). Imaging brain connectivity in children with diverse reading ability. *NeuroImage*, *25*(4), 1266–1271. <https://doi.org/10.1016/j.neuroimage.2004.12.053>
- Bernal, B., & Ardila, A. (2009). The role of the arcuate fasciculus in conduction aphasia. *Brain*, *132*(9), 2309-2316. <https://doi.org/10.1093/brain/awp206>
- Carter, J. C., Lanham, D. C., Cutting, L. E., Clements-Stephens, A. M., Chen, X., Hadzipasic, M., ... Kaufmann, W. E. (2009). A dual DTI approach to analyzing white matter in children with dyslexia. *Psychiatry Research - Neuroimaging*, *172*(3), 215–219. <https://doi.org/10.1016/j.psychresns.2008.09.005>
- Catani, M., Allin, M. P. G., Husain, M., Pugliese, L., Mesulam, M. M., Murray, R. M., & Jones, D. K. (2007). Symmetries in human brain language pathways correlate with verbal recall. *Proceedings of the National Academy of Sciences of the United States of America*, *104*(43), 17163–17168. <https://doi.org/10.1073/pnas.0702116104>
- Catts, H. W., Fey, M. E., Tomblin, J. B., & Zhang, X. (2002). A longitudinal investigation of reading outcomes in children with language impairments. *Journal of Speech, Language, and Hearing Research*, *45*(6), 1142–1157. [https://doi.org/10.1044/1092-4388\(2002/093\)](https://doi.org/10.1044/1092-4388(2002/093))
- Catts, H. W., Hogan, T. P., & Adlof, S. M. (2005). Developmental changes in reading and reading disabilities. In *The Connections Between Language and Reading Disabilities*. <https://doi.org/10.4324/9781410612052>
- Catts, H. W., Hogan, T. P., & Fey, M. E. (2003). Subgrouping poor readers on the basis of individual differences in reading-related abilities. *Journal of Learning Disabilities*, *36*(2), 151–164. <https://doi.org/10.1177/002221940303600208>
- Christodoulou, J. A., Cyr, A., Murtagh, J., Chang, P., Lin, J., Guarino, A. J., ... Gabrieli, J. D. E. (2017). Impact of intensive summer reading intervention for children with reading disabilities and difficulties in early elementary school. *Journal of Learning Disabilities*, *50*(2), 115–127. <https://doi.org/10.1177/0022219415617163>
- Christodoulou, J. A., Murtagh, J., Cyr, A., Perrachione, T. K., Chang, P., Halverson, K., ... Gabrieli, J. D. E. (2017). Relation of white-matter microstructure to reading ability and disability in beginning readers. *Neuropsychology*, *31*(5), 508–515. <https://doi.org/10.1037/neu0000243>
- Cummine, J., Dai, W., Borowsky, R., Gould, L., Rollans, C., & Boliek, C. (2013). Investigating the ventral-lexical, dorsal-sublexical model of basic reading processes using diffusion tensor imaging. *Brain Structure and Function*, *220*(1), 445–455.

- <https://doi.org/10.1007/s00429-013-0666-8>
- Denckla, M. B., & Rudel, R. G. (1976). Rapid “automatized” naming (RAN): Dyslexia differentiated from other learning disabilities. *Neuropsychologia*, *14*(4), 471–479. [https://doi.org/10.1016/0028-3932\(76\)90075-0](https://doi.org/10.1016/0028-3932(76)90075-0)
- Deutsch, G. K., Dougherty, R. F., Bammer, R., Siok, W. T., Gabrieli, J. D. E., & Wandell, B. (2005). Children’s reading performance is correlated with white matter structure measured by diffusion tensor imaging. *Cortex*, *41*(3), 354–363. [https://doi.org/10.1016/S0010-9452\(08\)70272-7](https://doi.org/10.1016/S0010-9452(08)70272-7)
- Dick, A. S., & Tremblay, P. (2012). Beyond the arcuate fasciculus: Consensus and controversy in the connectional anatomy of language. *Brain*, *135*(12), 3529–3550. <https://doi.org/10.1093/brain/aws222>
- Dougherty, R. F., Ben-Shachar, M., Deutsch, G. K., Hernandez, A., Fox, G. R., & Wandell, B. A. (2007). Temporal-callosal pathway diffusivity predicts phonological skills in children. *Proceedings of the National Academy of Sciences of the United States of America*, *104*(20), 8556–8561. <https://doi.org/10.1073/pnas.0608961104>
- Epelbaum, S., Pinel, P., Gaillard, R., Delmaire, C., Perrin, M., Dupont, S., ... Cohen, L. (2008). Pure alexia as a disconnection syndrome: New diffusion imaging evidence for an old concept. *Cortex*, *44*(8), 962–974. <https://doi.org/10.1016/j.cortex.2008.05.003>
- Ferrer, E., Shaywitz, B. A., Holahan, J. M., Marchione, K., & Shaywitz, S. E. (2010). Uncoupling of reading and IQ over time: Empirical evidence for a definition of dyslexia. *Psychological Science*, *21*(1), 93–101. <https://doi.org/10.1177/0956797609354084>
- Finn, E. S., Shen, X., Holahan, J. M., Scheinost, D., Lacadie, C., Papademetris, X., ... Constable, R. T. (2014). Disruption of functional networks in dyslexia: A whole-brain, data-driven analysis of connectivity. *Biological Psychiatry*, *76*(5), 397–404. <https://doi.org/10.1016/j.biopsych.2013.08.031>
- Frye, R. E., Ph, D., Hasan, K., Xue, L., Strickland, D., Malmberg, B., ... Papanicolaou, A. (2009). Splenium microstructure is related to two dimensions of reading skill. *Neuroreport*, *19*, 1627–1631. <https://doi.org/10.1097/WNR.0b013e328314b8ee.Splenium>
- Gathercole, S. E., Alloway, T. P., Willis, C., & Adams, A. M. (2006). Working memory in children with reading disabilities. *Journal of Experimental Child Psychology*, *93*(3), 265–281. <https://doi.org/10.1016/j.jecp.2005.08.003>
- Gebauer, D., Fink, A., Filippini, N., Johansen-Berg, H., Reishofer, G., Koschutnig, K., ... Enzinger, C. (2012). Differences in integrity of white matter and changes with training in spelling impaired children: A diffusion tensor imaging study. *Brain Structure and Function*, *217*(3), 747–760. <https://doi.org/10.1007/s00429-011-0371-4>
- Gold, B. T., Powell, D. K., Xuan, L., Jiang, Y., & Hardy, P. A. (2007). Speed of lexical decision correlates with diffusion anisotropy in left parietal and frontal white matter: Evidence from diffusion tensor imaging. *Neuropsychologia*, *45*(11), 2439–2446. <https://doi.org/10.1016/j.neuropsychologia.2007.04.011>
- Grossman, M., McMillan, C., Moore, P., Ding, L., Glosser, G., Work, M., & Gee, J. (2004). What’s in a name: Voxel-based morphometric analyses of MRI and naming difficulty in Alzheimer’s disease, frontotemporal dementia and corticobasal



- degeneration. *Brain*, *127*(3), 628–649. <https://doi.org/10.1093/brain/awh075>
- Gullick, M. M., & Booth, J. R. (2015). The direct segment of the arcuate fasciculus is predictive of longitudinal reading change. *Developmental Cognitive Neuroscience*, *13*, 68–74. <https://doi.org/10.1016/j.dcn.2015.05.002>
- Hoefft, F., McCandliss, B. D., Black, J. M., Gantman, A., Zakerani, N., Hulme, C., ... Gabrieli, J. D. E. (2011). Neural systems predicting long-term outcome in dyslexia. *Proceedings of the National Academy of Sciences of the United States of America*, *108*(1), 361–366. <https://doi.org/10.1073/pnas.1008950108>
- Hoover, W. A., & Gough, P. B. (1990). The simple view of reading. *Reading and Writing*, *2*(2), 127–160. <https://doi.org/10.1007/BF00401799>
- Horowitz-Kraus, T., Wang, Y., Plante, E., & Holland, S. K. (2014). Involvement of the right hemisphere in reading comprehension: A DTI study. *Brain Research*, *1582*, 34–44. <https://doi.org/10.1016/j.brainres.2014.05.034>
- Howe, A. E., Arnell, K. M., Klein, R. M., Joanisse, M. F., & Tannock, R. (2006). The ABCs of computerized naming: Equivalency, reliability, and predictive validity of a computerized rapid automatized naming (RAN) task. *Journal of Neuroscience Methods*, *151*(1), 30–37. <https://doi.org/10.1016/j.jneumeth.2005.07.014>
- Hulslander, J., Talcott, J., Witton, C., DeFries, J., Pennington, B., Wadsworth, S., ... Olson, R. (2004). Sensory processing, reading, IQ, and attention. *Journal of Experimental Child Psychology*, *88*(3), 274–295. <https://doi.org/10.1016/j.jecp.2004.03.006>
- Keller, T. A., & Just, M. A. (2009). Altering cortical connectivity: remediation-induced changes in the white matter of poor readers. *Neuron*, *64*(5), 624–631. <https://doi.org/10.1016/j.neuron.2009.10.018>
- Klingberg, T., Hedehus, M., Temple, E., Salz, T., Gabrieli, J. D. E., Moseley, M. E., & Poldrack, R. A. (2000). Microstructure of temporo-parietal white matter as a basis for reading ability: Evidence from diffusion tensor magnetic resonance imaging. *Neuron*, *25*(2), 493–500. [https://doi.org/10.1016/S0896-6273\(00\)80911-3](https://doi.org/10.1016/S0896-6273(00)80911-3)
- Le Bihan, D., Mangin, J. F., Poupon, C., Clark, C. A., Pappata, S., Molko, N., & Chabriat, H. (2001). Diffusion tensor imaging: Concepts and applications. *Journal of Magnetic Resonance Imaging*, *13*(4), 534–546. <https://doi.org/10.1002/jmri.1076>
- Lebel, C., Walker, L., Leemans, A., Phillips, L., & Beaulieu, C. (2008). Microstructural maturation of the human brain from childhood to adulthood. *NeuroImage*, *40*(3), 1044–1055. <https://doi.org/10.1016/j.neuroimage.2007.12.053>
- Lebel, Catherine, Shaywitz, B., Holahan, J., Shaywitz, S., Marchione, K., & Beaulieu, C. (2013). Diffusion tensor imaging correlates of reading ability in dysfluent and non-impaired readers. *Brain and Language*, *125*(2), 215–222. <https://doi.org/10.1016/j.bandl.2012.10.009>
- Ling, J., Merideth, F., Caprihan, A., Pena, A., Teshiba, T., & Mayer, A. R. (2012). Head injury or head motion? Assessment and quantification of motion artifacts in diffusion tensor imaging studies. *Human Brain Mapping*, *33*(1), 50–62. <https://doi.org/10.1002/hbm.21192>
- Lou, C., Duan, X., Altarelli, I., Sweeney, J. A., Ramus, F., & Zhao, J. (2019). White matter network connectivity deficits in developmental dyslexia. *Human Brain Mapping*, *40*(2), 505–516. <https://doi.org/10.1002/hbm.24390>
- Lu, L. H., Crosson, B., Nadeau, S. E., Heilman, K. M., Gonzalez-Rothi, L. J., Raymer,

- A., ... Roper, S. N. (2002). Category-specific naming deficits for objects and actions: Semantic attribute and grammatical role hypotheses. *Neuropsychologia*, *40*(9), 1608–1621. [https://doi.org/10.1016/S0028-3932\(02\)00014-3](https://doi.org/10.1016/S0028-3932(02)00014-3)
- Lyon, G. R., Shaywitz, S. E., & Shaywitz, B. A. (2003). A definition of dyslexia. *Annals of Dyslexia*, *53*(1), 1-14. <https://doi.org/10.1007/s11881-003-0001-9>
- Mandonnet, E., Nouet, A., Gatignol, P., Capelle, L., & Duffau, H. (2007). Does the left inferior longitudinal fasciculus play a role in language? A brain stimulation study. *Brain*, *130*(3), 623–629. <https://doi.org/10.1093/brain/awl361>
- Marchina, S., Zhu, L. L., Norton, A., Zipse, L., Wan, C. Y., & Schlaug, G. (2011). Impairment of speech production predicted by lesion load of the left arcuate fasciculus. *Stroke*, *42*(8), 2251–2256. <https://doi.org/10.1161/STROKEAHA.110.606103>
- Nagy, Z., Westerberg, H., & Klingberg, T. (2004). Maturation of white matter is associated with the development of cognitive functions during childhood. *Journal of Cognitive Neuroscience*, *16*(7), 1227–1233. <https://doi.org/10.1162/0898929041920441>
- Nichols, T. E., & Holmes, A. P. (2002). Nonparametric permutation tests for functional neuroimaging: A primer with examples. *Human Brain Mapping*, *15*(1), 1–25. <https://doi.org/10.1002/hbm.1058>
- Niogi, S. N., & McCandliss, B. D. (2006). Left lateralized white matter microstructure accounts for individual differences in reading ability and disability. *Neuropsychologia*, *44*(11), 2178–2188. <https://doi.org/10.1016/j.neuropsychologia.2006.01.011>
- Norton, E. S., & Wolf, M. (2012). Rapid automatized naming (RAN) and reading fluency: Implications for understanding and treatment of reading disabilities. *Annual Review of Psychology*, *63*(1), 427–452. <https://doi.org/10.1146/annurev-psych-120710-100431>
- Plante, E., Ramage, A. E., & Magloire, J. (2006). Processing narratives for verbatim and gist information by adults with language learning disabilities: A functional neuroimaging study. *Learning Disabilities Research and Practice*, *21*(1), 61–76. <https://doi.org/10.1111/j.1540-5826.2006.00207.x>
- Plante, E., Schmithorst, V. J., Holland, S. K., & Byars, A. W. (2006). Sex differences in the activation of language cortex during childhood. *Neuropsychologia*, *44*(7), 1210–1221. <https://doi.org/10.1016/j.neuropsychologia.2005.08.016>
- Price, C. J. (2012). A review and synthesis of the first 20 years of PET and fMRI studies of heard speech, spoken language and reading. *NeuroImage*, *62*(2), 816–847. <https://doi.org/10.1016/j.neuroimage.2012.04.062>
- Ramus, F. (2003). Developmental dyslexia: Specific phonological deficit or general sensorimotor dysfunction? *Current Opinion in Neurobiology*, *13*(2), 212-218. [https://doi.org/10.1016/S0959-4388\(03\)00035-7](https://doi.org/10.1016/S0959-4388(03)00035-7)
- Richards, T., Stevenson, J., Crouch, J., Johnson, L. C., Maravilla, K., Stock, P., ... Berninger, V. (2008). Tract-based spatial statistics of diffusion tensor imaging in adults with dyslexia. *American Journal of Neuroradiology*, *29*(6), 1134–1139. <https://doi.org/10.3174/ajnr.A1007>
- Rimrodt, S. L., Peterson, D. J., Denckla, M. B., Kaufmann, W. E., & Cutting, L. E. (2010). White matter microstructural differences linked to left perisylvian language

- network in children with dyslexia. *Cortex*, 46(6), 739–749.  
<https://doi.org/10.1016/j.cortex.2009.07.008>
- Robertson, D. A., Gernsbacher, M. A., Guidotti, S. J., Robertson, R. R. W., Irwin, W., Mock, B. J., & Campana, M. E. (2000). Functional neuroanatomy of the cognitive process of mapping during discourse comprehension. *Psychological Science*, 11(3), 255–260. <https://doi.org/10.1111/1467-9280.00251>
- Sandak, R., Frost, S. J., Rueckl, J. G., Landi, N., Mencl, W. E., Katz, L., & Pugh, K. R. (2012). How does the brain read words? In *The Cambridge Handbook of Psycholinguistics* (pp. 218–236). <https://doi.org/10.1017/cbo9781139029377.015>
- Saygin, Z. M., Norton, E. S., Osher, D. E., Beach, S. D., Cyr, A. B., Ozernov-Palchik, O., ... Gabrieli, J. D. E. (2013). Tracking the roots of reading ability: White matter volume and integrity correlate with phonological awareness in prereading and early-reading kindergarten children. *Journal of Neuroscience*, 33(33), 13251–13258. <https://doi.org/10.1523/JNEUROSCI.4383-12.2013>
- Shinoura, N., Midorikawa, A., Onodera, T., Tsukada, M., Yamada, R., Tabei, Y., ... Yagi, K. (2013). Damage to the left ventral, arcuate fasciculus and superior longitudinal fasciculus-related pathways induces deficits in object naming, phonological language function and writing, respectively. *International Journal of Neuroscience*, 123(7), 494–502. <https://doi.org/10.3109/00207454.2013.765420>
- Siegel, L. S. (2006). Perspectives on dyslexia. *Paediatrics and Child Health*, 11(9), 581–587. <https://doi.org/10.1093/pch/11.9.581>
- Snowling, M. J., Gooch, D. C., & Henderson, L. M. (2012). Dyslexia. In *Encyclopedia of Human Behavior: Second Edition* (pp. 732–739). <https://doi.org/10.1016/B978-0-12-375000-6.00139-7>
- Steinbrink, C., Vogt, K., Kastrup, A., Müller, H. P., Juengling, F. D., Kassubek, J., & Riecker, A. (2008). The contribution of white and gray matter differences to developmental dyslexia: Insights from DTI and VBM at 3.0 T. *Neuropsychologia*, 46(13), 3170–3178. <https://doi.org/10.1016/j.neuropsychologia.2008.07.015>
- Thiebaut de Schotten, M., Cohen, L., Amemiya, E., Braga, L. W., & Dehaene, S. (2014). Learning to read improves the structure of the arcuate fasciculus. *Cerebral Cortex*, 24(4), 989–995. doi:10.1093/cercor/bhs383
- Torgesen, J. K., Wagner, R. K., & Rashotte, C. A. (2012). *Test of Word Reading Efficiency* (2<sup>nd</sup> ed.). Austin, TX: Pro-Ed.
- Vanderauwera, J., Wouters, J., Vandermosten, M., & Ghesquière, P. (2017). Early dynamics of white matter deficits in children developing dyslexia. *Developmental Cognitive Neuroscience*, 27, 69–77. <https://doi.org/10.1016/j.dcn.2017.08.003>
- Vandermosten, M., Boets, B., Poelmans, H., Sunaert, S., Wouters, J., & Ghesquière, P. (2012). A tractography study in dyslexia: Neuroanatomic correlates of orthographic, phonological and speech processing. *Brain*, 135(3), 935–948. <https://doi.org/10.1093/brain/awr363>
- Vandermosten, M., Boets, B., Wouters, J., & Ghesquière, P. (2012). A qualitative and quantitative review of diffusion tensor imaging studies in reading and dyslexia. *Neuroscience and Biobehavioral Reviews*, 36(6), 1532–1552. <https://doi.org/10.1016/j.neubiorev.2012.04.002>
- Vandermosten, M., Poelmans, H., Sunaert, S., Ghesquière, P., & Wouters, J. (2013). White matter lateralization and interhemispheric coherence to auditory modulations

- in normal reading and dyslexic adults. *Neuropsychologia*, 51(11), 2087–2099.  
<https://doi.org/10.1016/j.neuropsychologia.2013.07.008>
- Wagner, R. K., Torgesen, J. K., Laughon, P., Simmons, K., & Rashotte, C. A. (1993). Development of young readers' phonological processing abilities. *Journal of Educational Psychology*, 85(1), 83–103. <https://doi.org/10.1037/0022-0663.85.1.83>
- Wakana, S., Caprihan, A., Panzenboeck, M. M., Fallon, J. H., Perry, M., Gollub, R. L., ... Mori, S. (2007). Reproducibility of quantitative tractography methods applied to cerebral white matter. *NeuroImage*, 36(3), 630–644.  
<https://doi.org/10.1016/j.neuroimage.2007.02.049>
- Welcome, S. E., & Joanisse, M. F. (2014). Individual differences in white matter anatomy predict dissociable components of reading skill in adults. *NeuroImage*, 96, 261–275. <https://doi.org/10.1016/j.neuroimage.2014.03.069>
- Wechsler, D. (1999). *Wechsler Abbreviated Scale of Intelligence*. San Antonio, TX: The Psychological Corporation.
- Wilson, S. M., Galantucci, S., Tartaglia, M. C., Rising, K., Patterson, D. K., Henry, M. L., ... Gorno-Tempini, M. L. (2011). Syntactic processing depends on dorsal language tracts. *Neuron*, 72(2), 397–403.  
<https://doi.org/10.1016/j.neuron.2011.09.014>
- Woodcock, R. W., McGrew, K. S., & Mather, N. (2001). *Woodcock-Johnson III*. Itasca, IL: Riverside Publishing.
- Yeatman, J. D., Dougherty, R. F., Ben-Shachar, M., & Wandell, B. A. (2012). Development of white matter and reading skills. *Proceedings of the National Academy of Sciences of the United States of America*, 109(44).  
<https://doi.org/10.1073/pnas.1206792109>
- Yeatman, J. D., Dougherty, R. F., Myall, N. J., Wandell, B. A., & Feldman, H. M. (2012). Tract profiles of white matter properties: Automating fiber-tract quantification. *PLoS ONE*, 7(11), e49790.  
<https://doi.org/10.1371/journal.pone.0049790>
- Yeatman, J. D., Dougherty, R. F., Rykhlevskaia, E., Sherbondy, A. J., Deutsch, G. K., Wandell, B. A., & Ben-Shachar, M. (2011). Anatomical properties of the arcuate fasciculus predict phonological and reading skills in children. *Journal of Cognitive Neuroscience*, 23(11), 3304–3317. [https://doi.org/10.1162/jocn\\_a\\_00061](https://doi.org/10.1162/jocn_a_00061)
- Ziegler, J. C., Perry, C., Ma-Wyatt, A., Ladner, D., & Schulte-Körne, G. (2003). Developmental dyslexia in different languages: Language-specific or universal? *Journal of Experimental Child Psychology*, 86(3), 169–193.  
[https://doi.org/10.1016/S0022-0965\(03\)00139-5](https://doi.org/10.1016/S0022-0965(03)00139-5)

## **Chapter 4: Functional and Structural Connectivity and Reading Intervention in Children**

### **4.1 Introduction**

Although many children learn to read quickly and accurately, approximately 10% of otherwise typically developing children struggle to learn to read (Lyon et al., 2003). Reading disability (RD), sometimes known as dyslexia, is characterized by difficulties reading words fluently and accurately, and is associated with difficulty processing phonological information (Ramus, 2003; Snowling et al., 2012; Wagner et al., 1993). Phonology-based interventions have been shown to be effective in improving reading in children with RD (Bus & Van Ijzendoorn, 1999; Duff & Clarke, 2011; National Reading Panel, 1989) and result in measurable improvements in phonological reading skills (Lovett, Steinbach, & Frijters, 2000). However, significant challenges remain in characterizing the cause of RD and understanding variability in the degree to which individuals respond to reading intervention. Although a large body of neuroimaging research has identified specific neural differences associated with RD (Maisog et al., 2008; Paulesu et al., 2014; Richlan, Kronbichler, & Wimmer, 2009b), much remains to be understood with respect to the neural correlates of RD and response to reading intervention.

Previous studies of changes in the brain related to reading instruction have tended to focus on differences in functional activity of the brain before, during, and after intervention. A descriptive review of 22 reading intervention studies using fMRI and magnetoencephalography (MEG) found that pre-intervention, RD was generally associated with underactivity in bilateral regions including the inferior, middle, and superior frontal gyri, middle and superior temporal gyri, occipital regions, postcentral

gyri, inferior parietal lobule, and insulae, with a relative increase in activity in these regions post-intervention (Barquero, Davis, & Cutting, 2014). A further meta-analysis of a subset of eight of the 22 studies found that participants with RD exhibited increased activation in the left thalamus, right insula, bilateral inferior frontal gyri, right posterior cingulate, and left middle occipital gyrus following reading intervention. Overall, this body of research suggests that differences in localized brain activity are associated with intervention in individuals with RD.

Relatively fewer studies have examined how reading intervention is related to changes in functional and structural connectivity between brain regions, although this is of great interest given that efficient reading requires coordinated processing across many areas of the brain. *Functional* connectivity can be measured based on interregional correlations in neural activity during an fMRI scan, either using a task-based or resting-state approach. In a task-based approach, the participant might complete a reading or related phonological processing task during the fMRI scan, and functional connectivity is assessed by examining the correlations in the time course of the BOLD response during that task. Alternatively, functional networks can be studied while the participant is in a resting-state, by measuring temporal correlations in the low frequency fluctuations of the fMRI signal of different brain regions (Biswal et al., 1995). Resting-state functional connectivity reflects the brain's functional networks (Fox & Raichle, 2007), such that areas of the brain that are functionally-related tend to be highly correlated in terms of their time courses of spontaneous BOLD activity. The resting-state functional connectivity (RSFC) technique is advantageous in that the functional data is not influenced by particular task demands, differences in task performance, or differences in

participants' processing strategies. An alternate method of assessing connectivity in the brain is via diffusion tensor imaging (DTI), which can serve as a measure of *structural* connectivity of the brain's white matter tracts. DTI is a structural MRI technique which measures diffusion of water molecules in the brain. The directionality of water diffusion, quantified as fractional anisotropy (FA), characterizes structure of the brain's white matter tracts including factors such as fiber density, axon diameter, and myelination (Basser & Pierpaoli, 1996). Reading ability in typical readers as well as individuals with RD has been linked to both RSFC (Farris et al., 2011; Koyama et al., 2013, 2011; Schurz et al., 2015; Chapter 2 of this thesis) and DTI connectivity (for a review see Vandermosten, Boets, Wouters, & Ghesquière, 2012; Chapter 3 of this thesis), demonstrating the role of functional and structural connectivity in reading.

A small number of studies have used RSFC approaches to quantify differences in the brain's functional connectivity before and after reading intervention, shedding light on the changes in the brain's function which underlie behavioural improvements in reading ability. Koyama et al. (2013) used a cross-sectional approach to compare RSFC between typically developing (TD) controls and three groups of children with RD that had not been remediated, partially remediated, and fully remediated. Findings showed that, compared to TD controls, RSFC was reduced between the left intraparietal sulcus and left middle frontal gyrus in all groups with RD, regardless of treatment status. However, when compared to the TD controls and RD group with no remediation, the partial and full remediation groups exhibited increased RSFC between the left fusiform gyrus and right middle occipital gyrus, suggesting a role for remediation in increasing reliance on visual reading areas, perhaps as a form of compensation for weak

phonological processing. Koyama et al. (2013) also observed more negative RSFC between the left fusiform gyrus and right medial prefrontal cortex in the full remediation group relative to the other RD groups and the TD controls, and suggested this may be related to functional segregation between the reading network and default mode network.

Additionally, a series of longitudinal studies examining changes in RSFC following an executive-function based reading training program documented increased RSFC within the cingulo-opercular network (Horowitz-Kraus, Toro-Serey, et al., 2015) as well as increased RSFC between the cingulo-opercular network, specifically the right anterior cingulate cortex, and the left fusiform gyrus (Horowitz-Kraus & Holland, 2015). Children with RD completing this program also exhibited increased RSFC between the visual processing network and networks associated with executive function, dorsal attention, and language (Horowitz-Kraus, Difrancesco, Kay, Wang, & Holland, 2015) as well as increased overall functional connectivity in the brain, based on measures of global efficiency (Horowitz-Kraus, Toro-Serey, et al., 2015). Changes in RSFC observed in these studies were positively correlated with improvement on behavioural measures of word reading (Horowitz-Kraus, Difrancesco, et al., 2015; Horowitz-Kraus & Holland, 2015; Horowitz-Kraus, Toro-Serey, et al., 2015), reading comprehension (Horowitz-Kraus, Difrancesco, et al., 2015), and visual attention (Horowitz-Kraus & Holland, 2015). As a whole, these studies suggest that reading intervention is associated with changes in RSFC within the reading network as well as RSFC to areas outside of the reading network, and these changes in functional connectivity tend to also correlate with the degree of reading improvement observed behaviourally. However, no studies to date have



used a longitudinal approach to examine what changes in RSFC are present following a phonology-based intervention.

Similarly, studies using DTI approaches have suggested that changes in white matter structure are associated with improvement in reading skills. For example, in children with a wide range of reading abilities, changes white matter volume in left temporo-parietal regions predicted gains in reading skill, above and beyond other factors such as familiar risk, environment, preliteracy ability, and cognitive capacity (Myers et al., 2014). In children with RD, although reduced FA in the left anterior centrum semiovale was observed pre-intervention compared to good readers, no between-group differences were observed in FA in this left frontal region following a phonology-based reading intervention (Keller & Just, 2009). DTI data collected at more regular intervals throughout an intensive 8-week intervention suggests that observed changes in white matter are distributed and occur jointly with improvements in reading skill (Huber, Donnelly, Rokem, & Yeatman, 2018a). Specifically, participants were scanned before beginning the intervention, and following 2.5 weeks, five weeks, and eight weeks of intervention. Huber et al. (2018) observed an increase in FA as a function of intervention time in the left arcuate fasciculus and the left inferior longitudinal fasciculus. Further changes in white matter were widespread across both association and projection tracts. However, the intervention group was not more similar to typical readers in terms of white matter properties following the intervention, suggesting that the observed white matter changes represent compensatory mechanisms rather than normalization of neural properties.

Comparisons of groups who do and do not respond to reading intervention also suggest that structural connectivity following intervention is related to the degree of improvement observed in reading skills. Davis and colleagues (2010) showed that greater response to reading intervention, as measured by pre- and post-intervention word identification, decoding, and fluency tasks, was associated with greater white matter connectivity between the left angular gyrus and left insula following the intervention. Additionally, better intervention response on a word attack task was related to greater connectivity between the left inferior frontal gyrus pars triangularis and the superior temporal gyrus. Interestingly, response to intervention was also negatively correlated with structural connections from the right thalamus to the right inferior frontal gyrus pars triangularis, from the left thalamus to the left superior temporal gyrus, and from the right inferior frontal gyrus pars triangularis to the right superior temporal gyrus. Together, these studies demonstrate that reading intervention is associated with measurable changes in white matter distributed across many white matter tracts, and that these neural changes are related to the degree of improvement observed behaviourally.

Given that there is significant variability in the degree to which children with RD respond to intervention, one question of interest is whether response to intervention may also be predicted by differences in the brain that are present prior to reading intervention. Research suggests that this variability can be predicted by performance on behavioural pre-reading tasks such as rapid automatized naming (Al Otaiba & Fuchs, 2002; Fletcher et al., 2011; Frijters et al., 2011; Partanen, Siegel, & Giaschi, 2019; Tilanus, Segers, & Verhoeven, 2019) and phonological awareness (Barth, Catts, & Anthony, 2009; Jongejan, Verhoeven, & Siegel, 2007; Misra et al., 2004; Partanen et al., 2019; Tilanus et al., 2019),

as well as reading tasks including word recognition, decoding, reading comprehension, reading fluency, and spelling (Partanen et al., 2019; Tilanus et al., 2019). However, the neurobiological factors that underlie these behavioural predictors are not well understood.

Although no studies to date have examined how RSFC may predict response to intervention, fMRI studies focusing on localized brain activity during reading tasks suggest that pre-intervention brain function in reading network regions is a predictor of behavioural reading improvement following intervention. For example, adolescents with RD with greater activation in the right inferior frontal gyrus during a rhyme-judgement task showed better behavioural response during a subsequent reading intervention (Hoeft et al., 2011). Similarly, increased MEG activity in left middle, superior temporal, and ventral occipitotemporal regions and in right medial temporal regions predicted greater reading improvement in adolescents (Rezaie et al., 2011). This same study also found that activity in these regions was a better predictor of intervention response than behavioural measures of pre-intervention reading accuracy or fluency. With respect to white matter connectivity, children with RD with greater FA in the right superior longitudinal fasciculus, including the arcuate fasciculus, showed greater improvement in single word reading skills over the subsequent 2.5 years (Hoeft et al., 2011). These studies demonstrate that some structural and functional differences in the brain can predict subsequent gains in reading ability. However, further research is needed to understand how functional connectivity between reading network areas may predict response following intervention, and to examine whether structural connectivity is also a predictor of response following intervention in more widespread white matter tracts known to support reading.

The present study aimed to extend the existing body of research examining how changes in structural and functional connectivity relate to the amount of growth observed in reading skills following a phonology-based reading intervention. Specifically, participants in the present study completed the Empower Reading: Decoding and Spelling program (Lovett, Lacerenza, Steinbach, & De Palma, 2014), which combines a phonology-based approach with explicit instruction of word identification strategies and metacognitive strategies. Readers are trained to use a metacognitive dialogue to select and implement word recognition strategies and monitor their effectiveness of each word recognition strategy in successfully decoding the word. The Empower Reading: Decoding and Spelling program has been shown to result in significant and generalizable gains in decoding, word recognition, reading accuracy, reading rate, and reading comprehension in children with RD from a variety of socioeconomic statuses, races, and IQ levels (Lovett & Steinbach, 1997; Morris et al., 2012).

In the present study, we measured DTI connectivity and RSFC in children with RD before and after they completed the Empower program, to assess changes in connectivity from pre- to post-intervention and examine how these changes may vary based on individual differences in improvement in reading skills. DTI connectivity and RSFC were also measured at the beginning and end of the academic year in a second group of children with a wide range of reading abilities, for the purposes of comparing how any changes in connectivity in children receiving intervention may compare to changes associated with regular classroom reading instruction. The present study also aimed to examine whether any measures of connectivity prior to intervention were predictors of behavioural gains in reading following intervention.

## 4.2 Methods

### 4.2.1 Participants

Thirty-eight children between 8 and 11 years old were recruited through local schools and social media advertisements in the London, Ontario community. These participants represent a subset of those who participated in the studies described in Chapters 2 and 3 of this thesis. Participants were categorized into two groups based on their participation in a reading intervention. The reading intervention (RI) group was comprised of 19 children who had been identified by school professionals as having significant reading difficulties and were enrolled in Empower Reading: Decoding and Spelling, a reading intervention administered in their school. The non-intervention (NI) group was made up of the remaining 18 participants, who were not receiving any reading intervention beyond their regular classroom reading instruction. The participants in the non-intervention group had a wide range of reading abilities but any poor readers in this group had not been formally identified with reading difficulties. The parents of all participants reported via a structured questionnaire that the children had normal or corrected-to-normal vision, no hearing impairments, and were neurologically healthy. All parents provided informed consent and children provided assent to participate at the beginning of the study.

### 4.2.2 Procedures

At the beginning of study, all participants completed a battery of standardized behavioural measures to assess reading ability and nonverbal intelligence in both groups prior to reading intervention. For the participants in the RI group, this session took place in the fall before they began the Empower Reading program. The *Woodcock-Johnson III*

(WJ-III; Woodcock et al., 2001) *Letter-Word Identification*, *Reading Fluency*, and *Passage Comprehension* subtests were used to assess single word reading, sentence reading fluency, and reading comprehension, respectively. The *Sight Word Efficiency* subtest of the *Test of Word Reading Efficiency II* (TOWRE-2; Torgesen et al., 2012) assessed sight word reading fluency, while the *Phonemic Decoding Efficiency* subtest of the TOWRE-2 measured fluency of decoding of pronounceable pseudowords. Nonverbal intelligence was assessed using the *Weschler Abbreviated Scale of Intelligence Second Edition* (WASI-II; Weschler, 2011) Performance IQ measures, which includes the *Block Design* and *Matrix Reasoning* subtests. The scores on these two subtests were combined to provide a Performance IQ score measuring nonverbal intelligence. More details regarding these standardized measures are available in Chapters 2 and 3 of this thesis.

MRI sessions took place between one and two weeks following the first session, including an anatomical, resting-state, and diffusion tensor imaging scan. Participants in the RI group then began the Empower Reading program at their school. Informal Empower progress measures were administered by teachers at the beginning and end of the Empower program. Between eight and ten months later, after completing the Empower program, participants completed a second, similar MRI session. Participants in the NI group only received regular classroom reading instruction as per the Ontario education curriculum, following their first MRI scan. Their second scan was completed between eight and ten months later. A total of 14 participants did not participate in the second MRI scan ( $n = 7$  in RI group,  $n = 7$  in NI group) because they had moved, were not available, or were no longer able to safely participate in an MRI scan due to permanent dental appliances. This yielded a total sample size of 24 for the present study:

13 participants in the RI group (7 female; 12 right-handed) and 11 participants in the NI group (8 female; 10 right-handed).

### 4.2.3 Intervention

The participants in the RI group received the Empower Reading: Decoding and Spelling program within their school over the course of one academic year. The program consists of 110 lessons with one hour of instruction each, delivered in a small-group format approximately 3-4 times per week. The program content is focused on word identification and word attack strategies to facilitate reading fluency and reading comprehension. Additionally, the program emphasizes use of metacognitive strategies for children to monitor their own use of the decoding and spelling strategies. Teachers administering the intervention received training workshops, in-school coaching, and mentorship, continued in every year in which they were instructing the Empower Reading program (Lovett et al., 2008). For more details on the Empower Reading: Decoding and Spelling program, see Lovett, Lacerenza, Steinbach, and De Palma (2014).

As part of the Empower Reading program, children in the RI group also completed a number of informal assessments of reading skills to measure progress, as described below (see Appendix B). These measures were administered by teachers prior to beginning the program and in the final lessons of the 110-hour program ( $M = 105$  hours of intervention completed,  $SD = 8.66$  hours). All the tasks described below were scored based on the percent correct items.

***Letter sound identification.*** The participants were shown letters one at a time and were asked to identify the sound the letter makes. For letters with more than one associated sound (e.g. *a, g, y*), participants were prompted to provide an additional

response. The stimuli and scoring sheets for this measure are presented in Appendix B (Letter Sound Identification task).

***Sound combinations.*** The participants viewed 26 cards with letter combinations (e.g., *oo, ing, tion*) that are targeted in the Empower Reading program and were asked to identify the sound made by the letter combination. For letter combinations with more than one associated sound (e.g. *oo, ea, ow*), participants were prompted to provide an additional response. The stimuli and scoring sheets for this measure are presented in Appendix B (Sound Combinations task).

***Target word reading.*** Participants were asked to read each of the 40 mono- or bi-syllabic keywords (e.g. *cow, good, baby*) taught in the Empower Reading program's rhyming strategy materials. Children were given seven seconds to read each word. The stimuli and scoring sheets for this measure are presented in Appendix B (Keyword Test).

***Mono- and bi-syllabic word reading.*** The children read 60 mono- and bi-syllabic words not taught in the Empower Reading program (e.g. *fuzz, mode, queenly*). This task measured children's ability to generalize their knowledge of keywords and sounds taught in Empower Reading to new words. Children were given seven seconds to read each word. The stimuli and scoring sheets for this measure are presented in Appendix B (Transfer Word Test).

***Multisyllabic word reading.*** The participants were asked to read multisyllabic words (e.g. *needlessly, unemployment, distress*). This task measured children's ability to decode multi-syllabic words using the Empower Reading strategies. Participants completed 55 items and were allowed up to one minute to read each word. The stimuli and scoring sheets for this measure are presented in Appendix B (Challenge Word Test).



#### 4.2.4 MRI acquisition and processing

Pre-intervention MRI sessions took place between one and two weeks following the behavioural session. A second MRI session using the same scanning parameters and protocols took place between 8 and 10 months following the first MRI scan, after the RI group had completed the Empower Reading intervention. All imaging was performed at the University of Western Ontario's Centre for Functional and Metabolic Mapping on a Siemens Magnetom Prisma 3 Tesla scanner with a 32-channel head coil. Foam pads were used to minimize head movement. A 6-minute T2-weighted resting-state fMRI scan was first acquired using an echo planar imaging pulse sequence and oblique axial orientation (TR = 1000 ms; TE = 30ms; flip angle = 45; voxel size = 3 x 3 x 3 mm; FOV = 210 x 210 mm; 48 slices). During the resting-state scan, the participants were instructed to lie still and look at a fixation cross on a display. The DTI scans were next acquired in the transverse plane using an echo planar imaging sequence (64 slices with 2mm slice thickness; in-plane voxel size = 2.041 x 2.041 mm; matrix = 96 x 96 x 68; field of view = 200 x 200 mm; 64 diffusion directions with  $b = 1000 \text{ s/mm}^2$ ; TR = 3.0 s; TE = 50.6 ms; GRAPPA acceleration factor = 3). Finally, a high-resolution 3-D T1-weighted anatomical scan was acquired in the sagittal plane (MPRAGE; GRAPPA acceleration factor = 2; TR = 2.3 s; TE = 2.98 ms; field of view = 256 x 256 mm; voxel size = 1 mm<sup>3</sup>; 192 slices). Participants watched a movie during the DTI and anatomical scans. In total, scan time was approximately 15 minutes.

#### 4.2.5 Resting-state fMRI data processing and analysis

The resting-state fMRI data was pre-processed using the same steps described in Chapter 2, with the CONN-fMRI toolbox 17.a (Whitfield-Gabrieli & Nieto-Castanon,

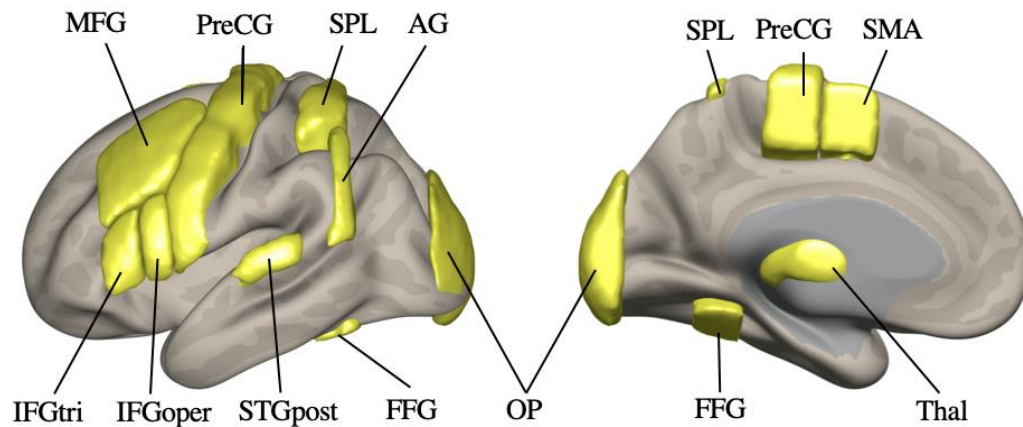
2012) for SPM12 in Matlab R2016b. These pre-processing steps included realignment, normalization to the MNI anatomical template, and functional smoothing of data using a Gaussian filter of 5mm. Next, structural data was segmented into gray matter, white matter, and cerebrospinal fluid. The aCompCor noise reduction method (Behzadi et al., 2007) was used to compute the BOLD signal from white matter and cerebrospinal fluid masks and these signals were included as nuisance parameters within the final analysis models. Subject motion was estimated based on three axes each of rotation and translation and the resulting time series was regressed out of the BOLD functional data. Functional outliers, defined as volumes that differed more than 95% from the mean BOLD signal amplitude, were removed from analysis. Band pass filtering was performed between 0.008 Hz to 0.09 Hz on the resulting BOLD time-series. The seed regions of interest (ROIs) for the resting-state connectivity analyses were selected, as in Chapter 2 of this thesis, based on a previous resting-state functional connectivity study of reading in children (Koyama et al., 2011) and a meta-analysis of brain areas associated with reading in children (Houdé et al., 2010). The seed ROIs, pictured in Figure 4.1, consisted of the middle frontal gyrus (MFG), inferior frontal gyrus pars opercularis (IFGoper), inferior frontal gyrus pars triangularis (IFGtri), precentral gyrus (PreCG), posterior superior temporal gyrus (STGpost), angular gyrus (AG), superior parietal lobule (SPL) including the intraparietal sulcus, supplementary motor area (SMA), posterior fusiform gyrus (FFG), occipital pole (OP), and thalamus (Thal), all within the left hemisphere. The seeds were all identified for analysis using the CONN atlas image volume which defines ROIs jointly across all subjects within MNI space (FSL Harvard-Oxford atlas and AAL atlas, developed based on: Desikan et al., 2006; Frazier et al., 2005; Goldstein et al., 2007;

Makris et al., 2006; Tzourio-Mazoyer et al., 2002). The coordinates of the centre of each seed ROI are detailed in Table 4.1.

Each subject's residual BOLD time course was extracted for each seed ROI. A weighted general linear model was used to measure correlations between time series of the seed region and all other voxels in the brain for each subject, to estimate functional connectivity from each seed region to the rest of the brain. The correlation coefficients were Fisher transformed into z-scores to increase normality for the second-level analyses. General linear modelling was used to examine RSFC from each seed region, with time (Time 1, Time 2) included as a within-subjects independent variable and group (RI, NI) as a between-subjects independent variable. False positive control was implemented at the cluster-level using a cluster size threshold, defined by false-discovery rate (FDR) corrected *p*-values.

**Table 4.1** MNI coordinates of centre of seed ROIs.

Seed ROI (left hemisphere only)	MNI Coordinate of Seed Centre		
	<i>x</i>	<i>y</i>	<i>z</i>
MFG: Middle frontal gyrus	-38	18	42
IFGoper: Inferior frontal gyrus, pars opercularis	-51	15	15
IFGtri: Inferior frontal gyrus, pars triangularis	-50	29	9
PreCG: Precentral gyrus	-34	-12	49
STGpost: Superior temporal gyrus, posterior	-62	-29	4
AG: Angular gyrus	-50	-56	30
SPL: Superior parietal lobule	-29	-49	57
SMA: Supplementary motor area	-5	-3	56
FFG: Fusiform gyrus, posterior	-34	-54	-16
OP: Occipital pole	-17	-97	7
Thal: Thalamus	-10	-19	6



**Figure 4.1** Seed regions of interest, shown in a lateral and medial view.

Subsequent analyses focused on how resting-state functional connectivity prior to intervention was related to change in reading skills throughout reading intervention. Behavioural change in reading skills was calculated by subtracting pre-intervention scores from post-intervention scores on each of the progress monitoring measures, including the letter sound identification, sound combination, target word reading, mono- and bi-syllabic word reading, and multisyllabic word reading tasks. General linear models were then used to examine whether Time 1 resting-state functional connectivity between seed ROIs and other voxels was uniquely associated with behavioural change on any intervention progress monitoring measures, independent of age. False positive control again consisted of a cluster size threshold, defined by false-discovery rate (FDR) corrected  $p$ -values.

#### 4.2.6 DTI data processing and analysis

DTI images were processed using the same steps described in Chapter 3, with the automatic fiber quantification (AFQ) version 1.2 (Yeatman, Dougherty, Myall, Wandell,

& Feldman, 2012) and SPM8 toolboxes in MATLAB. The preprocessing steps consisted of motion and eddy current correction and alignment of the DTI data to the anatomical image. A deterministic streamlined tracking algorithm (Yeatman et al., 2012) was implemented for white matter tractography, beginning from each white matter voxel with a fractional anisotropy (FA) value greater than 0.3. This algorithm traced streamlines from the seed voxels, continuing along the principal diffusion axes until the estimated FA was less than 0.2. Tracking was also stopped if the angle between two segments was greater than 30 degrees, in order to avoid effects of crossing fibers. Tracts were segmented in MNI standard space and transformed into single-subject space using waypoint ROI masks (Wakana et al., 2007). Tracts of interest included the arcuate fasciculus, inferior longitudinal fasciculus (ILF), inferior fronto-occipital fasciculus (IFOF), and uncinate fasciculus in both hemispheres, based on previous findings implicating these tracts in reading and findings in Chapter 3 of this thesis. These tracts of interest were identified using region of interest (ROI) inclusion, exclusion and waypoint masks as detailed in Wakana et al. (2007). As expected, based on previous research suggesting the right arcuate fasciculus can sometimes not be identified by deterministic tracking algorithms (Catani et al., 2007; Yeatman et al., 2011), the right arcuate fasciculus was only identified at both time points in 16 out of the 24 subjects. This included one subject in the RI group and four subjects in the NI group in which the right arcuate fasciculus could not be identified at both time points, one subject in the RI group in which it was identified in the Time 1 scan data but not at Time 2, and two subjects in the NI group in which it was not identified in the Time 2 scan data but not at Time 1. All other tracts of interest were identified in all subjects at both time points.

As described in Chapter 2, each tract was cleaned by removing fibers that deviated in length by more than four standard deviations above or below the mean fiber length or that deviated spatially by more than five standard deviations from the averaged centroid of the fiber tract (Yeatman et al., 2012). Each fiber tract was divided into 100 nodes spaced equally along the length of the tract and FA was calculated at each node of each tract.

Changes in DTI connectivity were examined using mixed ANOVAs with group (RI, NI) as a between-subjects factor and time (Time 1, Time 2) as a within-subjects factor. These were conducted in each tract of interest at 100 nodes along the tract. To examine how structural connectivity prior to intervention was related to the amount of behavioural change in reading skills during the intervention, partial correlations were performed between the Time 1 scan FA values and the behavioural change scores for each progress monitoring measure. These were performed at each of 100 nodes on every tract, with age added as a covariate.

Due to the small sample size of the present study and consequent lack of statistical power, the permutation-based correction for family-wise error used in Chapter 3 of this thesis was likely to be overly conservative for implementation in the DTI analyses. Instead, a smaller cluster threshold of 10 was used, such that only clusters of 10 or more consecutive (directly adjacent) nodes reaching an individual significance level of  $p < .05$  were considered as significant findings.

## 4.3 Results

### 4.3.1 Behavioural results

Descriptive statistics for the standardized measures administered at the beginning of the study are shown in Table 4.2 for the NI group and RI group. Independent samples t-tests comparing the NI group and RI group showed that the two groups did not differ significantly in age ( $t(22) = 1.13, p = .27$ ) and in nonverbal intelligence ( $t(22) = 1.85, p = .07$ ). As expected, the RI group scored significantly lower than the NI group on all pre-intervention measures of reading, including sight word reading efficiency ( $t(22) = 5.85, p < .01$ ), phonemic decoding efficiency ( $t(22) = 4.34, p < .01$ ), letter word identification ( $t(22) = 3.82, p < .01$ ), reading fluency ( $t(22) = 4.55, p < .01$ ), and reading comprehension ( $t(22) = 3.65, p < .01$ ).

Table 4.3 presents the descriptive statistics for the progress monitoring measures administered in the RI group at the beginning and end of the reading intervention program. As expected, paired-samples t-tests showed that scores on all measures were significantly higher at the final assessment compared to the initial assessment, including the letter sound identification task ( $t(12) = -2.28, p < .05$ ), sound combinations task ( $t(12) = -10.49, p < .01$ ), target word reading task ( $t(12) = -3.86, p < .01$ ), mono- and bi-syllabic word reading task ( $t(12) = -5.74, p < .01$ ), and multisyllabic word reading task ( $t(12) = -7.89, p < .01$ ). Figure 4.2 shows a boxplot of percent change on each measure, calculated by subtracting each participant's percent correct score at the initial assessment from the percent correct at the final assessment.

**Table 4.2** Demographic characteristics of the sample.

	NI Group (n=11) Mean (SD)	RI Group (n=13) Mean (SD)
Age (years)	10.43 (0.81)	10.09 (0.69)
<i>Reading Measures</i>		
TOWRE-2 Sight Word Efficiency	91.36 (10.30)	67.46 (9.69)*
TOWRE-2 Phonemic Decoding Efficiency	87.27 (9.49)	71.08 (8.76)*
WJ-III Letter Word Identification	98.64 (12.83)	79.15 (12.11)*
WJ-III Reading Fluency	96.09 (9.18)	76.77 (11.26)*
WJ-III Passage Comprehension	92.45 (8.56)	75.00 (13.73)*
<i>Nonverbal Intelligence</i>		
WASI-II Performance IQ	109.64 (20.42)	97.23 (11.92)

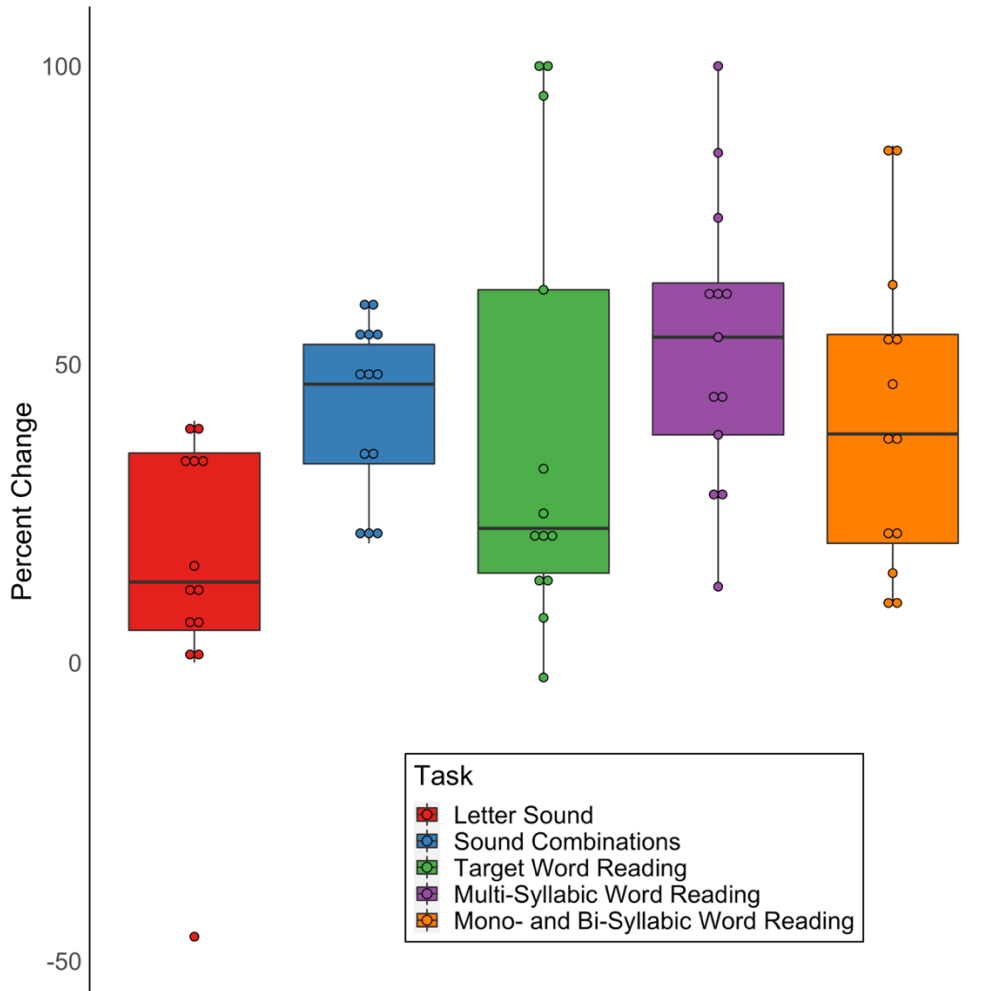
Note: \* denotes a significant difference between groups ( $p < .01$ ).

**Table 4.3** Intervention progress monitoring data collected in RI group.

Measure	Initial (0 lessons) Mean (SD)	Final (90-110 lessons) Mean (SD)
Letter Sound Identification (% correct)	77.34 (16.68)	92.10 (25.29) *
Sound Combinations (% correct)	41.03 (12.87)	84.10 (10.55) **
Target Word Reading (% correct)	60.00 (37.37)	99.23 (1.57) **
Mono- and Bi-Syllabic Word Reading (% correct)	43.33 (28.64)	85.13 (10.98) **
Multisyllabic Words (% correct)	33.56 (29.09)	87.13 (11.31) **

Note: \* denotes a significant difference between initial and final assessments at  $p < .05$ ,  
\*\* denotes a significant difference at  $p < .01$ .





**Figure 4.2** Boxplot showing percent change from pre- to post-intervention for each progress monitoring task. Dots show individual data points for each task.

Because movement during MRI scanning is known to create artifacts in brain imaging data and can drive false positive group differences in connectivity (Power, Barnes, Snyder, Schlaggar, & Petersen, 2012), two-sample t-tests were used to compare motion parameters in each of the resting-state and DTI scans between the RI group and the NI group. The RI and NI groups did not differ significantly in terms of their maximum motion,  $t(22) = -1.62, p = .12$ , and mean motion,  $t(22) = -1.79, p = .09$ , in the resting-state MRI scans at both time points. Similarly, maximum motion (Time 1:  $t(22) =$

-0.99,  $p = .33$ ; Time 2:  $t(22) = 0.08$ ,  $p = .94$ ) and mean motion (Time 1:  $t(22) = -1.03$ ,  $p = .32$ ; Time 2:  $t(22) = -0.18$ ,  $p = .85$ ) did not differ between groups in the DTI scan at both time points. This suggests that motion artifacts in the resting-state and DTI data are unlikely to contribute to between-group differences in functional and structural connectivity. To account for the possibility that motion effects were not completely captured in these analyses, functional connectivity analyses also regressed out subject motion and DTI preprocessing steps included motion correction.

#### 4.3.2 Changes in resting-state functional connectivity over time

In order to examine changes in RSFC in the RI group, general linear models were conducted at each seed ROI with time as a within-subjects factor and group as a between-subjects factor. Significant interactions of group and time were observed for RSFC from the left PreCG and the left SMA seed ROIs. Specifically, significant interactions were observed for RSFC from the left PreCG seed to two clusters of voxels, both of which were located in the left frontal pole (Cluster A:  $t(22) = 6.50$ ,  $p_{corr} < .001$ ; Cluster B:  $t(22) = 6.03$ ,  $p_{corr} < .001$ ; Figure 4.3A; summarized in Table 4.4). For both of these clusters, the RI group exhibited significantly more negative RSFC compared to the NI group at Time 1 (Cluster A:  $t(22) = -2.91$ ,  $p < .01$ ; Cluster B:  $t(12) = -2.90$ ,  $p < .01$ ), however at Time 2 this pattern was reversed and the NI group demonstrated significantly more negative RSFC than the RI group (Cluster A;  $t(22) = 3.88$ ,  $p < .01$ ; Cluster B:  $t(22) = 6.44$ ,  $p < .001$ ). Within-group comparisons showed that the RSFC between these regions became significantly less negative in the RI group from Time 1 to Time 2 (Cluster A:  $t(12) = -3.36$ ,  $p < .01$ ; Cluster B:  $t(12) = -2.38$ ,  $p < .05$ ) but significantly more negative in the NI group (Cluster A:  $t(10) = 5.66$ ,  $p < .001$ ; Cluster B:  $t(10) = 5.46$ ,  $p <$

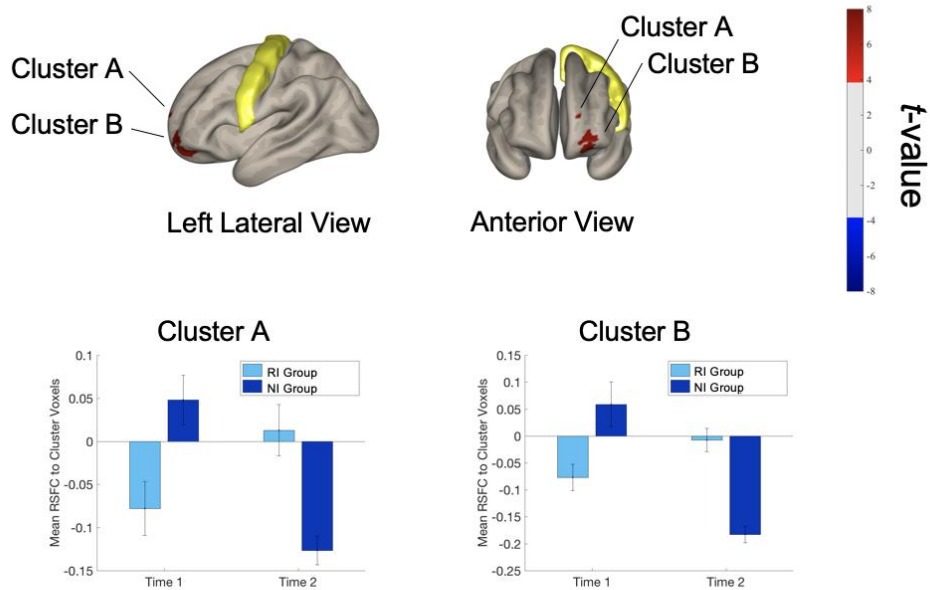
.001). These results suggest that the PreCG and frontal lobe regions became significantly less anti-correlated in the RI group, whereas a greater degree of anti-correlation in functional activity was observed over time in the NI group.

The left SMA seed also showed significant interactions of group and time for RSFC to a voxel cluster in the left frontal pole ( $t(22) = 5.72, p_{corr} < .001$ ; Figure 4.3B; summarized in Table 4.4). Further between-group comparisons showed that Time 1 RSFC from the SMA seed to the left frontal pole was significantly more negative in the RI group relative to the NI group ( $t(22) = -3.69, p < .01$ ), while at Time 1 RSFC was significantly more negative in the NI group compared to the RI group ( $t(22) = 4.21, p < .001$ ). RSFC to this cluster did not change significantly from Time 1 to Time 2 in the RI group ( $t(12) = -1.88, p = .08$ ), whereas it became significantly more negative in the NI group ( $t(10) = 5.94, p < .001$ ). These results suggest that the RI group exhibited anti-correlations between the SMA and left frontal regions prior to intervention and did not change significantly over time, whereas the NI group exhibited little functional connection between these regions initially with a shift towards anti-correlation over time.

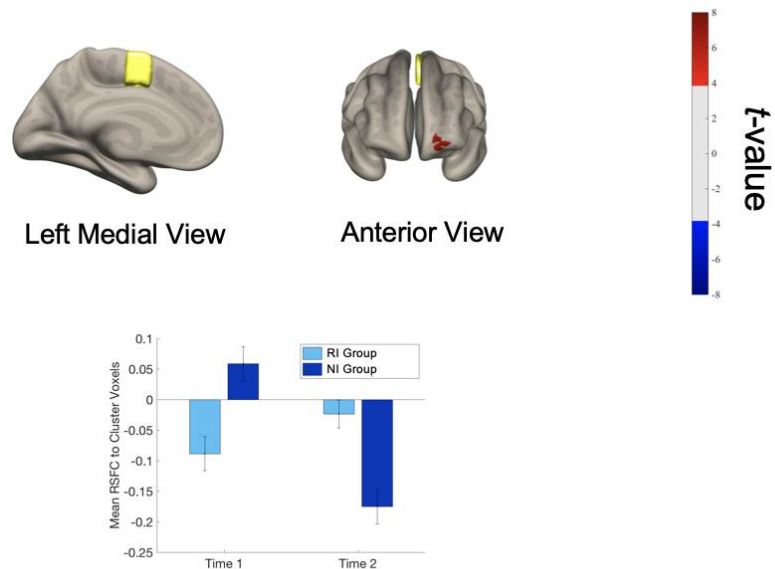
**Table 4.4** Summary of significant interaction effects in resting-state functional connectivity data.

Seed Region	Between groups at Time 1	Between groups at Time 2	Change over time within RI Group	Change over time within NI Group
Left PreCG	Greater anti-correlation in RI Group	Greater anti-correlation in NI Group	Reduced anti-correlation	Increased anti-correlation
Left SMA	Greater anti-correlation in RI Group	Greater anti-correlation in NI Group	No significant change	Increased anti-correlation

### A. Left PreCG Seed

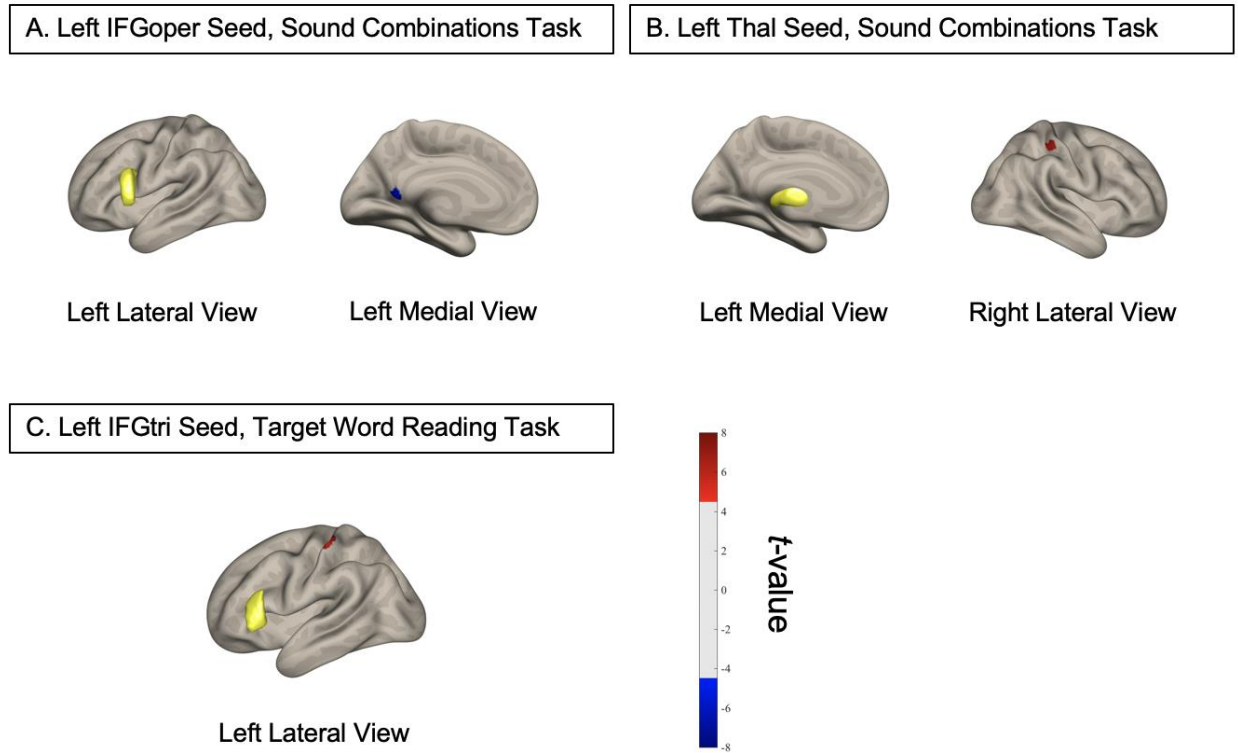


### B. Left SMA Seed



**Figure 4.3** Seed-to-voxel clusters showing significant group by time interaction by seed region. Seeds are shown in yellow and cluster colour represents significant  $t$ -values. Bar graphs show RSFC for each group and time point, error bars represent standard error of the mean.

To examine whether change in RSFC was related to change in behavioural reading ability, general linear models were conducted on RSFC in the RI group only, with time as a within-subjects factor and behavioural change scores for each reading task as a between-subjects factor. Behavioural change scores were calculated by subtracting each individual's initial progress monitoring measure scores from their final scores for each of the progress monitoring tasks. Analyses were then conducted at each seed ROI for each progress monitoring task. Change on the sound combinations task was negatively related to change in RSFC from the IFGoper seed to a cluster on the precuneus and left lingual gyrus ( $t(12) = -7.95, p \text{ corr} < .001$ ; Figure 4.4A) and positively related to change from the thalamus seed to a cluster on the right postcentral gyrus ( $t(12) = 6.05, p \text{ corr} < .001$ ; Figure 4.4B). Change on the target word reading task was positively associated with change in RSFC from the left IFGtri seed to a cluster of voxels within the left postcentral gyrus ( $t(12) = 7.64, p \text{ corr} < .001$ ; Figure 4.4C). Change scores for the letter sound identification, mono- and bi-syllabic word reading, and multi-syllabic word reading tasks were not significantly associated with change in RSFC from any seed ROIs.



**Figure 4.4** Seed-to-voxel clusters showing significant association with change in behavioural scores by seed region and task. Seeds are shown in yellow and cluster colour represents significant  $t$ -values.

### 4.3.3 Changes in DTI connectivity over time

Changes in DTI connectivity over time were examined using mixed ANOVAs, which were conducted in each tract of interest with group as a between-subjects factor and time as a within-subjects factor. The purpose of these analyses was to examine changes in FA over time in the whole sample, and to examine whether any changes in FA were specific to the group receiving reading intervention, relative to the group receiving only classroom reading instruction. Analyses in the right arcuate fasciculus included only the 16 participants in which the right arcuate was identified by the deterministic tracking

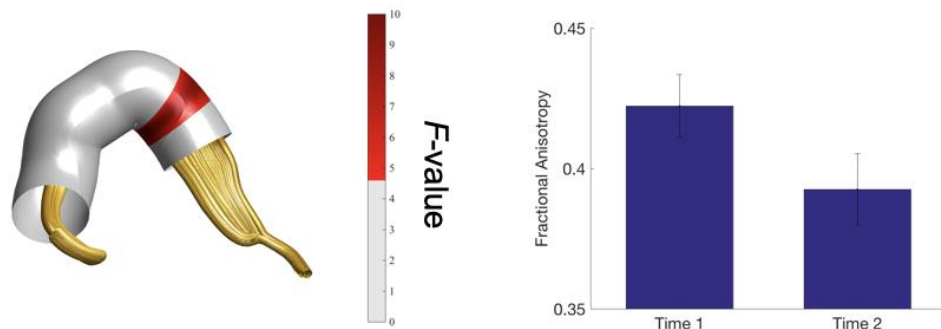
algorithm in the DTI data from both time points. For the purposes of visualization and post-hoc analyses of significant interactions, the mean FA of all nodes in each significant cluster was calculated. Post-hoc t-tests were then performed using the mean FA in each cluster to further examine any interactions and main effects. For the purposes of correcting for Type 1 error, only clusters of 10 or more consecutive nodes reaching an individual significance level of  $p < .05$  were considered to as significant findings.

In the right arcuate fasciculus, a main effect of time was observed in more frontal nodes of this tract (13 nodes, Figure 4.5A), demonstrating significantly reduced FA at Time 2 compared to Time 1. No significant group by time interaction was present in the right arcuate fasciculus. Similarly, in the right uncinate fasciculus (Figure 4.5B), a main effect of time was also observed in a cluster of 15 nodes located near the middle of the tract, but no significant interaction of group and time was found. The main effect of time in the right uncinate fasciculus was characterized by significantly greater FA at Time 2 compared to Time 1. In the left arcuate fasciculus, left uncinate fasciculus, bilateral ILF, and bilateral IFOF, no significant main effects or interactions were observed in 10 or more consecutive nodes.

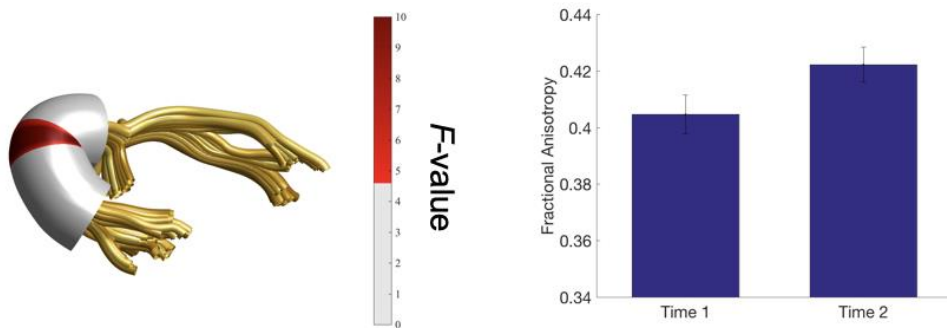
To examine whether change in FA was related to change in behavioural reading ability, Pearson's correlations were conducted between the behavioural change scores for each progress monitoring measure and change in FA. Change in FA was calculated by subtracting Time 1 FA values from Time 2 FA values for each subject, in each of the 100 nodes within each tract of interest. A cluster threshold of 10 or more consecutive nodes showing individual significant effects ( $p < .05$ ) was again applied to correct these analyses for multiple comparisons. Change in multi-syllabic word reading was positively

correlated with change in FA values in 13 consecutive nodes in the right arcuate fasciculus (average  $r = 0.70$ ; Figure 4.6). No correlations passed the cluster correlation in any other tracts and for any other behavioural measures.

### A. Right Arcuate Fasciculus

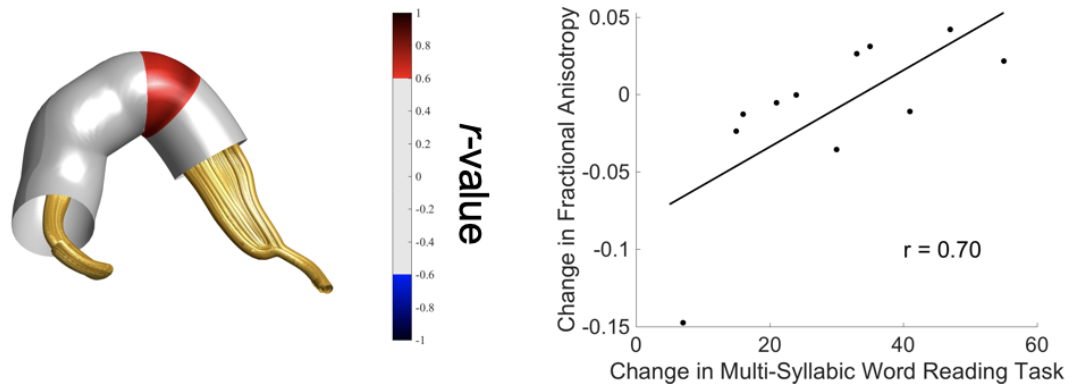


### B. Right Uncinate Fasciculus



**Figure 4.5** Significant main effects of time in the right arcuate fasciculus (A) and right uncinat fasciculus (B). The colourbar shows significant  $F$ -values. Bar plots show FA values averaged across significant nodes, with error bars representing standard error of the mean.





**Figure 4.6** Correlation between change in FA and change in multi-syllabic reading scores within the right arcuate fasciculus. The colourbar shows significant  $r$ -values. The scatterplot shows the correlation between change in reading skills and change in FA averaged across all nodes within the significant cluster.

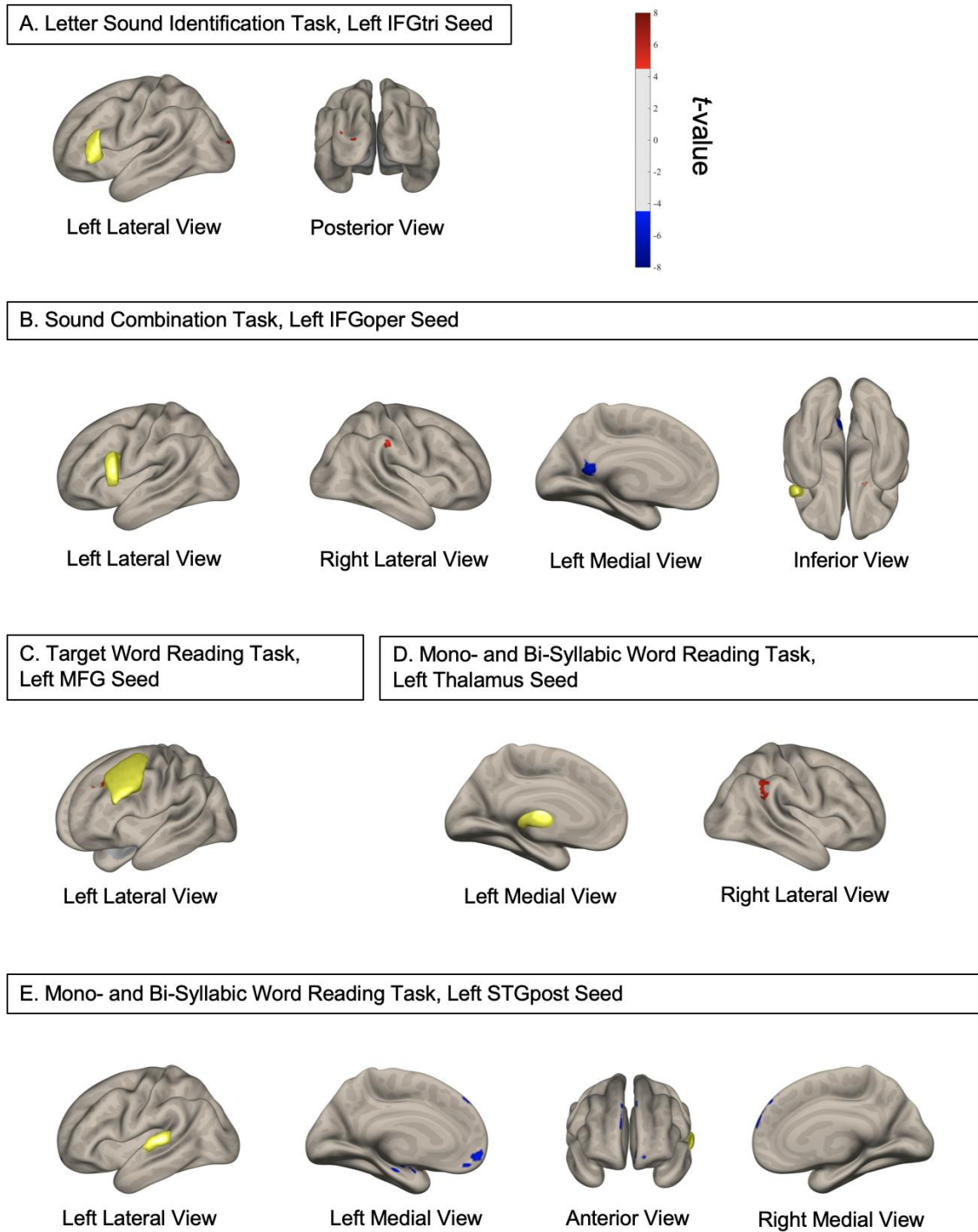
#### 4.3.4 Resting-state functional connectivity predictors of response following

##### intervention

Subsequent analyses focused on how resting-state functional connectivity prior to intervention may predict change in reading skills throughout reading intervention. Here, multiple regression analyses were used to examine whether Time 1 resting-state functional connectivity between seed ROIs and other voxels were uniquely associated with behavioural change on any intervention progress monitoring measures, independent of age.

Behavioural change on the letter sound identification task was positively associated with Time 1 RSFC from the left IFGtri seed to a cluster of voxels located in the left occipital pole ( $p_{corr} < .05$ ; Figure 4.7A). For the sound combination task, three clusters of significant associations with behavioural change were observed for Time 1

RSFC from the left IFGoper seed ( $p \text{ corr} < .05$ ; Figure 4.7B). Change in sound combination scores was positively associated with RSFC from the IFGoper seed to voxels in the right putamen as well as voxels in the right anterior supramarginal gyrus and right postcentral gyrus. In addition, negative associations were found between change in sound combination scores and RSFC from the IFGoper seed to a cluster in the precuneus cortex and posterior cingulate gyrus. For the target word reading task, change in behavioural scores was positively associated with Time 1 RSFC from the left MFG seed to an adjacent cluster of voxels located in the left frontal pole and left superior frontal gyrus ( $p \text{ corr} < .05$ ; Figure 4.7C). Change in scores on the mono- and bi-syllabic word reading task was negatively associated with Time 1 RSFC from the left STGpost seed to three clusters of voxels: a cluster located in the right frontal pole and superior frontal gyrus, a cluster in the left frontal pole, paracingulate gyrus, and frontal medial cortex, and a cluster in the left hippocampus and amygdala ( $p \text{ corr} < .05$ ; Figure 4.7E). Change on this task was also negatively associated with Time 1 RSFC from the left thalamus seed to voxels in the right angular gyrus and posterior supramarginal gyrus ( $p \text{ corr} < .05$ ; Figure 4.7D). No significant relationships were observed between change in scores on the multisyllabic word reading task and RSFC from any of the seed ROIs.



**Figure 4.7** Seed-to-voxel clusters showing significant association between Time 1 RSFC and change in reading skills, by task. Seeds are shown in yellow and cluster colour represents significant *t*-values.

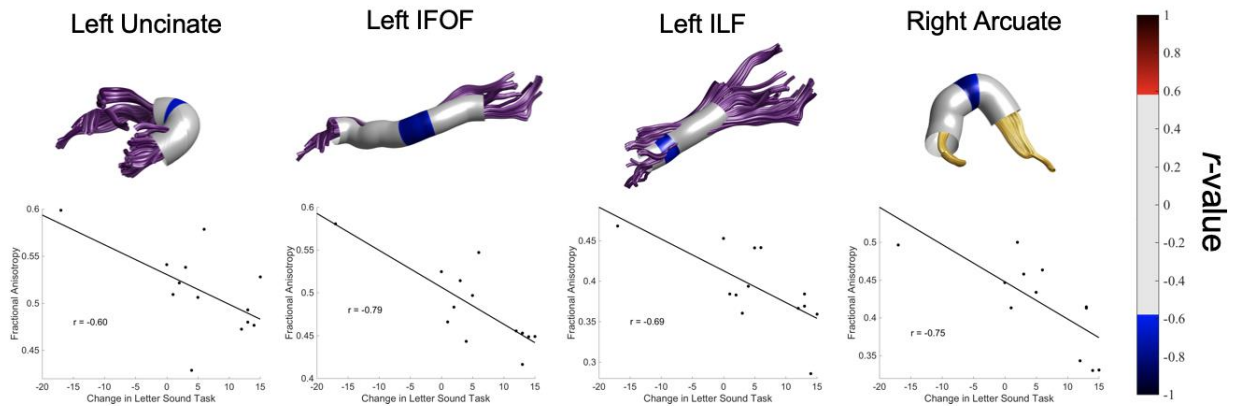
#### 4.3.5 DTI predictors of behavioural response following intervention

To examine how structural connectivity prior to intervention was related to the amount of behavioural change in reading skills during the intervention, partial correlations were performed between the Time 1 scan FA values and the behavioural change scores for each progress monitoring measure. A cluster threshold of 10 or more consecutive nodes showing individual significant effects ( $p < .05$ ) was again used to correct these analyses for multiple comparisons. Analyses in the right arcuate fasciculus included only the 12 participants from the RI group in which the right arcuate was identified by the deterministic tracking algorithm in the Time 1 DTI data.

Behavioural changes in scores on the letter sound identification (Figure 4.8A) were negatively correlated with FA in the left uncinate fasciculus (13 nodes, average  $r = -0.60$ ), left ILF (18 nodes, average  $r = -0.69$ ), and left IFOF (18 nodes, average  $r = -0.79$ ). In the right hemisphere tracts, changes in letter sound identification scores were also negatively correlated with FA only in the right arcuate fasciculus (14 nodes, average  $r = -0.75$ ). No correlations between FA and change in letter sound identification scores passed the cluster correction in the left arcuate fasciculus, right uncinate fasciculus, right ILF, and right IFOF. For the target word reading task (Figure 4.8B), changes in behavioural scores were positively correlated with FA in the left uncinate fasciculus (14 nodes, average  $r = 0.78$ ). Significant correlations passing the cluster correlation were not observed in the right uncinate fasciculus or in the bilateral arcuate fasciculus, ILF, and IFOF. Finally, changes in multisyllabic word reading (Figure 4.8C) were positively correlated with FA in the left uncinate fasciculus (14 nodes, average  $r = 0.82$ ) and right uncinate fasciculus (13 nodes, average  $r = 0.64$ ). Negative correlations with FA were

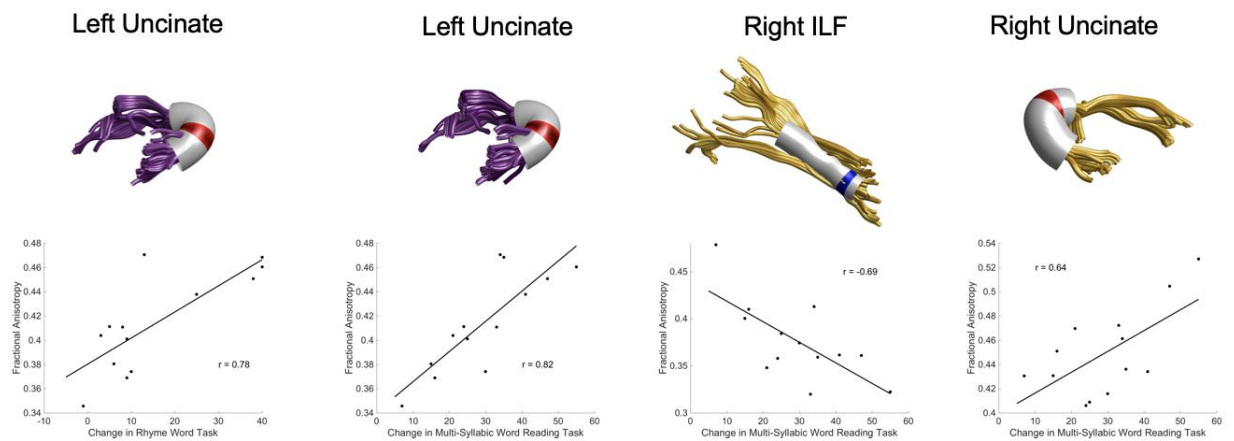
observed in the right ILF (10 nodes, average  $r = -0.69$ ). No significant effects passing the cluster correlation were observed in the left ILF, bilateral arcuate fasciculus, or bilateral IFOF when examining correlations between FA and change in multisyllabic word reading scores. When examining correlations between FA and change in sound combination scores and between FA and change in mono- and bi-syllabic word reading scores, no clusters of correlations passed the threshold for multiple comparisons for any of the tracts of interest.

### A. Letter Sound Identification



### B. Target Word Reading

### C. Multi-Syllabic Word Reading



**Figure 4.8** Correlations between FA and change in reading skills, by task. The colourbar shows significant  $r$ -values for all correlations. Scatterplots show correlation between change in reading skills and average FA across nodes showing significant correlation.

## 4.4 Discussion

The present study examined brain connectivity correlates of reading ability in children with RD before and after completing the Empower Reading program. The results of the present study suggest that some measurable changes in RSFC accompanied improvements in behavioural reading ability following the 110-hour, phonology-based

reading intervention program. However, the results failed to replicate previous findings (Huber, Donnelly, Rokem, & Yeatman, 2018b; Keller & Just, 2009) demonstrating changes in white matter microstructure linked to reading intervention in RD. Although significant improvements in reading ability were observed on each of the progress monitoring measures in the reading intervention group, there was a large degree of individual variability in the amount of improvement on each task. Subsequent analyses examining pre-intervention connectivity and response following intervention suggested that distinct characteristics of white matter connectivity and RSFC prior to intervention were associated with these individual differences in behavioural growth in reading ability.

#### **4.4.1 Resting-state functional connectivity and reading intervention**

The primary findings with respect to changes in RSFC from pre- to post-intervention showed that the RI group exhibited an increase in RSFC (reduced anti-correlation) between the left precentral gyrus and left frontal lobe regions, while the NI group exhibited a decrease in RSFC (increased anti-correlation). In addition, RSFC between the left SMA and left frontal lobe regions decreased in the NI group (increased anti-correlation) but did not change in the RI group. Anti-correlations are thought to represent opposing functionality or inhibitory relationships between regions, resulting in negatively correlated activity during the fMRI scan (Fox et al., 2005; Fransson, 2005; Greicius, Krasnow, Reiss, & Menon, 2003). Previously, anti-correlation between areas of the reading network and frontal regions has been linked to greater automatization of reading abilities (Koyama et al., 2011, 2010). In line with this, the present findings suggest greater functional segregation of left frontal lobe regions from the left precentral

gyrus and left supplementary motor area increased over time in school-aged children with average reading abilities. Although gains in behavioural reading ability over time were not measured in the NI group, it is possible that this change in RSFC in the NI group was related to increased automatization of reading ability over the course of the nine months between MRI scans. Interestingly, the present findings suggest that the group with RD exhibited reduced functional segregation post-intervention between the left frontal lobe and left precentral gyrus, which is suggestive of a compensatory shift in connectivity following reading intervention rather than a process of normalization towards the patterns of connectivity observed in the NI group. RD has often been linked to increased compensatory engagement of frontal regions including the inferior frontal gyrus and other areas of the prefrontal cortex (Brunswick, McCrory, Price, Frith, & Frith, 1999; Richards et al., 1999; Rumsey et al., 1997; Salmelin, Service, Kiesilä, Uutela, & Salonen, 1996; Shaywitz et al., 1998), however this has been associated with persistent poor reading (Shaywitz et al., 2003) rather than with partially or fully remediated RD. One possible explanation is that over the course of the intervention, children in the reading intervention group learned compensatory reading strategies that required increased reliance on frontal lobe regions. For example, the Empower Reading program includes a significant focus on training children to use metacognitive strategies to monitor their success using decoding and spelling strategies. Frontal lobe regions, particularly the prefrontal cortex, have been consistently linked to metacognitive processes (Baird, Smallwood, Gorgolewski, & Margulies, 2013; Fleck, Daselaar, Dobbins, & Cabeza, 2006; Fleming, Huijgen, & Dolan, 2012; Fleming, Weil, Nagy, Dolan, & Rees, 2010; Hilgenstock, Weiss, & Witte, 2014; McCurdy et al., 2013; Yokoyama et al., 2010). In



line with this, the present results suggest that post-intervention, children with RD relied increasingly on connectivity between reading network regions and the frontal lobe to support use of these compensatory metacognitive strategies when reading.

Given the observed variability in response following intervention, our subsequent RSFC analyses focused on how individual differences in this regard were related to changes in RSFC, and whether these differences in response could be predicted by characteristics of RSFC prior to the intervention. Interestingly, the findings of both these analyses consistently implicated the left IFG, both in terms of change in RSFC post-intervention and in predicting response following intervention. Specifically, improved ability to identify sound combinations was associated with reduced RSFC over time between the left IFG and precuneus, while improved performance on the target word reading task was related to increased RSFC over time from the left IFG to the left postcentral gyrus. With respect to predictors of response following intervention, greater pre-intervention RSFC from the left IFG to left occipital regions, right putamen, right supramarginal gyrus, and right postcentral gyrus, and lower pre-intervention RSFC from the left IFG to the precuneus and posterior cingulate were associated with greater response following intervention on tasks involving identification of grapheme-phoneme correspondences (letter sound identification and sound combinations tasks). These findings are novel given that no previous studies using a resting-state approach have related characteristics of RSFC to response to a phonology-based reading intervention. They contrast with previous findings of greater activation of the *right* IFG in children with RD who subsequently showed greater improvement in reading (Hoeft et al., 2011), although this work examined local activation rather than functional connectivity.

However, previous neurobiological models of reading have highlighted the left IFG as crucial for binding orthographic and phonological information and for articulatory processes (Sandak et al., 2004).

In addition, the implication of anti-correlations between the left IFG to default mode network regions including the precuneus and cingulate gyrus is consistent with previous work suggesting that automatization of reading is related to functional segregation of reading and default mode networks (Koyama et al., 2013, 2011, 2010). In a comparison of groups of children with RD that had not been remediated, had been partially remediated, and had been fully remediated, Koyama et al. (2013) found greater functional segregation between reading network and default mode network regions, possibly associated with greater automatization of reading following successful reading intervention. In line with this, the present results suggest that children with RD who exhibit greater pre-intervention functional segregation of the left IFG with default mode network regions, along with greater pre-intervention functional coordination with left occipital, right striatal, and right parietal regions, go on to show greater subsequent improvement in identifying grapheme-phoneme correspondences. In addition, children with a greater response following intervention also showed increased functional segregation of the default mode network when comparing pre- and post-intervention RSFC. Because no Time 2 reading data was collected in the NI group in the present study, it cannot be determined whether this represents a process of compensation or normalization in the RI group. However, previous evidence showing greater functional segregation of the reading and default mode network in proficient readers (Koyama et al., 2011, 2010) suggests the findings of the present study are more consistent with a process

of normalization of functional connectivity between the reading and default mode networks in the group receiving reading intervention.

The left thalamus seed was also implicated in analyses examining changes in RSFC over time and predicting subsequent response following intervention. Specifically, improved ability to identify sound combinations was associated with increased RSFC over time between the left thalamus and right postcentral gyrus. Increased response following intervention with respect to mono- and bi-syllabic reading was predicted by greater pre-intervention RSFC from the left thalamus to the right angular and supramarginal gyri. Together, these results suggest that gains in reading skill were associated with greater pre-intervention functional coordination of the left thalamus and right parietal areas and a further increase in functional coordination among these areas following intervention. Previous research linking activation of the thalamus to reading skill has been mixed, with some studies linking increased functional activation to RD (Díaz, Hintz, Kiebel, & Von Kriegstein, 2012; Maisog et al., 2008) and others finding greater thalamic activation in stronger readers (Pugh et al., 2013). With respect to functional connectivity, learning to read has been linked to increased RSFC between the bilateral thalamus and right occipital cortex in previously illiterate adults (Skeide et al., 2017). The results of the present study extend these findings to children with RD to suggest that gains in reading are associated with increased functional connectivity of the left thalamus and right parietal regions, both in terms of pre-intervention RSFC and changes in RSFC over time. This relationship may be specific to children or to global measures of functional connectivity, as a recent study of local connectivity showed that reduced intrinsic functional connectivity of the thalamus with neighbouring voxels was

associated with better performance on measures of reading, arithmetic, and intelligence in adults (Koyama, Molfese, Milham, Mencl, & Pugh, 2020).

#### **4.4.2 DTI connectivity and reading intervention**

With respect to the DTI analyses, although changes in white matter microstructure were observed over time in the right arcuate and uncinate fasciculi in the full sample, the present results did not find any changes in white matter microstructure that were specifically associated with the reading intervention group. This was surprising, given previous findings of distributed changes in white matter associated with reading intervention in RD (Huber et al., 2018b; Keller & Just, 2009). A likely explanation is that the small sample size of the present study did not offer sufficient statistical power to reveal significant longitudinal effects. A relatively conservative correction for multiple comparisons was implemented in the analyses to reduce the risk of Type I error, likely also contributing to the null results.

Interestingly, examining the relationship between change in FA and change in behavioural reading ability in the reading intervention group revealed that increased FA in the right arcuate from pre- to post-intervention was strongly related to improved multi-syllabic word reading ability. This strong correlation between change in FA and gains in reading abilities suggests a role for the right arcuate fasciculus in supporting improved word reading from pre- to post-intervention. Much of previous research has linked integrity of the *left* arcuate fasciculus to phonological processes (Bernal & Ardila, 2009; Dick & Tremblay, 2012; Marchina et al., 2011; Saygin et al., 2013; Shinoura et al., 2013; Vandermosten et al., 2012; Yeatman et al., 2011), which readers are likely to rely on when reading multi-syllabic, low familiarity words as was required by the multi-syllabic

word reading measure. Our findings suggest a possible role for contralateral white matter integrity in developing word reading skills in struggling readers. This is also consistent with the findings of Chapter 3 of this thesis, which showed that FA of the right arcuate fasciculus was positively correlated with decoding efficiency and sight word reading efficiency.

Analyses examining whether response following intervention could be predicted by pre-intervention FA showed that improvement on the letter sound identification task was associated with reduced pre-intervention FA within the left uncinate fasciculus, left ILF, left IFOF, and right arcuate fasciculus. Improvement on the target word reading and multi-syllabic word reading tasks was related to greater pre-intervention FA in an overlapping region of the left uncinate fasciculus, with multi-syllabic word reading improvement also linked to greater pre-intervention FA in the right uncinate fasciculus and lower pre-intervention FA in the right ILF. Previous research has linked ventral tracts including the uncinate fasciculus, ILF, and IFOF with processing lexical and semantic stimuli (Epelbaum et al., 2008; Grossman et al., 2004; Lu et al., 2002; Mandonnet et al., 2007; Marchina et al., 2011; Wilson et al., 2011). The present findings build on this to suggest that strong pre-intervention integrity of the uncinate fasciculus is important for subsequent word reading success, however reduced pre-intervention integrity within ventral tracts is associated with greater subsequent letter-word identification success. The result linking right arcuate integrity to subsequent letter-sound knowledge improvement contrasts with findings of Hoefft et al. (2011), which linked stronger integrity of the right superior longitudinal fasciculus (including the right arcuate fasciculus) to greater single word reading improvement over the subsequent 2.5 years.

Previous DTI work including four timepoints of behavioural and neuroimaging data over eight weeks of reading intervention has demonstrated that changes in white matter are rapid, occur in concert with changes in reading ability, and vary in terms of the time course of change observed across tracts (Huber et al., 2018b). Huber et al. (2018b) hypothesize that environmental differences between groups at the time of data collection could potentially influence FA measurements and impact brain-behaviour effects. A similar longitudinal design has not been implemented in functional connectivity research, however given the link between brain structure and function it is likely that changes in functional connectivity also occur rapidly and jointly with behavioural changes. The present study included two MRI sessions approximately nine months apart, and therefore cannot fully capture the time course of changes in structural and functional connectivity accompanying gains in reading skill. This is of particular interest given the design of the Empower program, in which different types of reading and metacognitive strategies are introduced at various points throughout the 110-hour program. A study with more frequently collected behavioural and neuroimaging data could shed light on the changes in neural connectivity that occur in concert with the introduction of particular types of strategies and resulting growth in reading skill.

As mentioned, a limitation of the present study is the relatively small sample size of both participant groups, and as a result the findings of the present study should be interpreted with caution. This was a particular concern with respect to the DTI analyses examining the right arcuate fasciculus, as the deterministic tracking algorithm only identified this tract in a subset of participants. Additionally, the present study compared a group of children with RD receiving reading intervention to a group of children with a

wide range of reading abilities not receiving intervention. This work was not intended to be a randomized control trial, due to the lack of power and the ethical limitations on withholding intervention from children who would otherwise be eligible. The non-intervention group in the present study was included for the purpose of capturing changes in connectivity linked to maturation and regular classroom reading instruction and comparing these effects with the changes observed in the reading intervention group. However, the pre-intervention discrepancy in reading ability between the two groups could have impacted the effects observed in the present study. Future research including a reading-matched control group receiving no intervention or receiving an alternate reading intervention could more specifically link changes in connectivity to gains in reading following phonology-based reading intervention.

An additional limitation of the present study is that response following intervention was measured simply by calculating the difference between pre- and post-intervention scores on the informal progress monitoring measures. While this method captured individual differences in the amount of change in performance on this task, it did not take into account whether changes in neuroimaging data or behavioural data differed based on initial severity of RD. Given that response following intervention is known to be associated with pre-intervention reading skills, including word recognition, decoding, reading comprehension, reading fluency, and spelling (Partanen et al., 2019; Tilanus et al., 2019), it is possible that changes in structural and functional connectivity could differ based on pre-intervention severity of RD.

The difference scores approach for assessing response following intervention also did not provide information about whether the changes observed in each individual

represent meaningful changes in reading ability. Frijters, Lovett, Sevcik, and Morris (2013) suggest four possible methods for characterizing individual change following intervention: 1) comparing post-intervention scores to age-appropriate standard scores; 2) using the Jacobson-Truax index (Jacobson, Follette, & Revenstorf, 1984) to assess whether change from pre- to post-intervention is statistically reliable; 3) estimating individuals' growth rates using hierarchical linear modelling if data is available for multiple timepoints; and 4) assessing change based on a fixed criterion across multiple outcome measures. These methods could not be implemented in the present study because norms were not available for the progress monitoring measures, because no well-matched control group was available, and because data was only collected at two timepoints. However, these methods may provide additional sensitivity for future studies in characterizing individual differences in meaningful response to intervention.

#### **4.4.3 Conclusions**

In summary, the present study provides some evidence of changes in RSFC and white matter associated with gains in reading skills in children with RD following a phonology-based reading intervention. Children with RD showed increasing functional connectivity among reading network regions and frontal regions from pre- to post-intervention, increased functional segregation of reading and default mode networks, and increased white matter integrity of the right arcuate fasciculus. Response following intervention was also predicted by reduced pre-intervention functional connectivity between reading regions and default mode network and by increased pre-intervention function connectivity between the left thalamus and right parietal regions. Structural predictors of response following intervention included lower pre-intervention white



matter integrity of ventral tracts with respect to gains in letter-sound identification, and greater pre-intervention white matter integrity of the bilateral uncinate fasciculi with respect to gains in single word reading. These findings shed new light on the changes in functional and structural connectivity underlying gains in reading following reading intervention, suggesting these changes represent a combination of processes of compensation and normalization of brain connectivity. Additionally, the present study showed that functional and structural connectivity are related to subsequent gains on different types of reading tasks, suggesting that distinct characteristics of brain networks prior to reading intervention can predict response to intervention.

## References

- Al Otaiba, S., & Fuchs, D. (2002). Characteristics of children who are unresponsive to early literacy intervention: A review of the literature. *Remedial and Special Education, 23*(5), 300-316. <https://doi.org/10.1177/07419325020230050501>
- Baird, B., Smallwood, J., Gorgolewski, K. J., & Margulies, D. S. (2013). Medial and lateral networks in anterior prefrontal cortex support metacognitive ability for memory and perception. *Journal of Neuroscience, 33*(42), 16657–16665. <https://doi.org/10.1523/JNEUROSCI.0786-13.2013>
- Barquero, L. A., Davis, N., & Cutting, L. E. (2014). Neuroimaging of reading intervention: A systematic review and activation likelihood estimate meta-analysis. *PLoS ONE*. <https://doi.org/10.1371/journal.pone.0083668>
- Barth, A. E., Catts, H. W., & Anthony, J. L. (2009). The component skills underlying reading fluency in adolescent readers: A latent variable analysis. *Reading and Writing, 22*(5), 567–590. <https://doi.org/10.1007/s11145-008-9125-y>
- Basser, P. J., & Pierpaoli, C. (1996). Microstructural and physiological features of tissues elucidated by quantitative-diffusion-tensor MRI. *Journal of Magnetic Resonance - Series B, 111*(3), 209–219. <https://doi.org/10.1006/jmrb.1996.0086>
- Behzadi, Y., Restom, K., Liau, J., & Liu, T. T. (2007). A component based noise correction method (CompCor) for BOLD and perfusion based fMRI. *NeuroImage, 37*(1), 90–101. <https://doi.org/10.1016/j.neuroimage.2007.04.042>
- Bernal, B., & Ardila, A. (2009). The role of the arcuate fasciculus in conduction aphasia. *Brain, 132*(9), 2309-2316. <https://doi.org/10.1093/brain/awp206>
- Biswal, B., Zerrin Yetkin, F., Haughton, V. M., & Hyde, J. S. (1995). Functional connectivity in the motor cortex of resting human brain using echo-planar mri. *Magnetic Resonance in Medicine, 34*(4), 537–541. <https://doi.org/10.1002/mrm.1910340409>
- Brunswick, N., McCrory, E., Price, C. J., Frith, C. D., & Frith, U. (1999). Explicit and implicit processing of words and pseudowords by adult developmental dyslexics. A search for Wernicke's Wortschatz? *Brain, 122*(10), 1901–1917. <https://doi.org/10.1093/brain/122.10.1901>
- Bus, A. G., & Van Ijzendoorn, M. H. (1999). Phonological awareness and early reading: A meta-analysis of experimental training studies. *Journal of Educational Psychology, 91*(3), 403–414. <https://doi.org/10.1037/0022-0663.91.3.403>
- Catani, M., Allin, M. P. G., Husain, M., Pugliese, L., Mesulam, M. M., Murray, R. M., & Jones, D. K. (2007). Symmetries in human brain language pathways correlate with verbal recall. *Proceedings of the National Academy of Sciences of the United States of America, 104*(43), 17163–17168. <https://doi.org/10.1073/pnas.0702116104>
- Davis, N., Fan, Q., Compton, D. L., Fuchs, D., Fuchs, L. S., Cutting, L. E., ... Anderson, A. W. (2010). Influences of neural pathway integrity on children's response to reading instruction. *Frontiers in Systems Neuroscience, 4*. <https://doi.org/10.3389/fnsys.2010.00150>
- Desikan, R. S., Ségonne, F., Fischl, B., Quinn, B. T., Dickerson, B. C., Blacker, D., ... Killiany, R. J. (2006). An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *NeuroImage, 31*(3), 968–980. <https://doi.org/10.1016/j.neuroimage.2006.01.021>
- Díaz, B., Hintz, F., Kiebel, S. J., & Von Kriegstein, K. (2012). Dysfunction of the

- auditory thalamus in developmental dyslexia. *Proceedings of the National Academy of Sciences of the United States of America*, *109*(34), 13841–13846.  
<https://doi.org/10.1073/pnas.1119828109>
- Dick, A. S., & Tremblay, P. (2012). Beyond the arcuate fasciculus: Consensus and controversy in the connectional anatomy of language. *Brain*, *135*(12), 3529–3550.  
<https://doi.org/10.1093/brain/aws222>
- Duff, F. J., & Clarke, P. J. (2011). Practitioner Review: Reading disorders: What are the effective interventions and how should they be implemented and evaluated? *Journal of Child Psychology and Psychiatry and Allied Disciplines*.  
<https://doi.org/10.1111/j.1469-7610.2010.02310.x>
- Epelbaum, S., Pinel, P., Gaillard, R., Delmaire, C., Perrin, M., Dupont, S., ... Cohen, L. (2008). Pure alexia as a disconnection syndrome: New diffusion imaging evidence for an old concept. *Cortex*, *44*(8), 962–974.  
<https://doi.org/10.1016/j.cortex.2008.05.003>
- Farris, E. A., Odegard, T. N., Miller, H. L., Ring, J., Allen, G., & Black, J. (2011). Functional connectivity between the left and right inferior frontal lobes in a small sample of children with and without reading difficulties. *Neurocase*, *17*(5), 425–439.  
<https://doi.org/10.1080/13554794.2010.532141>
- Fleck, M. S., Daselaar, S. M., Dobbins, I. G., & Cabeza, R. (2006). Role of prefrontal and anterior cingulate regions in decision-making processes shared by memory and nonmemory tasks. *Cerebral Cortex*, *16*(11), 1623–1630.  
<https://doi.org/10.1093/cercor/bhj097>
- Fleming, S. M., Huijgen, J., & Dolan, R. J. (2012). Prefrontal contributions to metacognition in perceptual decision making. *Journal of Neuroscience*, *32*(18), 6117–6125. <https://doi.org/10.1523/JNEUROSCI.6489-11.2012>
- Fleming, S. M., Weil, R. S., Nagy, Z., Dolan, R. J., & Rees, G. (2010). Relating introspective accuracy to individual differences in brain structure. *Science*, *329*(5998), 1541–1543. <https://doi.org/10.1126/science.1191883>
- Fletcher, J. M., Stuebing, K. K., Barth, A. E., Denton, C. A., Cirino, P. T., Francis, D. J., & Vaughn, S. (2011). Cognitive correlates of inadequate response to reading intervention. *School Psychology Review*, *40*(1), 3–22.
- Fox, M. D., & Raichle, M. E. (2007). Spontaneous fluctuations in brain activity observed with functional magnetic resonance imaging. *Nature Reviews Neuroscience*, *8*(9), 700–711. <https://doi.org/10.1038/nrn2201>
- Fox, M. D., Snyder, A. Z., Vincent, J. L., Corbetta, M., Van Essen, D. C., & Raichle, M. E. (2005). The human brain is intrinsically organized into dynamic, anticorrelated functional networks. *Proceedings of the National Academy of Sciences of the United States of America*, *102*(27), 9673–9678. <https://doi.org/10.1073/pnas.0504136102>
- Fransson, P. (2005). Spontaneous low-frequency BOLD signal fluctuations: An fMRI investigation of the resting-state default mode of brain function hypothesis. *Human Brain Mapping*, *26*(1), 15–29. <https://doi.org/10.1002/hbm.20113>
- Frazier, J. A., Chiu, S., Breeze, J. L., Makris, N., Lange, N., Kennedy, D. N., ... Biederman, J. (2005). Structural brain magnetic resonance imaging of limbic and thalamic volumes in pediatric bipolar disorder. *American Journal of Psychiatry*, *162*(7), 1256–1265. <https://doi.org/10.1176/appi.ajp.162.7.1256>
- Frijters, J. C., Lovett, M. W., Sevcik, R. A., & Morris, R. D. (2013). Four methods of

- identifying change in the context of a multiple component reading intervention for struggling middle school readers. *Reading and Writing*, 26(4), 539–563.  
<https://doi.org/10.1007/s11145-012-9418-z>
- Frijters, J. C., Lovett, M. W., Steinbach, K. A., Wolf, M., Sevcik, R. A., & Morris, R. D. (2011). Neurocognitive predictors of reading outcomes for children with reading disabilities. *Journal of Learning Disabilities*, 44(2), 150–166.  
<https://doi.org/10.1177/0022219410391185>
- Goldstein, J. M., Seidman, L. J., Makris, N., Ahern, T., O'Brien, L. M., Caviness, V. S., ... Tsuang, M. T. (2007). Hypothalamic abnormalities in schizophrenia: Sex effects and genetic vulnerability. *Biological Psychiatry*, 61(8), 935–945.  
<https://doi.org/10.1016/j.biopsych.2006.06.027>
- Greicius, M. D., Krasnow, B., Reiss, A. L., & Menon, V. (2003). Functional connectivity in the resting brain: A network analysis of the default mode hypothesis. *Proceedings of the National Academy of Sciences of the United States of America*, 100(1), 253–258. <https://doi.org/10.1073/pnas.0135058100>
- Grossman, M., McMillan, C., Moore, P., Ding, L., Glosser, G., Work, M., & Gee, J. (2004). What's in a name: Voxel-based morphometric analyses of MRI and naming difficulty in Alzheimer's disease, frontotemporal dementia and corticobasal degeneration. *Brain*, 127(3), 628–649. <https://doi.org/10.1093/brain/awh075>
- Hilgenstock, R., Weiss, T., & Witte, O. W. (2014). You'd better think twice: Post-decision perceptual confidence. *NeuroImage*, 99, 323–331.  
<https://doi.org/10.1016/j.neuroimage.2014.05.049>
- Hoefl, F., McCandliss, B. D., Black, J. M., Gantman, A., Zakerani, N., Hulme, C., ... Gabrieli, J. D. E. (2011). Neural systems predicting long-term outcome in dyslexia. *Proceedings of the National Academy of Sciences of the United States of America*, 108(1), 361–366. <https://doi.org/10.1073/pnas.1008950108>
- Horowitz-Kraus, T., Difrancesco, M., Kay, B., Wang, Y., & Holland, S. K. (2015). Increased resting-state functional connectivity of visual- and cognitive-control brain networks after training in children with reading difficulties. *NeuroImage: Clinical*, 8, 619–630. <https://doi.org/10.1016/j.nicl.2015.06.010>
- Horowitz-Kraus, T., & Holland, S. K. (2015). Greater functional connectivity between reading and error-detection regions following training with the reading acceleration program in children with reading difficulties. *Annals of Dyslexia*, 65(1), 1–23.  
<https://doi.org/10.1007/s11881-015-0096-9>
- Horowitz-Kraus, T., Toro-Serey, C., & Difrancesco, M. (2015). Increased resting-state functional connectivity in the cingulo-opercular cognitive-control network after intervention in children with reading difficulties. *PLoS ONE*, 10(7).  
<https://doi.org/10.1371/journal.pone.0133762>
- Houdé, O., Rossi, S., Lubin, A., & Joliot, M. (2010). Mapping numerical processing, reading, and executive functions in the developing brain: An fMRI meta-analysis of 52 studies including 842 children. *Developmental Science*, 13(6), 876–885.  
<https://doi.org/10.1111/j.1467-7687.2009.00938.x>
- Huber, E., Donnelly, P. M., Rokem, A., & Yeatman, J. D. (2018). Rapid and widespread white matter plasticity during an intensive reading intervention. *Nature Communications*, 9(1), 1–13. <https://doi.org/10.1038/s41467-018-04627-5>
- Jacobson, N. S., Follette, W. C., & Revenstorff, D. (1984). Psychotherapy outcome

- research: Methods for reporting variability and evaluating clinical significance. *Behavior Therapy*, 15(4), 336–352. [https://doi.org/10.1016/S0005-7894\(84\)80002-7](https://doi.org/10.1016/S0005-7894(84)80002-7)
- Jongejan, W., Verhoeven, L., & Siegel, L. S. (2007). Predictors of reading and spelling abilities in first- and second-language learners. *Journal of Educational Psychology*, 99(4), 835–851. <https://doi.org/10.1037/0022-0663.99.4.835>
- Keller, T. A., & Just, M. A. (2009). Altering cortical connectivity: remediation-induced changes in the white matter of poor readers. *Neuron*, 64(5), 624–631. <https://doi.org/10.1016/j.neuron.2009.10.018>
- Koyama, M. S., Di Martino, A., Kelly, C., Jutagir, D. R., Sunshine, J., Schwartz, S. J., ... Milham, M. P. (2013). Cortical signatures of dyslexia and remediation: An intrinsic functional connectivity approach. *PLoS ONE*, 8(2). <https://doi.org/10.1371/journal.pone.0055454>
- Koyama, M. S., di Martino, A., Zuo, X. N., Kelly, C., Mennes, M., Jutagir, D. R., ... Milham, M. P. (2011). Resting-state functional connectivity indexes reading competence in children and adults. *Journal of Neuroscience*, 31(23), 8617–8624. <https://doi.org/10.1523/JNEUROSCI.4865-10.2011>
- Koyama, M. S., Kelly, C., Shehzad, Z., Penesetti, D., Castellanos, F. X., & Milham, M. P. (2010). Reading networks at rest. *Cerebral Cortex*, 20(11), 2549–2559. <https://doi.org/10.1093/cercor/bhq005>
- Koyama, M. S., Molfese, P. J., Milham, M. P., Mencl, W. E., & Pugh, K. R. (2020). Thalamus is a common locus of reading, arithmetic, and IQ: Analysis of local intrinsic functional properties. *Brain and Language*, 209(June), 104835. <https://doi.org/10.1016/j.bandl.2020.104835>
- Lovett, M., Lacerenza, L., Steinbach, K., & De Palma, M. (2014). Development and evaluation of a research-based intervention program for children and adolescents with reading disabilities. *Perspectives on Language and Literacy*, 40(3), 21.
- Lovett, M. W., & Steinbach, K. A. (1997). The effectiveness of remedial programs for reading disabled children of different ages: Does the benefit decrease for older children? *Learning Disability Quarterly*, 20(3), 189–209. <https://doi.org/10.2307/1511308>
- Lovett, M. W., Steinbach, K. A., & Frijters, J. C. (2000). Remediating the core deficits of developmental reading disability: A double-deficit perspective. *Journal of Learning Disabilities*, 33(4), 334–358. <https://doi.org/10.1177/002221940003300406>
- Lu, L. H., Crosson, B., Nadeau, S. E., Heilman, K. M., Gonzalez-Rothi, L. J., Raymer, A., ... Roper, S. N. (2002). Category-specific naming deficits for objects and actions: Semantic attribute and grammatical role hypotheses. *Neuropsychologia*, 40(9), 1608–1621. [https://doi.org/10.1016/S0028-3932\(02\)00014-3](https://doi.org/10.1016/S0028-3932(02)00014-3)
- Lyon, G. R., Shaywitz, S. E., & Shaywitz, B. A. (2003). A definition of dyslexia. *Annals of Dyslexia*, 53(1), 1–14. <https://doi.org/10.1007/s11881-003-0001-9>
- Maisog, J. M., Einbinder, E. R., Flowers, D. L., Turkeltaub, P. E., & Eden, G. F. (2008). A meta-analysis of functional neuroimaging studies of dyslexia. In *Annals of the New York Academy of Sciences* (Vol. 1145, pp. 237–259). <https://doi.org/10.1196/annals.1416.024>
- Makris, N., Goldstein, J. M., Kennedy, D., Hodge, S. M., Caviness, V. S., Faraone, S. V., ... Seidman, L. J. (2006). Decreased volume of left and total anterior insular lobule in schizophrenia. *Schizophrenia Research*, 83(2–3), 155–171.

- <https://doi.org/10.1016/j.schres.2005.11.020>
- Mandonnet, E., Nouet, A., Gatignol, P., Capelle, L., & Duffau, H. (2007). Does the left inferior longitudinal fasciculus play a role in language? A brain stimulation study. *Brain*, *130*(3), 623–629. <https://doi.org/10.1093/brain/awl361>
- Marchina, S., Zhu, L. L., Norton, A., Zipse, L., Wan, C. Y., & Schlaug, G. (2011). Impairment of speech production predicted by lesion load of the left arcuate fasciculus. *Stroke*, *42*(8), 2251–2256. <https://doi.org/10.1161/STROKEAHA.110.606103>
- Martin, A., Schurz, M., Kronbichler, M., & Richlan, F. (2015). Reading in the brain of children and adults: A meta-analysis of 40 functional magnetic resonance imaging studies. *Human Brain Mapping*, *36*(5), 1963–1981. <https://doi.org/10.1002/hbm.22749>
- McCurdy, L. Y., Maniscalco, B., Metcalfe, J., Liu, K. Y., de Lange, F. P., & Lau, H. (2013). Anatomical coupling between distinct metacognitive systems for memory and visual perception. *Journal of Neuroscience*, *33*(5), 1897–1906. <https://doi.org/10.1523/JNEUROSCI.1890-12.2013>
- Misra, M., Katzir, T., Wolf, M., & Poldrack, R. A. (2004). Neural systems for rapid automatized naming in skilled readers: Unraveling the RAN-reading relationship. *Scientific Studies of Reading*, *8*(3), 241–256. [https://doi.org/10.1207/s1532799xssr0803\\_4](https://doi.org/10.1207/s1532799xssr0803_4)
- Morris, R. D., Lovett, M. W., Wolf, M., Sevcik, R. A., Steinbach, K. A., Frijters, J. C., & Shapiro, M. B. (2012). Multiple-component remediation for developmental reading disabilities: Iq, socioeconomic status, and race as factors in remedial outcome. *Journal of Learning Disabilities*, *45*(2), 99–127. <https://doi.org/10.1177/0022219409355472>
- Myers, C. A., Vandermosten, M., Farris, E. A., Hancock, R., Gimenez, P., Black, J. M., ... & Hulme, C. (2014). White matter morphometric changes uniquely predict children's reading acquisition. *Psychological Science*, *25*(10), 1870–1883. <https://doi.org/10.1177/0956797614544511>
- Partanen, M., Siegel, L. S., & Giaschi, D. E. (2019). Longitudinal outcomes of an individualized and intensive reading intervention for third grade students. *Dyslexia*, *25*(3), 227–245. <https://doi.org/10.1002/dys.1616>
- Paulesu, E., Danelli, L., & Berlinger, M. (2014). Reading the dyslexic brain: Multiple dysfunctional routes revealed by a new meta-analysis of PET and fMRI activation studies. *Frontiers in Human Neuroscience*, *8*, 830. <https://doi.org/10.3389/fnhum.2014.00830>
- Power, J. D., Barnes, K. A., Snyder, A. Z., Schlaggar, B. L., & Petersen, S. E. (2012). Spurious but systematic correlations in functional connectivity MRI networks arise from subject motion. *NeuroImage*, *59*(3), 2142–2154. <https://doi.org/10.1016/j.neuroimage.2011.10.018>
- Pugh, K. R., Landi, N., Preston, J. L., Mencl, W. E., Austin, A. C., Sibley, D., ... Frost, S. J. (2013). The relationship between phonological and auditory processing and brain organization in beginning readers. *Brain and Language*, *125*(2), 173–183. <https://doi.org/10.1016/j.bandl.2012.04.004>
- Ramus, F. (2003). Developmental dyslexia: Specific phonological deficit or general sensorimotor dysfunction? *Current Opinion in Neurobiology*, *13*(2), 212–218.

- [https://doi.org/10.1016/S0959-4388\(03\)00035-7](https://doi.org/10.1016/S0959-4388(03)00035-7)
- Report of the National Reading Panel (2000): *Teaching Children to Read: An Evidence Based Assessment of the Scientific Research Literature on Reading and its Implications for Reading Instruction* (Vol. NIH Pub. No. 00-4754): U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Institute of Child Health and Human Development.
- Rezaie, R., Simos, P. G., Fletcher, J. M., Cirino, P. T., Vaughn, S., & Papanicolaou, A. C. (2011). Engagement of temporal lobe regions predicts response to educational interventions in adolescent struggling readers. *Developmental Neuropsychology*, *36*(7), 869–888. <https://doi.org/10.1080/87565641.2011.606404>
- Richards, T. L., Dager, S. R., Corina, D., Serafini, S., Heide, A. C., Steury, K., ... Berninger, V. W. (1999). Dyslexic children have abnormal brain lactate response to reading-related language tasks. *American Journal of Neuroradiology*, *20*(8), 1393–1398.
- Richlan, F., Kronbichler, M., & Wimmer, H. (2009). Functional abnormalities in the dyslexic brain: A quantitative meta-analysis of neuroimaging studies. *Human Brain Mapping*, *30*(10), 3299–3308. <https://doi.org/10.1002/hbm.20752>
- Rumsey, J. M., Horwitz, B., Donohue, B. C., Nace, K., Maisog, J. M., & Andreason, P. (1997). Phonological and orthographic components of word recognition. A PET-rCBF study. *Brain*, *120*(5), 739–759. <https://doi.org/10.1093/brain/120.5.739>
- Salmelin, R., Service, E., Kiesilä, P., Uutela, K., & Salonen, O. (1996). Impaired visual word processing in dyslexia revealed with magnetoencephalography. *Annals of Neurology*, *40*(2), 157–162. <https://doi.org/10.1002/ana.410400206>
- Sandak, R., Mencl, W. E., Frost, S. J., & Pugh, K. R. (2004). The neurobiological basis of skilled and impaired reading: Recent findings and new directions. *Scientific Studies of Reading*, *8*(3), 273–292. [https://doi.org/10.1207/s1532799xssr0803\\_6](https://doi.org/10.1207/s1532799xssr0803_6)
- Saygin, Z. M., Norton, E. S., Osher, D. E., Beach, S. D., Cyr, A. B., Ozernov-Palchik, O., ... Gabrieli, J. D. E. (2013). Tracking the roots of reading ability: White matter volume and integrity correlate with phonological awareness in prereading and early-reading kindergarten children. *Journal of Neuroscience*, *33*(33), 13251–13258. <https://doi.org/10.1523/JNEUROSCI.4383-12.2013>
- Schurz, M., Wimmer, H., Richlan, F., Ludersdorfer, P., Klackl, J., & Kronbichler, M. (2015). Resting-state and task-based functional brain connectivity in developmental dyslexia. *Cerebral Cortex*, *25*(10), 3502–3514. <https://doi.org/10.1093/cercor/bhu184>
- Shaywitz, S. E., Shaywitz, B. A., Fulbright, R. K., Skudlarski, P., Mencl, W. E., Constable, R. T., ... Gore, J. C. (2003). Neural systems for compensation and persistence: Young adult outcome of childhood reading disability. *Biological Psychiatry*, *54*(1), 25–33. [https://doi.org/10.1016/S0006-3223\(02\)01836-X](https://doi.org/10.1016/S0006-3223(02)01836-X)
- Shaywitz, S. E., Shaywitz, B. A., Pugh, K. R., Fulbright, R. K., Constable, R. T., Mencl, W. E., ... Gore, J. C. (1998). Functional disruption in the organization of the brain for reading in dyslexia. *Proceedings of the National Academy of Sciences of the United States of America*, *95*(5), 2636–2641. <https://doi.org/10.1073/pnas.95.5.2636>
- Shinoura, N., Midorikawa, A., Onodera, T., Tsukada, M., Yamada, R., Tabei, Y., ... Yagi, K. (2013). Damage to the left ventral, arcuate fasciculus and superior longitudinal fasciculus-related pathways induces deficits in object naming,

- phonological language function and writing, respectively. *International Journal of Neuroscience*, 123(7), 494–502. <https://doi.org/10.3109/00207454.2013.765420>
- Skeide, M. A., Kumar, U., Mishra, R. K., Tripathi, V. N., Guleria, A., Singh, J. P., ... Huettig, F. (2017). Learning to read alters cortico-subcortical cross-talk in the visual system of illiterates. *Science Advances*, 3(5). <https://doi.org/10.1126/sciadv.1602612>
- Snowling, M. J., Gooch, D. C., & Henderson, L. M. (2012). Dyslexia. In *Encyclopedia of Human Behavior: Second Edition* (pp. 732–739). <https://doi.org/10.1016/B978-0-12-375000-6.00139-7>
- Tilanus, E. A. T., Segers, E., & Verhoeven, L. (2019). Predicting responsiveness to a sustained reading and spelling intervention in children with dyslexia. *Dyslexia*, 25(2), 190–206. <https://doi.org/10.1002/dys.1614>
- Torgesen, J. K., Wagner, R. K., & Rashotte, C. A. (2012). *Test of Word Reading Efficiency* (2<sup>nd</sup> ed.). Austin, TX: Pro-Ed.
- Tzourio-Mazoyer, N., Landeau, B., Papathanassiou, D., Crivello, F., Etard, O., Delcroix, N., ... Joliot, M. (2002). Automated anatomical labeling of activations in SPM using a macroscopic anatomical parcellation of the MNI MRI single-subject brain. *NeuroImage*, 15(1), 273–289. <https://doi.org/10.1006/nimg.2001.0978>
- Vandermosten, M., Boets, B., Wouters, J., & Ghesquière, P. (2012). A qualitative and quantitative review of diffusion tensor imaging studies in reading and dyslexia. *Neuroscience and Biobehavioral Reviews*, 36(6), 1532–1552. <https://doi.org/10.1016/j.neubiorev.2012.04.002>
- Wagner, R. K., Torgesen, J. K., Laughon, P., Simmons, K., & Rashotte, C. A. (1993). Development of young readers' phonological processing abilities. *Journal of Educational Psychology*, 85(1), 83–103. <https://doi.org/10.1037/0022-0663.85.1.83>
- Wakana, S., Caprihan, A., Panzenboeck, M. M., Fallon, J. H., Perry, M., Gollub, R. L., ... Mori, S. (2007). Reproducibility of quantitative tractography methods applied to cerebral white matter. *NeuroImage*, 36(3), 630–644. <https://doi.org/10.1016/j.neuroimage.2007.02.049>
- Wechsler, D. (1999). *Wechsler Abbreviated Scale of Intelligence*. San Antonio, TX: The Psychological Corporation.
- Whitfield-Gabrieli, S., & Nieto-Castanon, A. (2012). Conn: A functional connectivity toolbox for correlated and anticorrelated brain networks. *Brain Connectivity*, 2(3), 125–141. <https://doi.org/10.1089/brain.2012.0073>
- Wilson, S. M., Galantucci, S., Tartaglia, M. C., Rising, K., Patterson, D. K., Henry, M. L., ... Gorno-Tempini, M. L. (2011). Syntactic processing depends on dorsal language tracts. *Neuron*, 72(2), 397–403. <https://doi.org/10.1016/j.neuron.2011.09.014>
- Woodcock, R. W., McGrew, K. S., & Mather, N. (2001). *Woodcock-Johnson III*. Itasca, IL: Riverside Publishing.
- Yeatman, J. D., Dougherty, R. F., Myall, N. J., Wandell, B. A., & Feldman, H. M. (2012). Tract profiles of white matter properties: Automating fiber-tract quantification. *PLoS ONE*, 7(11), e49790. <https://doi.org/10.1371/journal.pone.0049790>
- Yeatman, J. D., Dougherty, R. F., Rykhlevskaia, E., Sherbondy, A. J., Deutsch, G. K., Wandell, B. A., & Ben-Shachar, M. (2011). Anatomical properties of the arcuate fasciculus predict phonological and reading skills in children. *Journal of Cognitive*



*Neuroscience*, 23(11), 3304–3317. [https://doi.org/10.1162/jocn\\_a\\_00061](https://doi.org/10.1162/jocn_a_00061)  
Yokoyama, O., Miura, N., Watanabe, J., Takemoto, A., Uchida, S., Sugiura, M., ...  
Nakamura, K. (2010). Right frontopolar cortex activity correlates with reliability of  
retrospective rating of confidence in short-term recognition memory performance.  
*Neuroscience Research*, 68(3), 199–206.  
<https://doi.org/10.1016/j.neures.2010.07.2041>

## **Chapter 5: General Discussion**

Despite growing research on the neural substrates of reading ability, much remains to be understood about the role of neural connectivity in developing readers. Many previous studies of brain connectivity and reading have used single word reading measures or composite measures of reading, and these measures do not capture the different subskills required for efficient reading. Additionally, much of previous literature has focused on comparisons of typical readers to individuals with reading disability (RD), although reading ability is known to be distributed continuously across these groups. In this thesis, I addressed these issues by examining how subskills of reading, including sight word reading efficiency, decoding efficiency, reading comprehension, and rapid naming, relate to structural and functional brain connectivity. Additionally, I used an individual differences approach to examine how functional and structural brain connectivity are associated with individual differences in reading ability and in response following intervention. In the present chapter, I will summarize the main findings from Chapters 2, 3, and 4, and make recommendations for future directions.

### **5.1 Relevant Findings**

#### **5.1.1 Brain connectivity correlates of individual differences in reading subskills**

Reading is known to rely on cortical regions distributed across many areas of the cortex. Studies of functional connectivity have consistently demonstrated the importance of coordinated activity for efficient and accurate reading, as measured using both task-based (Hampson et al., 2006; Horwitz, Rumsey, & Donohue, 1998; Pugh et al., 2000; van der Mark et al., 2011) and resting-state approaches (Farris et al., 2011; Hampson et al., 2006; Koyama et al., 2013, 2011, 2010; Schurz et al., 2015a). However, prior studies

have assessed reading based on single-word reading measures or composite measures of reading ability. I was interested in examining how discrete subskills related to reading, such as decoding efficiency, sight word reading efficiency, reading comprehension, and rapid automatized naming (RAN), were associated with resting-state functional connectivity (RSFC) in the brain's reading network.

The findings of Chapter 2 showed both positive and negative RSFC-behaviour relationships, some of which diverged across different reading subskills. Positive relationships included increased RSFC in bilateral dorsal and anterior regions in children with greater decoding efficiency, in bilateral ventral regions in children with greater sight word reading efficiency, within striatal and attentional networks in children with stronger reading comprehension skills, and between left frontal and bilateral fusiform and hippocampal regions in children with stronger rapid naming abilities. In contrast, negative relationships suggested compensatory patterns of functional connectivity with respect to connections between the left frontal and bilateral angular gyrus and occipital regions in children with poor single word reading and rapid naming skills, and connections between left superior temporal and fusiform areas and between the left superior parietal lobule and left frontal areas in children with poor reading comprehension skills. Importantly, the results suggest that although reading subskills rely to some extent on shared functional networks, there are also distinct functional connections supporting different components of reading ability in children.

Chapter 3 built on the findings reported in Chapter 2 by using a similar approach to examine the relationship between reading subskills and structural brain connectivity in children. Like research in functional connectivity, previous studies of structural

connectivity have largely measured reading as a single construct. A small number of diffusion tensor imaging (DTI) studies considering multiple subskills of reading have provided preliminary evidence that different neural pathways play discrete roles in supporting different reading processes (Horowitz-Kraus et al., 2014; Niogi & McCandliss, 2006; Welcome & Joanisse, 2014). I was interested in extending this research to examine reading in school-aged children and to include other reading subskills, such as sight word reading efficiency, decoding efficiency, reading comprehension, and RAN. Thus, in the study described in Chapter 3, I used DTI to assess white matter microstructure in reading-related tracts of the brain, and examined how white matter integrity was associated with individual differences in reading subskills.

The main findings of the study described in Chapter 3 were positive correlations between reading subskills and white matter integrity of the bilateral arcuate fasciculi, as well as negative correlations between reading subskills and white matter integrity of the right inferior longitudinal fasciculus and bilateral uncinate fasciculi. Specifically, increased fractional anisotropy in the left arcuate fasciculus was associated with better decoding efficiency and rapid naming abilities, consistent with a large body of previous research linking the left arcuate fasciculus to phonological and articulatory processing (Bernal & Ardila, 2009; Dick & Tremblay, 2012; Marchina et al., 2011; Saygin et al., 2013; Shinoura et al., 2013; Vandermosten et al., 2012; Yeatman et al., 2011). Similar to the resting-state functional connectivity findings detailed in Chapter 2, the results presented in Chapter 3 implicate right hemisphere tracts in addition to the left hemisphere tracts more frequently studied in reading research. Increased integrity of the right arcuate fasciculus was associated with better single word reading skills, although this effect was

partially accounted for by reading comprehension skills and nonverbal intelligence. The findings in ventral tracts suggest an overreliance on the bilateral uncinate fasciculi and right ILF in children struggling with reading comprehension, as well as rapid naming with respect to the right uncinate fasciculus.

Although previous reading research has tended to focus on left hemisphere connectivity, the findings presented in Chapters 2 and 3 both highlight the role of interhemispheric and right hemisphere connectivity in reading ability in children. This is consistent with developmental studies finding an early reliance on bilateral regions for reading, with a later shift towards more left lateralized reading function with age and reading experience (Finn et al., 2014; Shaywitz et al., 2007; Turkeltaub et al., 2003). These findings emphasize the importance of considering both left and right hemisphere cortical regions and white matter tracts in studies of reading in the brain.

One question of interest concerns whether there were commonalities in the findings of Chapters 2 and 3, given the intuitive relationship between functional and structural connectivity. However, little overlap was observed between the results of the two studies: in general the grey matter seed to voxel connections implicated in significant RSFC findings did not correspond to the grey matter regions linked by the white matter tracts implicated in the DTI findings. This is likely related to some extent to the methodology used in each study for examining connectivity. The analyses described in Chapter 2 examined resting-state functional connectivity extending from pre-identified left hemisphere seed regions to all other voxels in both hemispheres of the brain, and no right hemisphere seed regions were included as regions of interest in this study. The majority of the significant brain-behaviour relationships found in Chapter 2 implicated

resting-state functional connectivity from left hemisphere to clusters of voxels in the right hemisphere of the brain. In contrast, the analyses described in Chapter 3 examined white matter microstructure in four bilateral association tracts, which connect regions within the same hemisphere of the brain: the arcuate fasciculus, uncinate fasciculus, inferior fronto-occipital fasciculus, and inferior longitudinal fasciculus. The structural analyses did not include any commissural tracts, which cross between hemispheres of the brain and could therefore potentially overlap with the many functional connectivity findings crossing from the left hemisphere seeds to voxel clusters in the right hemisphere. An additional limitation in finding commonalities between the results of Chapters 2 and 3 is that the white matter tracts of interest in Chapter 3 do not involve fibers connecting to the parietal lobe, and the within-hemisphere functional connections found to be associated with reading in Chapter 2 tended to implicate functional connectivity between left hemisphere seed regions and left parietal regions. It is therefore possible that further analyses of these data or further studies examining functional seed regions in the right hemisphere, commissural white matter tracts, or tracts with fibers extending to the parietal lobe (for example, examining the whole superior longitudinal fasciculus rather than focusing only on the more lateral fibers forming the arcuate fasciculus) could potentially reveal more commonalities between patterns of resting-state functional connectivity and white matter microstructure.

Importantly, although brain function and structure are intuitively related to one another, functional connectivity is not expected to correspond directly to structural connectivity (Horwitz et al., 1992; Horwitz, 1994). A previous longitudinal study found that functional connectivity of the visual word form area in 8-year-old children was

predicted by structural connectivity at age 5, but not by functional connectivity at age 5, suggesting that early structural connectivity may precede and impact functional development of brain regions (Saygin et al., 2016). Additionally, as functional connectivity is measured based on temporal correlations in activation rather than direct neuronal communication, two brain regions that are structurally connected may not always show functional connectivity during the fMRI scan. This is particularly relevant for task-based functional connectivity studies as the specific demands of the task will impact local activation, in turn impacting patterns of correlation between different regions. Conversely, two regions that show functional connectivity may not be directly connected via white matter fibers, as they could both receive input from a third brain region resulting in correlation in the time course of activation. As a result, although functional and structural connectivity are related measures, they are not expected to overlap completely in their relationship to behaviour.

Together, Chapters 2 and 3 of this thesis present evidence of individual differences in structural and functional connectivity that are specifically linked to reading performance across a wide range of school-age years. These findings suggest the link between brain connectivity and reading is multifactorial, with reading subskills showing both overlapping and discrete relationships with functional and structural connectivity. This highlights the importance of considering multiple cognitive components of reading ability when measuring reading.

### **5.1.2 Brain connectivity and reading intervention in RD**

Given that individual differences in reading ability are linked to characteristics of functional and structural connectivity, one question of interest concerns how measures of

brain connectivity change following reading intervention in children with RD.

Phonology-based reading interventions are known to be effective in improving reading in RD (Bus & Van Ijzendoorn, 1999; Duff & Clarke, 2011; Lovett, Steinbach, & Frijters, 2000; National Reading Panel, 1989), however much remains to be understood with respect to how brain connectivity is related to gains in reading and response to intervention. I was interested in examining what changes in RSFC and white matter microstructure were observed in children with RD receiving a phonology-based reading intervention.

The findings presented in Chapter 4 showed that changes in RSFC associated with reading intervention in RD were characterized by reduced anti-correlation of the left parietal regions with left frontal lobe regions, suggesting an increase in functional coordination or a decrease in inhibitory relationships between these areas. Interestingly, the opposite pattern was observed in children with a wide range of reading skills receiving only classroom reading instruction. This group exhibited increased anti-correlation of left parietal and left frontal regions over time, consistent with previous studies linking functional segregation of reading network regions and frontal regions to automatization of reading abilities in more proficient readers (Koyama et al., 2011, 2010). The reverse effect in the group of children with RD may be related to development of compensatory strategies requiring coordination of reading network and frontal lobe regions, particularly as the Empower Reading program involves metacognitive strategy training. Further analyses also suggested that gains in reading in children with RD were associated with related patterns of RSFC from the left inferior frontal gyrus, both with respect to pre-intervention connectivity and changes in connectivity over time.



Specifically, children who showed greater gains in reading abilities exhibited increased RSFC over time from the left inferior frontal gyrus to left occipital, right parietal, and right striatal regions, as well as weaker pre-intervention RSFC and reduced RSFC over time from the left inferior frontal gyrus to default mode network regions. Additionally, gains in reading skill were associated with greater pre-intervention functional coordination of the left thalamus and right parietal areas and a further increase in functional coordination among these areas following intervention. These findings suggest that functional coordination of the left inferior frontal gyrus with left occipital, right parietal, and right striatal regions and of the left thalamus with right parietal regions, along with functional segregation of the inferior frontal gyrus with the default mode network, play an important role in gains in reading ability in children with RD.

Findings of changes in structural connectivity presented in Chapter 4 suggested that improved word reading abilities were related to increased white matter integrity of the right arcuate fasciculus. These findings were consistent with those of Chapter 3 of this thesis, which showed that greater integrity of the right arcuate was associated with stronger single word reading skills. Additionally, the results presented in Chapter 4 showed that distinct characteristics of white matter prior to intervention predicted gains on different reading tasks. Specifically, reduced pre-intervention integrity of the left uncinate fasciculus, left inferior longitudinal fasciculus, left inferior fronto-occipital fasciculus, and right arcuate fasciculus was associated with greater gains in letter sound identification, while greater pre-intervention integrity of the left uncinate and right uncinate and lower pre-intervention integrity in the right inferior longitudinal fasciculus were related to greater gains in single word reading abilities.

Importantly, the results presented in Chapter 4 should be interpreted with caution due to the small sample size and resulting low statistical power and small effects. However, the findings provide preliminary evidence that measurable changes in resting-state functional connectivity and white matter connectivity are linked to gains in reading in children with RD. In the context of previous research in typical readers, these findings suggest that changes in brain connectivity during intervention in children with RD include both normalization to more typical patterns of connectivity and compensatory reliance on atypical patterns of connectivity to support reading strategies targeted in the intervention.

The findings presented in Chapter 4 also show the importance of considering individual differences in response to intervention in studies of RD, as changes in functional and structural connectivity were related to individual differences in gains in reading. It is well known that there is significant variability in response to intervention in children with RD (Vellutino et al., 1996), and this has led to the implementation of a 3-tier response to intervention (RTI) approach to preventing, identifying, and remediating RD in educational settings (IDEA, 2004). The first tier of the RTI model focuses on prevention, via implementation of a core reading program at the classroom level. Children who do not respond at Tier 1 proceed to Tier 2, in which they receive more intensive treatment in a small group format, for example the Empower Reading program. Children who continue to be unresponsive at Tier 2 are then moved to Tier 3, in which they are provided with more direct, intensive intervention, generally in a one-on-one setting. The results of the present study advance the field's understanding of neurological factors underlying response following intervention at the Tier 2 level, and suggest that

brain structure and function differ significantly based on the degree to which children respond to intervention. Additionally, the relationship between connectivity and response following intervention varied for different types of progress monitoring measures, highlighting that, as shown in Chapters 2 and 3, the link between brain connectivity and reading is multifactorial. The results presented in Chapter 4 also showed that distinct pre-intervention characteristics of functional and structural connectivity were related to subsequent gains in reading. This suggests that neurological markers prior to intervention may predict subsequent response to intervention, which has important implications for improving identification and treatment of RD.

## **5.2 Directions for Future Research**

While the findings of this thesis add to the existing literature demonstrating the role of functional and structural connectivity in reading ability, they also generate additional questions to motivate future research. In particular, although this thesis showed that distinct characteristics of functional and structural connectivity are related to reading, the relationship between brain structure and function in supporting cognitive processes is not well understood. Recent developments in network-based analysis methods in neuroscience have focused on mapping and quantifying connectome patterns in the human brain (for reviews see Sporns, 2014; Tompson, Falk, Vettel, & Bassett, 2018). Network models of the brain describe the brain as a set of interrelated nodes, representing cortical regions, and edges, representing white matter tracts connecting nodes (Petersen & Sporns, 2015; Rubinov & Sporns, 2010). This approach extends studies of specific functional networks and white matter pathways, such as the present thesis, to examine the full connectome. A small number of recent studies have used whole-brain network

analysis methods to characterize local and global network deficits in RD with respect to functional connectivity (Bailey, Aboud, Nguyen, & Cutting, 2018; Finn et al., 2014), gray matter structure (Hosseini et al., 2013; Liu et al., 2015; Qi et al., 2016), and white matter structure (Bathelt, Gathercole, Butterfield, & Astle, 2018; Lou et al., 2019). Network-based analyses have not yet been applied in studies of reading to examine the relationships between connectome structure and function, however, these approaches hold much promise for understanding the relationships between network architecture and function in the brain and their role in individual differences in reading ability.

An additional area for future research would be to more clearly characterize neurological markers of response to intervention, as this has important implications for identification and treatment of RD. The present study is one of few to examine neural predictors of response following intervention in RD, and research is needed to further characterize these neurological markers and examine whether they are valid and reliable predictors of response to intervention. Further studies could also extend these findings to other neuroimaging techniques that are less costly than MRI and may be more feasible for use in an educational setting. For example, recent developments in functional near-infrared spectroscopy hold promise for studying cognitive development in educational settings (Soltanlou, Sitnikova, Nuerk, & Dresler, 2018). Further research in this area would assist in defining neurobiological markers of RD and of response to intervention, to ultimately improve identification of RD and implementation of reading intervention programs.

The findings of this thesis clearly showed that the relationship between reading and the brain is multifaceted, highlighting the importance of considering multiple

components of reading rather than using composite measures to assess reading ability. However, the battery of reading subskills assessed in Chapters 3 and 4 is by no means exhaustive, as many other cognitive skills are known to impact reading ability. For example, phonological awareness (Gathercole et al., 2006), listening comprehension (Catts et al., 2005, 2003; Hoover & Gough, 1990), oral language (Catts et al., 2002), and working memory (Gathercole et al., 2006) are all known to be related to reading ability in children and are likely to show distinct relationships to functional and structural connectivity in the brain. With the respect to reading intervention, an interesting consideration for future studies concerns the specific subskills targeted in the intervention program, as the timeline for introduction of different intervention targets may result in distinct changes in brain connectivity over time. For example, the Empower program includes metacognitive training as well as reading strategies introduced at different time points throughout program, beginning with letter-sound identification and sound blending training and moving towards strategies for identifying larger subsyllabic units such as vowel clusters, prefixes, and suffixes (Lovett, Lacerenza, Steinbach, & De Palma, 2014). Given the findings of Chapters 2 and 3 showing that different reading subskills are related to distinct characteristics of functional and structural connectivity, and the findings of Chapter 4 showing that gains in reading on different types of reading tasks were also distinctly related to changes in connectivity, one question of interest for future studies concerns how the time course of introduction of different types of reading strategies during intervention may be reflected in the time course of changes in the brain. This is particularly relevant given that changes in white matter structure are known to occur rapidly and in concert with gains in reading ability during intensive reading

intervention (Huber et al., 2018b). A similar design to that of Huber et al. (2018) in which neuroimaging data is collected at regular time points throughout the intervention would be well suited to examining the time course of changes in the brain and whether these changes are linked to the introduction of different types of reading strategies.

As this dissertation has explored, reading is an extraordinarily complex skill supported by an intricate network of brain regions. The complexity of reading is reflected in the many types of cognitive processing involved and the multi-faceted relationship of each of these cognitive processes to brain structure and function. Each of the studies described in this thesis showed that individual differences in reading ability modulate resting-state functional connectivity and white matter microstructure. Although recent advances in neuroimaging technology have furthered our understanding of the role of connectivity in reading ability and RD, there is yet to be a neurobiological model of reading and RD that fully accounts for the role of connectivity in individual differences in cognitive components of reading. By considering distinct reading subskills of reading, individual differences, and the role of connectivity, a comprehensive neurobiological model of reading and RD can be developed to more fully capture the neural substrates of reading. Such research will also contribute to improved methods of prevention, identification, and treatment of RD, to optimize long-term outcomes for children of all reading abilities.

## References

- Bailey, S. K., Aboud, K. S., Nguyen, T. Q., & Cutting, L. E. (2018). Applying a network framework to the neurobiology of reading and dyslexia. *Journal of Neurodevelopmental Disorders, 10*(1), 1–9. <https://doi.org/10.1186/s11689-018-9251-z>
- Bathelt, J., Gathercole, S. E., Butterfield, S., & Astle, D. E. (2018). Children's academic attainment is linked to the global organization of the white matter connectome. *Developmental Science, 21*(5), 1–14. <https://doi.org/10.1111/desc.12662>
- Bernal, B., & Ardila, A. (2009). The role of the arcuate fasciculus in conduction aphasia. *Brain, 132*(9), 2309–2316. <https://doi.org/10.1093/brain/awp206>
- Bus, A. G., & Van Ijzendoorn, M. H. (1999). Phonological awareness and early reading: A meta-analysis of experimental training studies. *Journal of Educational Psychology, 91*(3), 403–414. <https://doi.org/10.1037/0022-0663.91.3.403>
- Catts, H. W., Fey, M. E., Tomblin, J. B., & Zhang, X. (2002). A longitudinal investigation of reading outcomes in children with language impairments. *Journal of Speech, Language, and Hearing Research, 45*(6), 1142–1157. [https://doi.org/10.1044/1092-4388\(2002/093\)](https://doi.org/10.1044/1092-4388(2002/093))
- Catts, H. W., Hogan, T. P., & Adlof, S. M. (2005). Developmental changes in reading and reading disabilities. In *The Connections Between Language and Reading Disabilities*. <https://doi.org/10.4324/9781410612052>
- Catts, H. W., Hogan, T. P., & Fey, M. E. (2003). Subgrouping poor readers on the basis of individual differences in reading-related abilities. *Journal of Learning Disabilities, 36*(2), 151–164. <https://doi.org/10.1177/002221940303600208>
- Dick, A. S., & Tremblay, P. (2012). Beyond the arcuate fasciculus: Consensus and controversy in the connective anatomy of language. *Brain, 135*(12), 3529–3550. <https://doi.org/10.1093/brain/aws222>
- Duff, F. J., & Clarke, P. J. (2011). Practitioner Review: Reading disorders: What are the effective interventions and how should they be implemented and evaluated? *Journal of Child Psychology and Psychiatry and Allied Disciplines*. <https://doi.org/10.1111/j.1469-7610.2010.02310.x>
- Farris, E. A., Odegard, T. N., Miller, H. L., Ring, J., Allen, G., & Black, J. (2011). Functional connectivity between the left and right inferior frontal lobes in a small sample of children with and without reading difficulties. *Neurocase, 17*(5), 425–439. <https://doi.org/10.1080/13554794.2010.532141>
- Finn, E. S., Shen, X., Holahan, J. M., Scheinost, D., Lacadie, C., Papademetris, X., ... Constable, R. T. (2014). Disruption of functional networks in dyslexia: A whole-brain, data-driven analysis of connectivity. *Biological Psychiatry, 76*(5), 397–404. <https://doi.org/10.1016/j.biopsych.2013.08.031>
- Gathercole, S. E., Alloway, T. P., Willis, C., & Adams, A. M. (2006). Working memory in children with reading disabilities. *Journal of Experimental Child Psychology, 93*(3), 265–281. <https://doi.org/10.1016/j.jecp.2005.08.003>
- Hampson, M., Tokoglu, F., Sun, Z., Schafer, R. J., Skudlarski, P., Gore, J. C., & Constable, R. T. (2006). Connectivity-behavior analysis reveals that functional connectivity between left BA39 and Broca's area varies with reading ability. *NeuroImage, 31*(2), 513–519. <https://doi.org/10.1016/j.neuroimage.2005.12.040>
- Hoover, W. A., & Gough, P. B. (1990). The simple view of reading. *Reading and*

- Writing*, 2(2), 127–160. <https://doi.org/10.1007/BF00401799>
- Horowitz-Kraus, T., Wang, Y., Plante, E., & Holland, S. K. (2014). Involvement of the right hemisphere in reading comprehension: A DTI study. *Brain Research*, 1582, 34–44. <https://doi.org/10.1016/j.brainres.2014.05.034>
- Horwitz, B., Grady, C. L., Haxby, J. V., Schapiro, M. B., Rapoport, S. I., Ungerleider, L. G., & Mishkin, M. (1992). Functional associations among human posterior extrastriate brain regions during object and spatial vision. *Journal of Cognitive Neuroscience*, 4(4), 311–322. <https://doi.org/10.1162/jocn.1992.4.4.311>
- Horwitz, B., Rumsey, J. M., & Donohue, B. C. (1998). Functional connectivity of the angular gyrus in normal reading and dyslexia. *Proceedings of the National Academy of Sciences of the United States of America*, 95(15), 8939–8944. <https://doi.org/10.1073/pnas.95.15.8939>
- Horwitz, Barry. (1994). Data analysis paradigms for metabolic-flow data: Combining neural modeling and functional neuroimaging. *Human Brain Mapping*, 2(1–2), 112–122. <https://doi.org/10.1002/hbm.460020111>
- Hosseini, S. M. H., Black, J. M., Soriano, T., Bugescu, N., Martinez, R., Raman, M. M., ... Hoefl, F. (2013). Topological properties of large-scale structural brain networks in children with familial risk for reading difficulties. *NeuroImage*, 71, 260–274. <https://doi.org/10.1016/j.neuroimage.2013.01.013>
- Huber, E., Donnelly, P. M., Rokem, A., & Yeatman, J. D. (2018). Rapid and widespread white matter plasticity during an intensive reading intervention. *Nature Communications*, 9(1), 1–13. <https://doi.org/10.1038/s41467-018-04627-5>
- Individuals With Disabilities Education Act (IDEA), Pub. L. N. 108-446, 118 Stat. 2647, 2657–2658 (Dec. 3, 2004).
- Koyama, M. S., Di Martino, A., Kelly, C., Jutagir, D. R., Sunshine, J., Schwartz, S. J., ... Milham, M. P. (2013). Cortical signatures of dyslexia and remediation: An intrinsic functional connectivity approach. *PLoS ONE*, 8(2). <https://doi.org/10.1371/journal.pone.0055454>
- Koyama, M. S., di Martino, A., Zuo, X. N., Kelly, C., Mennes, M., Jutagir, D. R., ... Milham, M. P. (2011). Resting-state functional connectivity indexes reading competence in children and adults. *Journal of Neuroscience*, 31(23), 8617–8624. <https://doi.org/10.1523/JNEUROSCI.4865-10.2011>
- Koyama, M. S., Kelly, C., Shehzad, Z., Penesetti, D., Castellanos, F. X., & Milham, M. P. (2010). Reading networks at rest. *Cerebral Cortex*, 20(11), 2549–2559. <https://doi.org/10.1093/cercor/bhq005>
- Liu, K., Shi, L., Chen, F., Waye, M. M. Y., Lim, C. K. P., Cheng, P. wan, ... Wang, D. (2015). Altered topological organization of brain structural network in Chinese children with developmental dyslexia. *Neuroscience Letters*, 589, 169–175. <https://doi.org/10.1016/j.neulet.2015.01.037>
- Lou, C., Duan, X., Altarelli, I., Sweeney, J. A., Ramus, F., & Zhao, J. (2019). White matter network connectivity deficits in developmental dyslexia. *Human Brain Mapping*, 40(2), 505–516. <https://doi.org/10.1002/hbm.24390>
- Lovett, M., Lacerenza, L., Steinbach, K., & De Palma, M. (2014). Development and evaluation of a research-based intervention program for children and adolescents with reading disabilities. *Perspectives on Language and Literacy*, 40(3), 21.
- Lovett, M. W., Steinbach, K. A., & Frijters, J. C. (2000). Remediating the core deficits of



- developmental reading disability: A double-deficit perspective. *Journal of Learning Disabilities*, 33(4), 334-358. <https://doi.org/10.1177/002221940003300406>
- Marchina, S., Zhu, L. L., Norton, A., Zipse, L., Wan, C. Y., & Schlaug, G. (2011). Impairment of speech production predicted by lesion load of the left arcuate fasciculus. *Stroke*, 42(8), 2251-2256. <https://doi.org/10.1161/STROKEAHA.110.606103>
- Martin, A., Schurz, M., Kronbichler, M., & Richlan, F. (2015). Reading in the brain of children and adults: A meta-analysis of 40 functional magnetic resonance imaging studies. *Human Brain Mapping*, 36(5), 1963-1981. <https://doi.org/10.1002/hbm.22749>
- Niogi, S. N., & McCandliss, B. D. (2006). Left lateralized white matter microstructure accounts for individual differences in reading ability and disability. *Neuropsychologia*, 44(11), 2178-2188. <https://doi.org/10.1016/j.neuropsychologia.2006.01.011>
- Petersen, S. E., & Sporns, O. (2015). Brain networks and cognitive architectures. *Neuron*, 88(1), 207-219. <https://doi.org/10.1016/j.neuron.2015.09.027>
- Pugh, K. R., Mencl, W. E., Shaywitz, B. A., Shaywitz, S. E., Fulbright, R. K., Constable, R. T., ... Gore, J. C. (2000). The angular gyrus in developmental dyslexia: Task-specific differences in functional connectivity within posterior cortex. *Psychological Science*, 11(1), 51-56. <https://doi.org/10.1111/1467-9280.00214>
- Qi, T., Gu, B., Ding, G., Gong, G., Lu, C., Peng, D., ... Liu, L. (2016). More bilateral, more anterior: Alterations of brain organization in the large-scale structural network in Chinese dyslexia. *NeuroImage*, 124, 63-74. <https://doi.org/10.1016/j.neuroimage.2015.09.011>
- Report of the National Reading Panel (2000): *Teaching Children to Read: An Evidence Based Assessment of the Scientific Research Literature on Reading and its Implications for Reading Instruction* (Vol. NIH Pub. No. 00-4754): U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Institute of Child Health and Human Development.
- Rubinov, M., & Sporns, O. (2010). Complex network measures of brain connectivity: Uses and interpretations. *NeuroImage*, 52(3), 1059-1069. <https://doi.org/10.1016/j.neuroimage.2009.10.003>
- Saygin, Z. M., Norton, E. S., Osher, D. E., Beach, S. D., Cyr, A. B., Ozernov-Palchik, O., ... Gabrieli, J. D. E. (2013). Tracking the roots of reading ability: White matter volume and integrity correlate with phonological awareness in prereading and early-reading kindergarten children. *Journal of Neuroscience*, 33(33), 13251-13258. <https://doi.org/10.1523/JNEUROSCI.4383-12.2013>
- Saygin, Z. M., Osher, D. E., Norton, E. S., Youssoufian, D. A., Beach, S. D., Feather, J., ... & Kanwisher, N. (2016). Connectivity precedes function in the development of the visual word form area. *Nature Neuroscience*, 19(9), 1250-1255. <https://doi.org/10.1038/nn.4354>
- Schurz, M., Wimmer, H., Richlan, F., Ludersdorfer, P., Klackl, J., & Kronbichler, M. (2015). Resting-state and task-based functional brain connectivity in developmental dyslexia. *Cerebral Cortex*, 25(10), 3502-3514. <https://doi.org/10.1093/cercor/bhu184>
- Shaywitz, B. A., Skudlarski, P., Holahan, J. M., Marchione, K. E., Constable, R. T.,

- Fulbright, R. K., ... Shaywitz, S. E. (2007). Age-related changes in reading systems of dyslexic children. *Annals of Neurology*, *61*(4), 363–370. <https://doi.org/10.1002/ana.21093>
- Shinoura, N., Midorikawa, A., Onodera, T., Tsukada, M., Yamada, R., Tabei, Y., ... Yagi, K. (2013). Damage to the left ventral, arcuate fasciculus and superior longitudinal fasciculus-related pathways induces deficits in object naming, phonological language function and writing, respectively. *International Journal of Neuroscience*, *123*(7), 494–502. <https://doi.org/10.3109/00207454.2013.765420>
- Soltanlou, M., Sitnikova, M. A., Nuerk, H. C., & Dresler, T. (2018). Applications of functional near-infrared spectroscopy (fNIRS) in studying cognitive development: The case of mathematics and language. *Frontiers in Psychology*, *9*, 277. <https://doi.org/10.3389/fpsyg.2018.00277>
- Sporns, O. (2014). Contributions and challenges for network models in cognitive neuroscience. *Nature Neuroscience*, *17*(5), 652–660. <https://doi.org/10.1038/nn.3690>
- Tompson, S. H., Falk, E. B., Vettel, J. M., & Bassett, D. S. (2018). Network approaches to understand individual differences in brain connectivity: opportunities for personality neuroscience. *Personality Neuroscience*, *1*(5), 1–12. <https://doi.org/10.1017/pen.2018.4>
- Turkeltaub, P. E., Gareau, L., Flowers, D. L., Zeffiro, T. A., & Eden, G. F. (2003). Development of neural mechanisms for reading. *Nature Neuroscience*, *6*(7), 767–773. <https://doi.org/10.1038/nn1065>
- van der Mark, S., Klaver, P., Bucher, K., Maurer, U., Schulz, E., Brem, S., ... Brandeis, D. (2011). The left occipitotemporal system in reading: Disruption of focal fMRI connectivity to left inferior frontal and inferior parietal language areas in children with dyslexia. *NeuroImage*, *54*(3), 2426–2436. <https://doi.org/10.1016/j.neuroimage.2010.10.002>
- Vandermosten, M., Boets, B., Wouters, J., & Ghesquière, P. (2012). A qualitative and quantitative review of diffusion tensor imaging studies in reading and dyslexia. *Neuroscience and Biobehavioral Reviews*, *36*(6), 1532–1552. <https://doi.org/10.1016/j.neubiorev.2012.04.002>
- Vellutino, F. R., Scanlon, D. M., Sipay, E. R., Small, S. G., Chen, R., Pratt, A., & Denckla, M. B. (1996). Cognitive profiles of difficult-to-remediate and readily remediated poor readers: Early intervention as a vehicle for distinguishing between cognitive and experiential deficits as basic causes of specific reading disability. *Journal of Educational Psychology*, *88*(4), 601–638. <https://doi.org/10.1037/0022-0663.88.4.601>
- Welcome, S. E., & Joanisse, M. F. (2014). Individual differences in white matter anatomy predict dissociable components of reading skill in adults. *NeuroImage*, *96*, 261–275. <https://doi.org/10.1016/j.neuroimage.2014.03.069>
- Yeatman, J. D., Dougherty, R. F., Rykhlevskaia, E., Sherbondy, A. J., Deutsch, G. K., Wandell, B. A., & Ben-Shachar, M. (2011). Anatomical properties of the arcuate fasciculus predict phonological and reading skills in children. *Journal of Cognitive Neuroscience*, *23*(11), 3304–3317. [https://doi.org/10.1162/jocn\\_a\\_00061](https://doi.org/10.1162/jocn_a_00061)

## Appendices

### Appendix A: Letter RAN task administered in studies in Chapters 2 and 3

Participants were first shown the practice sheet below and asked to name the four letters. Participants were then shown the following form and asked to name each letter as quickly and accurately as possible, moving through the array row by row. Total naming time and number of letters named correctly and incorrectly were recorded. The task was scored based on the number of items named correctly per second.

k r m g

k r m g m r k g r k  
m k r m g r g m k r  
k m g r k r g k m g  
r k m g r k m r g m  
k m r m k r g k g r

**Appendix B:** Informal intervention progress monitoring materials administered in study described in Chapter 4

**I. Letter Sound Identification Task**

**Instructions:** "I am going to show you some letters one at a time. After I show you a letter, I want you to tell me the sound that letter makes. Do you understand? Good. What sound is this . . ." (Show first card with printed letter.)

\*Use the following prompt for a, e, i, o, u, c, g, y:  
 "Yes. This letter can also make another sound. Tell me the other sound this letter makes."

- |                     |                     |
|---------------------|---------------------|
| 1. * (a) (1) _____  | 17. (w) _____       |
| (2) _____           | 18. (k) _____       |
| 2. (m) _____        | 19. (v) _____       |
| 3. (s) _____        | 20. (p) _____       |
| 4. * (e) (1) _____  | 21. (b) _____       |
| (2) _____           | 22. * (y) (1) _____ |
| 5. (r) _____        | (2) _____           |
| 6. (d) _____        | 23. (x) _____       |
| 7. (f) _____        | 24. (j) _____       |
| 8. * (i) (1) _____  | 25. (qu) _____      |
| (2) _____           | 26. (z) _____       |
| 9. (t) _____        | 27. (th) _____      |
| 10. (n) _____       | 28. (sh) _____      |
| 11. * (c) (1) _____ | 29. (ch) _____      |
| (2) _____           |                     |
| 12. * (o) (1) _____ |                     |
| (2) _____           |                     |
| 13. (h) _____       |                     |
| 14. * (u) (1) _____ |                     |
| (2) _____           |                     |
| 15. * (g) (1) _____ |                     |
| (2) _____           |                     |
| 16. (l) _____       |                     |

Score=\_\_\_\_\_/37

## II. Sound Combinations

Student Name: \_\_\_\_\_  
 Examiner: \_\_\_\_\_

Date: \_\_\_\_\_

**Instructions:** "Now I'm going to show you some sound combinations. When these letters are together they usually make their own sound. I want you to tell me the sound these letters make. What sound?" (Show first card with printed letters.)

\*Use the following prompt for oo, ea, ow:

"Yes. These letters can also make another sound. Tell me the other sound these letters make".

- |      |        |       |       |        |       |
|------|--------|-------|-------|--------|-------|
| 1.   | er     | _____ | 16.   | igh    | _____ |
| 2.   | ar     | _____ | 17.   | tch    | _____ |
| 3.   | ing    | _____ | 18.   | oi     | _____ |
| 4.   | wh     | _____ | 19. * | ow (i) | _____ |
| 5.   | al     | _____ |       | (ii)   | _____ |
| 6.   | oo (i) | _____ | 20.   | tion   | _____ |
|      | (ii)   | _____ | 21.   | kn     | _____ |
| 7.   | or     | _____ | 22.   | ce     | _____ |
| 8.   | ou     | _____ | 23.   | ci     | _____ |
| 9. * | ea (i) | _____ | 24.   | ge     | _____ |
|      | (ii)   | _____ | 25.   | gi     | _____ |
|      | (iii)  | _____ | 26.   | oy     | _____ |
| 10.  | ee     | _____ |       |        |       |
| 11.  | ur     | _____ |       |        |       |
| 12.  | ol     | _____ |       |        |       |
| 13.  | oa     | _____ |       |        |       |
| 14.  | ai     | _____ |       |        |       |
| 15.  | ir     | _____ |       |        |       |

Score= \_\_\_\_/30

**LETTER SOUND IDENTIFICATION TASK  
SCORING KEY**

**Instructions:** "I am going to show you some letters one at a time. After I show you a letter, I want you to tell me the sound that letter makes. Do you understand?"

\* Prompt for a, e, i, o, u, c, g, y

"Yes. This letter can also make another sound. Tell me the other sound this letter makes".

"What sound is this..." (show card with printed letter)

- |                                           |                                                               |
|-------------------------------------------|---------------------------------------------------------------|
| 1. * (a) (1) <u>  a  </u> <u>  at  </u>   | 17. (w) <u>  w, woo, oo  </u> <u>  wish  </u>                 |
| (2) <u>  ā  </u> <u>  ate  </u>           | 18. (k) <u>  k  </u> <u>  kid  </u>                           |
| 2. (m) <u>  mm  </u> <u>  man  </u>       | 19. (v) <u>  vvv  </u> <u>  vine  </u>                        |
| 3. (s) <u>  sss  </u> <u>  sat  </u>      | 20. (p) <u>  p  </u> <u>  pin  </u>                           |
| 4. * (e) (1) <u>  e  </u> <u>  end  </u>  | 21. (b) <u>  b  </u> <u>  bill  </u>                          |
| (2) <u>  ē  </u> <u>  tree  </u>          | 22. * (y) (1) <u>  yē  </u> <u>  yes  </u> (see #4 below)     |
| 5. (r) <u>  rrr  </u> <u>  run  </u>      | (2) <u>  ī  </u> <u>  cry  </u>                               |
| 6. (d) <u>  d  </u> <u>  dad  </u>        | 23. (x) <u>  ks  </u> <u>  ox  </u>                           |
| 7. (f) <u>  fff  </u> <u>  fun  </u>      | 24. (j) <u>  j  </u> <u>  jump  </u>                          |
| 8. * (i) (1) <u>  i  </u> <u>  it  </u>   | 25. (qu) <u>  kwuh or coo  </u> <u>  queen  </u>              |
| (2) <u>  ī  </u> <u>  hi  </u>            | 26. (z) <u>  zzz  </u> <u>  zoo  </u>                         |
| 9. (t) <u>  t  </u> <u>  ten  </u>        | 27. * (th) <u>  th  </u> <u>  this/think  </u> (see #3 below) |
| 10. (n) <u>  nnn  </u> <u>  nap  </u>     | 28. (sh) <u>  sh  </u> <u>  ship  </u>                        |
| 11. * (c) (1) <u>  k  </u> <u>  cop  </u> | 29. (ch) <u>  ch  </u> <u>  champ  </u>                       |
| (2) <u>  sss  </u> <u>  city  </u>        |                                                               |
| 12. * (o) (1) <u>  o  </u> <u>  on  </u>  |                                                               |
| (2) <u>  ō  </u> <u>  go  </u>            |                                                               |
| 13. (h) <u>  h  </u> <u>  has  </u>       |                                                               |
| 14. * (u) (1) <u>  u  </u> <u>  up  </u>  |                                                               |
| (2) <u>  ū  </u> <u>  use  </u>           |                                                               |
| 15. * (g) (1) <u>  g  </u> <u>  got  </u> |                                                               |
| (2) <u>  j  </u> <u>  gym  </u>           |                                                               |
| 16. (l) <u>  lll  </u> <u>  let  </u>     |                                                               |

**Voiced Stop Cons:** d, g, b, j

**Unv. St. Cons:** t, p, c, h, k

- Continuous Consonants (e.g., r, m, s, v): a vowel sound heard following the consonant renders that consonant *incorrect* unless the vowel sound is an "uh" sound.  
e.g., mih, veh, mah, soh, --> these are wrong  
vuh, nuh, --> these are correct  
The reason for this is that most children are taught to say continuous sounds with the "uh" sound attached, so we do not want to penalize the children who respond as they have been taught.
- Voiced Stop Consonants: we accept uh at the end of both voiced and unvoiced consonants.
- Accept either the voiced (*th* as in *this*) or unvoiced (*th* as in *think*) sound of th.
- There are 5 acceptable responses for the sound of y.
  - yuh
  - yēē as in yellow
  - ē as in baby
  - i as in gym
  - ī as in spy

**SOUND COMBINATIONS  
SCORING KEY**

**Instructions:** "Now I'm going to show you some sound combinations. When these letters are together they usually make their own sound. I want you to tell me the sound these letters make. What sound?"

\* Prompt for: oo, ea, ow

"Yes. These letters can also make another sound. Tell me the other sound these letters make".

"What sound ? . ." (Show card with printed letters.)

- |     |          |                            |     |          |                                      |
|-----|----------|----------------------------|-----|----------|--------------------------------------|
| 1.  | er       | <u>her</u>                 | 16. | igh      | <u>high</u>                          |
| 2.  | ar       | <u>car</u>                 | 17. | tch      | <u>match</u> (i.e., ch)              |
| 3.  | ing      | <u>king</u>                | 18. | oi       | <u>oil</u>                           |
| 4.  | wh       | <u>when</u> (wuh, woo, oo) | 19. | * ow (i) | <u>glow</u>                          |
| 5.  | al       | <u>call, pal</u>           |     | (ii)     | <u>cow</u>                           |
| 6.  | oo (i)   | <u>zoo</u>                 | 20. | tion     | <u>action</u> (i.e., shun)           |
|     | (ii)     | <u>look</u>                | 21. | kn       | <u>knee</u> (nn or nuh)              |
| 7.  | or       | <u>for</u>                 | 22. | ce       | <u>sss, se (cent), see (receive)</u> |
| 8.  | ou       | <u>out</u>                 | 23. | ci       | <u>sss, si (city), si (exciting)</u> |
| 9.  | * ea (i) | <u>beach</u>               | 24. | ge       | <u>jjj, je (gem), jee (genie)</u>    |
|     | (ii)     | <u>head</u>                | 25. | gi       | <u>jjj, ji (gin), ji (giant)</u>     |
|     | (iii)    | <u>break</u>               | 26. | oy       | <u>boy</u>                           |
| 10. | ee       | <u>tree</u>                |     |          |                                      |
| 11. | ur       | <u>burn</u>                |     |          |                                      |
| 12. | ol       | <u>old, doll</u>           |     |          |                                      |
| 13. | oa       | <u>boat</u>                |     |          |                                      |
| 14. | ai       | <u>rain</u>                |     |          |                                      |
| 15. | ir       | <u>bird, irresistible</u>  |     |          |                                      |

**CHALLENGE WORD TEST**  
**Ceiling: 20 consecutive errors**

Student Name: \_\_\_\_\_

Date: \_\_\_\_\_

**Instructions: I will show you some words one at a time. The words are quite hard, but I'll give you lots of time so you can try your best with each one. It's really important that you give each word your best try.**

(1) Only fully blended words should be accepted as correct. The following prompt may be used up to 5 times during test administration for unblended but correct responses. "So, what is the word?" or "Tell me the word". Then remind the student each time, "Remember, you need to put all of the parts together for your final answer.

(2) Students often will say "I don't know" to words on this test. When this happens, examiners should encourage students to give each word a good try. (e.g., "Give it a good try", "Give it your best shot"). Please avoid using any terms that prompt the use of specific strategies such as sounding out. Use examiner judgement in determining how often to use these prompts with students.

(3) Examiners should ensure that students are completely finished attempting each word before moving on to the next word.

1	wishful
2	boyish
3	unpack
4	tanning
5	flopped
6	limping
7	sets
8	flatten
9	unfeeling
10	ringer
11	jobless
12	lumpy
13	chomping
14	ladder
15	slacker
16	worthless
17	enjoyable
18	smokeless



19	refill
20	lottery
21	grinned
22	toaster
23	retell
24	reckless
25	rashes
26	shiftless
27	unwashed
28	confess
29	repayment
30	helplessness
31	needlessly
32	disband
33	unluckily
34	mistakenly
35	rewrote
36	dotted
37	dampest
38	foolishly
39	rebuff
40	transplant
41	unsinkable
42	peppery
43	extant
44	unemployment
45	afloat
46	adornment
47	thickest
48	blissful
49	regretfully
50	unspeakably
51	irreplaceable
52	recurrently
53	soundly
54	strangulation
55	distress

# Keyword Test

20 consecutive errors to ceiling

Student Name: \_\_\_\_\_

Date: \_\_\_\_\_

**Administration:**

1. Place cards face down beside you. Read the instructions below to the child.
2. As soon as you expose the card to the child, start timing. Always ensure that the child is ready before presenting the card.
3. When the child responds, stop the stopwatch immediately. Record the child's response and the time on the protocol. If the child has responded with an incorrect word, record the error response phonetically.
4. The time limit per word is 7 seconds. If the child is clearly making an attempt at the word, let the child continue; do not remove the card unless you are sure the child is finished with it. Any responses provided after 7 seconds is considered an error, whether or not the answer was correct or incorrect.
5. The ceiling for the test is 20 consecutive errors.

**Instructions:**

*"I want you to read some words on these cards. Read each one as fast as you can. It is important that you try to get as many words right as you can. If you are not sure about a word, give it a good try anyhow. You'll have 7 seconds to read each word."*

- 1 pig \_\_\_\_\_
- 2 yes \_\_\_\_\_
- 3 it \_\_\_\_\_
- 4 cow \_\_\_\_\_
- 5 fun \_\_\_\_\_
- 6 jump \_\_\_\_\_
- 7 all \_\_\_\_\_
- 8 car \_\_\_\_\_
- 9 this \_\_\_\_\_
- 10 good \_\_\_\_\_
- 11 food \_\_\_\_\_
- 12 them \_\_\_\_\_
- 13 baby \_\_\_\_\_
- 14 rock \_\_\_\_\_
- 15 end \_\_\_\_\_
- 16 nose \_\_\_\_\_
- 17 let \_\_\_\_\_
- 18 dad \_\_\_\_\_

- 19 ship
- 20 nice
- 21 made
- 22 club
- 23 tent
- 24 luck
- 25 sweet
- 26 cry
- 27 her
- 28 oil
- 29 fool
- 30 round
- 31 champ
- 32 skunk
- 33 vine
- 34 broke
- 35 grab
- 36 page
- 37 sink
- 38 flew
- 39 file
- 40 scream

**TRANSFER WORD TEST**  
**Ceiling: 20 consecutive errors**

**Student Name:** \_\_\_\_\_

**Date:** \_\_\_\_\_

**Administration:**

1. Place cards face down beside you. Read the instructions below to the child.
2. As soon as you expose the card to the child, start timing. Always ensure that the child is ready before presenting the card.
3. When the child responds, stop the stopwatch immediately. Record the child's response and the time on the protocol. If the child has responded with an incorrect word, record the error response phonetically.
4. The time limit per word is 7 seconds. If the child is clearly making an attempt at the word, let the child continue; do not remove the card unless you are sure the child is finished with it. Any responses provided after 7 seconds is considered an error, whether or not the answer was correct or incorrect.
5. The ceiling for the test is 20 consecutive errors.


**Instructions:**

*"I want you to read some words on these cards. Read each one as fast as you can. It is important that you try to get as many words right as you can. If you are not sure about a word, give it a good try anyhow. You'll have 7 seconds to read each word."*

1	jumper
2	rap
3	net
4	teem
5	vent
6	fuzz
7	nip
8	goodly
9	pus
10	pug
11	talker
12	tint
13	cab
14	puck
15	mode
16	smack
17	flog
18	rainless
19	lust
20	musk
21	patch
22	mock

23	grub
24	drummer
25	queenly
26	nope
27	maze
28	glued
29	hive
30	luckless
31	lice
32	phoned
33	reck
34	strongest
35	drew
36	folder
37	pact
38	queer
39	extent
40	spear
41	lung
42	gleam
43	drown
44	potted
45	skunked
46	spook
47	remade
48	jade
49	ail
50	roan
51	clutch
52	drub
53	oink
54	sage
55	flirt
56	strife
57	bile
58	haw
59	kiln
60	scour

Appendix C: Ethics approval for the studies described in Chapters 3, 4, and 5



Research Ethics

**Western University Health Science Research Ethics Board  
HSREB Full Board Initial Approval Notice**

**Principal Investigator:** Prof. Marc Jeanisse  
**Department & Institution:** Social Science/Psychology, Western University

**Review Type:** Full Board  
**HSREB File Number:** 108197  
**Study Title:** Brain correlates of reading ability in children  
**Sponsor:** Natural Sciences and Engineering Research Council

**HSREB Initial Approval Date:** August 12, 2016  
**HSREB Expiry Date:** August 12, 2017

**Documents Approved and/or Received for Information:**

Document Name	Comments	Version Date
Western University Protocol	Received 2016/07/25	
Caregiver Letter of Information & Consent	Empower	2016/07/27
Caregiver Letter of Information & Consent	non Empower	2016/07/27
Assent		2016/05/15
Instruments	WASI Performance IQ forms/stimuli - Received 2016/06/22	
Instruments	RAN Letters - Received 2016/06/22	
Instruments	RAN Objects - Received 2016/06/22	
Instruments	WJ III - stimulus items sample - Received 2016/06/22	
Instruments	WJ III instrument response forms - Received 2016/06/22	
Instruments	TOWRE instrument - Received 2016/06/22	
Instruments	parent questionnaire	2016/06/21
Recruitment Items	Template for children in Empower class	2016/06/20
Recruitment Items	Template for children in non-Empower classrooms	2016/06/20
Recruitment Items	E-mail template for children from database of previous experiment participants	2016/06/21


The Western University Health Science Research Ethics Board (HSREB) has reviewed and approved the above named study, as of the HSREB Initial Approval Date noted above.

HSREB approval for this study remains valid until the HSREB Expiry Date noted above, conditional to timely submission and acceptance of HSREB Continuing Ethics Review.


The Western University HSREB operates in compliance with the Tri-Council Policy Statement Ethical Conduct for Research Involving Humans (TCPS2), the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use Guideline for Good Clinical Practice Practices (ICH E6 R1), the Ontario Personal Health Information Protection Act (PHIPA, 2004), Part 4 of the Natural Health Product Regulations, Health Canada Medical Device Regulations and Part C, Division 5, of the Food and Drug Regulations of Health Canada.

Members of the HSREB who are named as Investigators in research studies do not participate in discussions related to, nor vote on such studies when they are presented to the REB.

The HSREB is registered with the U.S. Department of Health & Human Services under the IRB registration number IRB 00000940.

  
Ethics Officer, on behalf of Dr. Joseph Gilbert, HSREB Chair

Ethics Officer: Erica Baile  Kaitlyn Harsh  Nicole Karbi  Cecile Kelly  Yvonne Tran  Karen O'Connell



## Curriculum Vitae

Alexandra M. Cross, M.Sc.

### Education

- In progress* Ph.D. Health and Rehabilitation Sciences, University of Western Ontario,  
Advisors: Drs. Marc Joanisse and Lisa Archibald
- In progress* M.Cl.Sc. Speech-Language Pathology, University of Western Ontario,
- 2015 M.Sc. Psychology, University of Western Ontario  
Advisor: Dr. Marc Joanisse  
Thesis: Eyetracking of coarticulatory cue responses in children and adults
- 2013 B.Sc.H. Psychology, Queen's University  
Advisor: Dr. Ingrid Johnsrude  
Thesis: Age-related differences in semantic priming of ambiguous words
- 2012 Bilateral Exchange Program (as part of B.Sc.H. Psychology), Victoria  
University of Wellington, New Zealand

### Honours Awarded

- 2020 Second Place, Three Minute Thesis University Finals, University of Western Ontario
- 2018-2020 Ontario Graduate Research Scholarship (awarded annually)
- 2018 NIH Student Travel Award, Symposium on Research in Child Language Disorders
- 2018 Mary Ann Underwood Small Global Opportunities Award, University of Western Ontario
- 2017 Best Oral Presentation, Health and Rehabilitation Sciences Graduate Research Conference
- 2013-2018 Western Graduate Research Scholarship (awarded annually)
- 2013 Teaching Assistantship Award, Department of Psychology, Queen's University

- 2013 Marion Ross Award for Athletic and Academic Excellence (awarded to top female athlete), Queen's University
- 2012 Health and Disability Intelligence Prize in Statistics (awarded for highest grade in STAT392 Sample Surveys course), Victoria University of Wellington

### Peer-Reviewed Publications

1. **Cross, A.M.**, Archibald, L.M.D., & Joannis, M.F. (2019). Mathematical abilities in children with developmental language disorder. *Language, Speech, and Hearing Services in Schools*, 50(1), 150-163.
2. **Cross, A.M.** & Joannis, M.F. (2018). Eyetracking of coarticulatory cue responses in children and adults. *Language, Cognition, and Neuroscience*, 33(10), 1315-1324.

### Peer-Reviewed Talks

1. **Cross, A.M.** "Exploring the association between reading and math: More similar than different?" Symposium presentation at the International Mind, Brain and Education Society Conference. July 2020 conference cancelled due to COVID-19.
2. **Cross, A.M.**, Lammert, J.M., Stager, C.L., Lovett, M.W., Steinbach, K.A., Frijters, J.C., Archibald, L.M.D., Joannis, M.F. "White matter correlates of reading subskills in children". Oral presentation at the "Society for the Scientific Study of Reading Annual Conference", Toronto, Ontario, Canada. July 2019.
3. Joannis, M.F., **Cross, A.M.**, & Archibald, L.M.D. "White matter correlates of reading vs. math difficulties in children." Oral presentation at the "Internal Mind, Brain and Education Society Conference", Los Angeles, California, United States of America. September 2018.
4. **Cross, A.M.**, Archibald, L.M.D., & Joannis, M.F. "Predicting children's response to reading intervention with neural connectivity." Oral presentation at the "Health and Rehabilitation Sciences Graduate Research Conference", London, Ontario, Canada. February 2018.
5. **Cross, A.M.**, Archibald, L.M.D., & Joannis, M.F. "Neural correlates of reading disability in children." Oral presentation at the "Health and Rehabilitation Sciences Graduate Research Conference", London, Ontario, Canada. February 2017.
6. Joannis, M.F., Perlmutter, K.R., **Cross, A.M.** "Linking reading and numerical knowledge in children: the role of symbols." Oral presentation at the "Psychonomic Society Annual Meeting", Chicago, United States of America. October 2015.

### Peer-Reviewed Posters

1. **Cross, A.M.**, Steinbach, K.A., Lovett, M.W., Frijters, J.C., Archibald, L.M.D., & Joannis, M.F. "Predicting response to reading intervention based on structural and functional brain connectivity". Poster presentation at the Symposium for Research in Child Language Disorders. June 2020 conference canceled due to COVID-19.



2. **Cross, A.M.**, Stager, C.L., Lovett, M.W., Steinbach, K.A., Frijters, J.C., Archibald, L.M.D., & Joanisse, M.F. Changes in resting-state functional brain connectivity and reading ability following reading intervention in children. Poster presented at the Society for Neurobiology of Language, Helsinki, Finland. August 2019.
3. **Cross, A.M.**, Stager, C.L., Lovett, M.W., Steinbach, K.A., Frijters, J.C., Archibald, L.M.D., & Joanisse, M. Changes in brain connectivity and behavioural reading ability following reading intervention in children. Poster presented at the Symposium for Research in Child Language Disorders, Madison, Wisconsin, United States. June 2019.
4. **Cross, A.M.**, Lammert, J.M., Stager, C.L., Lovett, M.W., Steinbach, K.A., Frijters, J.C., Archibald, L.M.D., & Joanisse, M. Changes in brain connectivity following reading intervention in children. Poster presented at the Speech and Hearing BC annual conference, Victoria, British Columbia, Canada. October 2018.
5. **Cross, A.M.**, Joanisse, M.F., & Archibald, L. Mathematical abilities in children with developmental language disorder. Poster presented at the Symposium for Research in Child Language Disorders, Madison, Wisconsin, United States. June 2018.
6. **Cross, A.M.**, Thornley, E., King, C., Skirving, E., Archibald, L., & Schwean, V. First steps in developing an interdisciplinary Child and Youth Development Clinic. Poster presented at the Symposium for Research in Child Language Disorders, Madison, Wisconsin, United States, June 2018.
7. **Cross, A.M.**, Ramdajal, R., Stager, C.L., Steinbach, K.A., Lovett, M.W., Frijters, J.C., Vandermeer, M., Hayden, E.P., Archibald, L.M.D., & Joanisse, M.F. Associating children's reading and math subskills with resting-state functional connectivity. Poster presented at the Ninth Annual Meeting of the Society for Neurobiology of Language, Baltimore, Maryland, United States. November 2017.
8. **Cross, A.M.**, Ramdajal, R., Stager, C.L., Steinbach, K.A., Lovett, M.W., Frijters, J.C., Hayden, E.P., Archibald, L.M.D., & Joanisse, M.F. Resting-state fMRI connectivity for reading and nonverbal ability in children with and without reading disability. Poster presented at the Symposium for Research in Child Language Disorders, Madison, Wisconsin, United States. June 2017.
9. **Cross, A.M.** & Joanisse, M.F. Association of children's coarticulatory sensitivity with language and reading skills revealed by eyetracking. Poster presented at the Symposium for Research in Child Language Disorders, Madison, Wisconsin, United States. June 2016.
10. Joanisse, M.F., Perlmutter, K.R., **Cross, A.M.** Children's numerical magnitude processing predicts subsequent early reading skill. Poster presented at Inaugural Brain and Mind Institute Symposium, London, Ontario, Canada. September 2015.
11. **Cross, A.M.** & Joanisse, M.F. Eyetracking of coarticulatory cue responses in children and adults. Poster presented at Inaugural Brain and Mind Institute Symposium, London, Ontario, Canada. September 2015.
12. **Cross, A.M.** & Joanisse, M.F. Sensitivity to coarticulatory cues in children and adults. Poster presented at the Lake Ontario Visionary Establishment 44th annual meeting, Niagara Falls, Ontario, Canada. February 2015.

## Professional Experience

- 2019 Student Clinician (Speech-Language Pathology), Thames Valley District School Board
- 2018 Student Clinician (Speech-Language Pathology), South Africa Placement Initiative, University of Western Ontario
- 2017-2018 Student Clinician (Speech-Language Pathology), Child and Youth Development Clinic, University of Western Ontario
- 2016-2018 Teaching Assistant for Language Acquisition and Developmental Language Disorders, School of Communication Sciences and Disorders, University of Western Ontario
- 2016-2018 Student Clinician (Speech-Language Pathology), H.A. Leeper Speech and Hearing Clinic
- 2016-2017 Abstract Review Committee Chair, Health and Rehabilitation Sciences Graduate Student Conference, University of Western Ontario
- 2015 Teaching Assistant for Introduction to Social Psychology, Department of Psychology, University of Western Ontario
- 2015 Teaching Assistant for Introduction to Cognitive Behavioural Neuroscience, Department of Psychology, University of Western Ontario
- 2014 Teaching Assistant for Cognitive Psychology, Department of Psychology, University of Western Ontario
- 2013-2015 Teaching Assistant for Language Development, Department of Psychology, University of Western Ontario
- 2013-2014 Research Assistant for FDK Screening of Early Childhood Learning, Department of Psychology & School of Communication Sciences, University of Western Ontario
- 2012-2013 Teaching Assistant for Introduction to Psychology, Department of Psychology, Queen's University
- 2012-2013 Research Assistant to Dr. Mark Sabbagh, Early Experiences Lab, Department of Psychology, Queen's University
- 2011 Research Assistant to Dr. Elizabeth Kelley, Autism Spectrum Disorders Lab, Department of Psychology, Queen's University

**Professional Service**

- 2017 – 2018 Student Representative, Child and Youth Development Clinic Training Committee, University of Western Ontario
- 2016- 2017 Combined Student Representative, Health and Rehabilitation Sciences Graduate Student Society, University of Western Ontario
- 2016 - 2017 Student Representative, Combined Program Working Group, Faculty of Health Sciences, University of Western Ontario
- 2016 - 2017 Co-supervisor for undergraduate honours thesis student, Alexandria Thornton, University of Western Ontario
- 2016 Ad-hoc reviewer, Applied Psycholinguistics
- 2015 Speaker, Western Women in Neuroscience High School Outreach, University of Western Ontario
- 2015 Volunteer for the 2015 London Brain Bee, University of Western Ontario
- 2014-2015 Representative and Treasurer, Psychology Graduate Student Association, University of Western Ontario
- 2012-2013 Disciplinary Panel Member, Queen's University Athletics and Recreation