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UNIVERSITY OF CALIFORNIA SAN DIEGO

SAN DIEGO STATE UNIVERSITY

The Brain Basis of Language Impairment Across the Lifespan

A Dissertation submitted in partial satisfaction of the requirements
for the degree of Doctor of Philosophy

in

Doctor of Philosophy in Language and Communicative Disorders

by

Noelle Abbott

Committee in charge:

University of California San Diego

Professor Timothy Brown
Professor Frank Haist
Professor Jeanne Townsend

San Diego State University

Professor Tracy Love, Chair
Professor Alyson Abel
Professor Inna Fishman

2024

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Chair

University of California San Diego

San Diego State University

2024

DEDICATION

To my pride and joy, the silliest of them all, my greatest accomplishment in life, Oliver Abbott. I hope you always pursue the things that make you happy and drive your curiosity.

For my mom, my biggest supporter, my beacon for advice, and the reason for my love of learning, this Ph.D. is for you.

EPIGRAPH

I'm pretty tired, I think I'll go home now.

Forrest Gump

TABLE OF CONTENTS

DISSERTATION APPROVAL PAGE	iii
DEDICATION	iv
EPIGRAPH	v
LIST OF FIGURES	viii
LIST OF TABLES	ix
ACKNOWLEDGEMENTS	x
VITA	xiv
ABSTRACT OF THE DISSERTATION	xviii
INTRODUCTION	1
Overview of Dissertation	2
References	4
Chapter 1 DEFINING HYPOPERFUSION IN CHRONIC APHASIA: AN INDIVIDUALIZED THRESHOLDING APPROACH	5
Preface	6
Acknowledgements	31
Chapter 2 BRIDGING THE DIVIDE: BRAIN AND BEHAVIOR IN DEVELOPMENTAL LANGUAGE DISORDER	32
Preface	33
Acknowledgements	73
Chapter 3 BRAIN FUNCTION IN DEVELOPMENTAL LANGAUGE DISORDER	74
1. Introduction	75
2. Methods	82
3. Results	95
4. Discussion	118
5. References	123

Chapter 4	RATE OF SPEECH AFFECTS THE COMPREHENSION OF PRONOUNS IN CHILDREN WITH DEVELOPMENTAL LANGUAGE DISORDER.....	132
	Preface.....	133
	Abstract	134
1.	Introduction	135
2.	Experiment 1: Online Processing via Cross-Modal Picture Priming	142
2.1.	Materials and methods	143
2.2.	Results	153
2.3.	Discussion: Experiment 1	158
3.	Experiment 2: Offline Processing via Sentence-Picture-Matching.....	160
3.1.	Materials and methods	161
3.2.	Results	163
3.3.	Discussion: Experiment 2	165
4.	Conclusion	166
	Appendix A: Post-hoc Exploration of Age Effects on Online Processing (Experiment 1)	169
	Appendix B: Post-hoc Exploration of Age Effects on Offline Processing (Experiment 2)....	173
5.	References	174
	Acknowledgements	177
Chapter 5	GENERAL DISCUSSION AND CONCLUSION.....	178

LIST OF FIGURES

Figure 3.1	96
Figure 3.2.	101
Figure 3.3.	103
Figure 3.4.	105
Figure 3.5.	106
Figure 3.6.	107
Figure 3.7.	108
Figure 3.8.	109
Figure 3.9.	111
Figure 3.10.	112
Figure 3.11.	113
Figure 3.12.	114
Figure 4.1.	145
Figure 4.2.	147
Figure 4.3.	148
Figure 4.4.	154
Figure 4.5.	157
Figure 4.6.	162
Figure 4.7.	164

LIST OF TABLES

Table 3.1.....	85
Table 3.2.....	97
Table 3.3.....	98
Table 3.4.....	99
Table 4.1.....	142
Table 4.2.....	144
Table 4.3.....	152
Table 4.4.....	155

ACKNOWLEDGEMENTS

I have the great fortune to say that this Ph.D. was not accomplished alone. So many people have supported me along the way, encouraging me to continue, pushing me to think through complex problems, and shaping me into the researcher I am today. I started the program so blissfully unaware of how little I knew, but I'm leaving the program fully aware of how little I know – and I mean that in the best way possible.

I would like to express my deepest gratitude to Dr. Tracy Love, my Ph.D. advisor and all-around powerhouse of a human being. Over the years you challenged me to not just sharpen my thinking, but to believe in my abilities. I think that is the greatest gift you can give someone. Whether it was a weekly meeting, or a practice talk for a presentation, you always prepared me to tackle the hard questions and to truly apply what I know; all while encouraging me to never be afraid of the unknown because that's where the fun in research begins! As I continue on to the next thing, and the thing after that, I will forever carry the tools you taught me, along with the sage piece of advice that, “every word matters”.

I would also like to thank my committee members for their guidance and advice over the years. Dr. Inna Fishman, thank you for taking a chance on me and agreeing to be a co-sponsor on my F31 application. It has been such a great experience getting to work with you and members of your lab. I am so grateful for your mentorship. Dr. Alyson Abel, thank you for the time you devoted to recruitment and listening to me complain about how difficult it is. From our first meeting with the school district to forming partnerships with local businesses, I learned so much about how to communicate with members of the community in an engaging and meaningful way. Dr. Frank Haist, thank you for introducing me to the world of neuroimaging software. I've come a long way from the student who couldn't find the hidden menu feature I needed in AFNI to the

researcher who uses multiple software packages based on my analysis goals. I would also like to thank Drs. Timothy Brown and Jeanne Townsend for their valuable feedback throughout this process. I feel lucky to have received feedback and advice from such renowned researchers in the field.

A special thanks to my fellow lab mates and lifelong friends, Dr. Niloofar Akhavan, Dr. Carolyn Baker, and Christina Sen. Your friendship and support have meant so much to me and have kept me sane through the hard times and smiling through the fun times! I will always look fondly on our LANG lab days together. Also, thank you to all of the research assistants in the LANG lab who have helped with many aspects of my research, and to the participants and families who dedicated their time to these projects. I truly could not have done it without you.

I would be remiss if I did not thank my dearest friends, Kari Maxwell and Sarah Sullivan. You two have been constants in my life and have unwaveringly supported my pursuit of higher education, even if that meant moving far away from you both or disappearing into a work hole. Whenever I emerged you were always ready with a cold drink and a good time. Love you guys!

I am also profoundly grateful to my parents. I can say without a doubt that they are the reason for my success. Dad, you worked day in and day out to provide me with a good life and the opportunities you never had. I will never forget my undergraduate graduation ceremony when I walked across the room to receive my diploma and I heard your voice rise above the others to say, “that’s my daughter”. Your pride was palpable, and my heart was full. As I have continued with my education, I’ve held that memory in my mind, always thankful for your sacrifices and unconditional love. Love you, pops. To my mom, we did it! From late nights helping me get through essays for my classes to making me good home cooked meals, rubbing my back when I was tired of sitting, and providing unending support, there is no way I would be

where I am today without you. You instilled in me a strong sense of purpose, a deep curiosity, and the desire to help those around me. Thank you for everything you've done and continue to do. Love you forever. I would also like to thank my other close family members including my brother, Blaine, and sister-in-law, Riva for always rallying behind me and my uncle Eric and aunt Terry for always showing up to celebrate. I'm so thankful to have you all in my life.

Last but certainly not least, I would like to thank my husband, Steve. I have thought so long about the words I would say to express my love and gratitude for your support and encouragement but there is just no way to sufficiently say what you mean to me. I still vividly remember sitting on a restaurant patio with you in Davis wondering if I was making the right decision to pursue my master's degree in northern CA while you stayed in southern CA. As we sat there, you told me that Davis seemed awesome, and you were looking forward to all the trips you would make to visit me. You eased my worries and made me feel so loved and supported. Fast forward to my Ph.D. program, so much life happened in this short(ish) span of time. We got married, bought a house, and had an awesome little guy. Through all of that, you were my rock, holding down the fort while I disappeared into deadline and dissertation voids and lifting me up when I felt down. We truly are better together. I can't wait for our next adventure together because there is no one I would rather be doing this life with.

Chapter 1, in full, is a reprint of the material as it appears in Abbott, N. T., Baker, C. J., Chen, C., Liu, T. T., & Love, T. E. (2021). Defining hypoperfusion in chronic aphasia: An individualized thresholding approach. *Brain Sciences*, 11(4), 491. The dissertation author was the primary investigator and author of this paper.

Chapter 2, in full, is a reprint of the material as it appears in Abbott, N., & Love, T. (2023). Bridging the Divide: Brain and Behavior in Developmental Language Disorder. *Brain*

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Abbott, N., and Love, T. (2023). Bridging the Divide: Brain and Behavior in Developmental Language Disorder. *Brain Sciences*, 13, 1606.
doi: 10.3390/brainsci13111606.

Akhavan, N., Sen, C., Baker, C., **Abbott, N.,** Ferrill, M., & Love, T. (2022). Do lexical-semantic cues during encoding help subsequent syntactic retrieval during sentence processing in individuals with aphasia? *Brain Sciences*, 12(3), 312.

Abbott, N., Baker, C., Chen, C., Liu, T. & Love, T. (2021). Defining hypoperfusion in chronic aphasia: an individualized thresholding approach. *Brain Sciences*, 11(4), 491.
doi: 10.3390/brainsci11040491.

Abbott, N. T., & Shahin, A. J. (2018). Cross-modal phonetic encoding facilitates the McGurk illusion and phonemic restoration. *Journal of Neurophysiology*, 120(6), 2988-3000.
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ABSTRACT OF THE DISSERTATION

The Brain Basis of Language Impairment Across the Lifespan

by

Noelle Abbott

Doctor of Philosophy in Language and Communicative Disorders

University of California San Diego, 2024

San Diego State University 2024

Professor Tracy Love, Chair

Language is a complex process and a unique human ability. However, this intricate process can become impaired, leading to significant challenges in comprehension and expression. This dissertation focuses on the brain basis of language impairments across two distinct populations: adults with post-stroke aphasia and children with Developmental Language Disorder (DLD). These populations are etiologically distinct; adults with aphasia have acquired

language impairments in an established language and neural system, while children with DLD have language impairments in a developing language and neural system. The dissertation consists of four studies that investigate the brain functions supporting language, focusing on cerebral blood flow (CBF) in both groups and functional connectivity in children with DLD, to better understand the relationship between these measures and language abilities. Chapter 1 emphasizes the importance of characterizing baseline CBF values in individuals with aphasia. This study demonstrates how regions distal to the site of neural damage exhibit reduced CBF, which contributes to resultant language abilities, highlighting the critical need to properly characterize CBF patterns in clinical populations. In Chapter 2, the focus shifts to children with DLD. The neural underpinnings of DLD are not well understood, thus this chapter synthesizes over 50 years of behavioral and neural research in DLD to identify key brain regions of interest (ROIs) and language deficits that characterize the disorder. Chapter 3 builds on these identified ROIs, exploring brain function in children with DLD. Results from this study provide preliminary evidence of a relationship between altered brain function in children with DLD and language impairments. However, Chapter 3 utilized standardized measures of language abilities, which may not capture nuanced differences in real-time language processing. To address this, Chapter 4 employs an online priming paradigm to investigate real-time syntactic dependency linking in children with DLD at regular and slow rates of speech. Results show that children with DLD possess intact linguistic knowledge, but real-time temporal constraints during sentence processing lead to comprehension breakdowns. These studies provide evidence of the impact of altered brain function on language comprehension in language-impaired populations and illustrate the importance of properly characterizing the neural underpinnings of language processing.

INTRODUCTION

Language is a remarkably intricate process that involves rapidly weaving together various linguistic components for successful communication. From the initial encoding of sound to the nuanced pragmatics of conversation, each step in the linguistic process plays a pivotal role in comprehending and producing language. Given the complex interplay of these linguistic components, it is not surprising that the language system is susceptible to impairment. The language network in the brain is comprised of distributed neural regions that all work in conjunction to process and produce language. If any of these regions are altered in any way, it can have downstream consequences for the carefully coordinated network and resulting behavior. As neuroimaging tools have advanced, the field has formed a deeper understanding of the brain's neural architecture through investigations of brain structure and function and the associated language profiles. Through this lens, both acquired brain injuries and neurodevelopmental disorders have offered a window into brain-behavior relationships.

In this dissertation, I explore how variations in brain structure and function impact language comprehension abilities across different language-impaired populations. The aim of this research is to elucidate the neural underpinnings of language with the long-term goal of identifying biomarkers of language impairment across the lifespan. To that end, the dissertation focuses on two etiologically distinct populations: adults with acquired post-stroke aphasia and children with developmental language disorder (DLD). As is discussed in more detail in **Chapter 1**, aphasia is an acquired language disorder that is typically the result of a left hemisphere vascular injury (e.g., clot or hemorrhage) that damages the language regions/networks of the brain. In the case of adult post-stroke aphasia, damage occurs to an already established language and neural system. The resulting impairments provide insight into

brain regions/networks that are crucial for language, as well as basic physiological assumptions (e.g., neurovascular, neurochemical, etc.) that have to be met to support the language system.

In contrast to aphasia (as discussed in **Chapters 2 and 3**), DLD is a neurodevelopmental language disorder that affects a child's ability to comprehend and/or produce spoken, written, or signed language but cannot be attributed to overt neurological damage (like with aphasia), or other factors such as hearing loss, Down syndrome, etc. In the case of DLD, the language and neural systems are still developing, which means that altered development of brain structures and/or brain function is directly related to impaired language processes. By attempting to understand brain-behavior relationships through both acquired and developmental disorders, a more comprehensive picture of the necessary neural architecture supporting language can be formed. It is through these understandings that may help identify biomarkers of language impairment.

Overview of Dissertation

In support of these research goals, this dissertation consists of four studies that explore the relationship between the underlying properties of brain function, including cerebral blood flow (CBF; in adults with post-stroke aphasia and children with DLD) and functional connectivity (in children with DLD) and resulting language abilities.

Chapter 1 emphasizes the importance of characterizing baseline CBF values in individuals with post-stroke aphasia. In this study, we aimed to enhance understanding of neuronal health and functionality in chronic aphasia by focusing on individualized patterns of altered cerebral blood flow (i.e., reduced or hypoperfused brain tissue). The approach involved three key steps: 1) defining hypoperfusion for each participant; 2) utilizing the personalized metrics to gauge the extent of hypoperfused tissue in perilesional bands; and 3) examining the relationship between hypoperfusion in language-related brain regions and language behavior in chronic aphasia. In

this study, we identified viable yet functionally impaired tissue in chronic aphasia and showed that the individualized thresholding approach better accounted for observed language impairments. Overall, the study demonstrated how aberrant brain function contributes to language impairment profiles and highlighted the critical need to properly characterize CBF patterns in clinical populations.

In **Chapter 2**, the focus shifts to children with DLD. As will be discussed in more detail, the brain-behavior basis for DLD is not well understood. The past 50 years of behavioral and neural research in DLD have created an unclear picture of the neural substrates that underlie the observed impairments. Complicating the picture, a number of theoretical accounts have been proposed to characterize language deficits in DLD, but the majority have lacked explanatory power and/or have not encompassed the full range of deficits. In this chapter, we aim to synthesize the neuroimaging research and theoretical accounts of DLD in an attempt to draw clearer connections between brain and language. Though more work is needed to understand the neural underpinnings of DLD, we identified neural regions that have consistently been implicated in DLD and discuss them in light of the theories they support.

Chapter 3 builds on these identified ROIs, exploring measures of brain function (CBF and functional connectivity) in children with DLD. Results from this study provide preliminary evidence of a relationship between altered brain function in children with DLD and language impairments. In particular, we demonstrate that altered coupling between CBF and resting-state functional connectivity in the brain (i.e., an inverse relationship) may underlie language deficits in DLD. However, Chapter 3 utilized standardized measures of language abilities, which may not capture nuanced differences in real-time language processing. To address this, the final chapter, **Chapter 4** employs an online cross-modal picture priming (CMPP) paradigm to

investigate whether children with DLD create syntactic dependency links during online and offline sentence processing and whether speech rate impacts these abilities. Results indicated that during real-time sentence processing children with DLD were able to make the appropriate link between pronouns and antecedents (the noun referred to by the pronoun) when the speech rate was slowed. However, during the offline portion of the task, children with DLD were unable to make the appropriate link regardless of speech rate. Overall, these results suggest that children with DLD possess intrinsic knowledge of syntactic binding principles but require more time to process this information during real-time tasks.

Taken together, these studies provide evidence for the significant impact of altered brain function on language comprehension in language-impaired populations and illustrate the importance of properly characterizing the neural underpinnings of language processing.

References

Fedorenko, E., Ivanova, A. A., & Regev, T. I. (2024). The language network as a natural kind within the broader landscape of the human brain. *Nature Reviews Neuroscience*, 1-24.

Chapter 1
**DEFINING HYPOPERFUSION IN CHRONIC APHASIA: AN INDIVIDUALIZED
THRESHOLDING APPROACH**

Preface

There is a long history in the field of neuroscience and communication disorders of studying people with aphasia (PWA) to better inform understanding of the brain-behavior basis for language. A classic approach in the literature has been to link sites of neural damage to specific language deficits. Though a lot has been learned through this approach, as neuroimaging methods have advanced, so has our understanding of the language network. We now know that the language network is more distributed throughout the brain and has many connections to other regions that support language function. Underlying this language network are a number of functional processes that have to be maintained to support neuronal function, one of which is cerebral blood flow (CBF). There is a tight coupling between neural activity and increased CBF. In PWA, the blood supply system is compromised. In areas surrounding the lesion (perilesional tissue), CBF is often reduced, but additional regions outside of the lesion that appear structurally intact have been shown to be functionally compromised (i.e., hypoperfused). In this chapter, we explore CBF patterns and their relationship to language deficits in PWA. Additionally, we outline an individualized thresholding approach for determining functionally compromised brain tissue. Through this chapter, we emphasize the importance of carefully characterizing underlying processes that support brain function in clinical populations.

Article

Defining Hypoperfusion in Chronic Aphasia: An Individualized Thresholding Approach

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Citation: Abbott, N.T.; Baker, C.J.; Chen, C.; Liu, T.T.; Love, T.E. Defining Hypoperfusion in Chronic Aphasia: An Individualized Thresholding Approach. *Brain Sci.* **2021**, *11*, 491. <https://doi.org/10.3390/brainsci11040491>

Academic Editor: Paola Marangolo

Received: 5 March 2021

Accepted: 12 April 2021

Published: 13 April 2021

Publisher's Note: MDPI stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.



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Abstract: Within the aphasia literature, it is common to link location of lesioned brain tissue to specific patterns of language impairment. This has provided valuable insight into the relationship between brain structure and function, but it does not capture important underlying alterations in function of regions that remain structurally intact. Research has demonstrated that in the chronic stage of aphasia, variable patterns of reduced cerebral blood flow (CBF; hypoperfusion) in structurally intact regions of the brain contribute to persisting language impairments. However, one consistent issue in this literature is a lack of clear consensus on how to define hypoperfusion, which may lead to over- or underestimation of tissue functionality. In the current study, we conducted an exploratory analysis in six individuals with chronic aphasia (>1 year post-onset) using perfusion imaging to (1) suggest a new, individualized metric for defining hypoperfusion; (2) identify the extent of hypoperfused tissue in perilesional bands; and (3) explore the relationship between hypoperfusion and language impairment. Results indicated that our individualized metric for defining hypoperfusion provided greater precision when identifying functionally impaired tissue and its effects on language function in chronic aphasia. These results have important implications for intervention approaches that target intact (or impaired) brain tissue.

Keywords: chronic aphasia; stroke; cerebral blood flow; hypoperfusion; perfusion imaging; perilesional tissue; language behavior; individual differences

1. Introduction

Aphasia is a language impairment that typically results from neurological injury to the perisylvian language zone in the language-dominant hemisphere of the brain (generally the left hemisphere). Aphasia can include disturbances of production and/or comprehension skills for spoken, written and/or signed language modalities. Aphasia is a pervasive disorder, with at least 2 million people in the USA currently living with the disease [1]. Disruption of language abilities has been linked to high levels of depression, poor social outcomes and a reduction in autonomy [2]; and has also been linked to greater levels of stress for caretakers of post-stroke individuals [3]. Given the enormous impact that aphasia has on quality of life for all of those affected, treatment approaches should be aimed at maximizing recovery to promote better outcomes for these individuals. One way to do so is to bootstrap recovery by taking advantage of intact neural mechanisms. This involves understanding both the structural and functional integrity of the brain-language network post-stroke. In this paper, we focus on one measure of brain function, cerebral blood flow (CBF), within structurally intact brain regions to understand how it supports language function and how it can be used to better inform novel treatment approaches in the chronic stage of aphasia.

Since the 1800s, scientists such as Paul Broca and Karl Wernicke have sought to characterize the relationship between different brain structures and their functions by mapping out how damage to a specific brain region alters behavior. However, one of the challenges to this localizationist approach has been that following a stroke, individuals with aphasia (IWA) often demonstrate variable patterns of language impairment and recovery [4,5]. With the advancement of neuroimaging techniques, structure-function relationships have been investigated with more sophisticated methods, such as voxel-based lesion-symptom mapping (VLSM) [6]. Although VLSM has begun to elucidate the role of specific brain regions in language, important individual differences in brain organization and function may be missed by only considering focal lesion damage in isolation, as it assumes normal neurophysiological function in structurally intact brain regions. Indeed, research in aphasia has found that while both lesion size and location are important factors in predicting language behavior post-stroke, factors such as language reorganization, the functional integrity of connected regions, and alterations in vascular physiology contribute to the recruitment of neural tissue [7–9]. Thus, studies that rely solely on structural brain mapping techniques to investigate isolated regions of a behavioral network will inevitably miss functional changes, such as when physical damage to one region of the brain results in disruptions of CBF both near and distal to the lesion, a process known as diaschisis [10–12]. This missing part of the picture is argued to underlie the variability that we see in linking brain and behavior. We believe one way to account for functional brain damage (as opposed to structural) is through the use of perfusion imaging.

1.1. Perfusion

Perfusion refers to the delivery of blood to neural tissue and can be quantified by measuring the amount of blood delivered to a given amount of tissue per unit of time (mL/100 g of tissue/min) [13]. There is a tight coupling between CBF and neuronal activity (e.g., neurovascular coupling) [14]. When blood is perfused throughout the brain, it delivers nutrients such as oxygen and glucose to neural tissue. When a neuron fires, blood flow to that region increases so that it has enough fuel to perform its specified function [15]. This increase in CBF underlies the methods historically used to gauge a region's engagement in behavioral tasks (e.g., fMRI). If CBF to neural tissue is disrupted in any way, it will impact neuronal function, which will ultimately affect behavior.

Throughout the literature, scientists have quantified the amount of CBF needed to sustain neuronal activity. In doing so, these quantified values (described below) have been assumed to capture functionality across individuals. Unfortunately, this standard approach may over- or underestimate the functional integrity of structurally intact neural tissue. Much like individuals demonstrate variability in behavior post-stroke, they also demonstrate variability in how much blood flows to a brain region over a specified time interval. It is these individualized patterns that are key when attempting to link brain and behavior.

CBF ranges change over the lifespan but in general, for unimpaired adults, normal CBF is between 50 and 60 mL of blood/100 g of tissue/min in gray matter [15–17]. According to standard cutoff values, when blood flow falls below 20 mL/100 g of tissue/min, oxygen levels become too low to support optimal neuronal metabolism, leading to impacts on cognitive function [18,19]. As CBF falls below 12 mL of blood/100 g of tissue/min, neurons become oxygen deprived and die, resulting in necrotic brain tissue. When regional baseline CBF levels are adequate enough to sustain neural tissue viability but inadequate for efficient brain function (i.e., within the range 12–20 mL of blood/100 g of tissue/min), they are referred to as hypoperfused, or in other words, are functionally rather than structurally lesioned. Following a stroke, hypoperfusion is commonly seen in regions proximal to the lesion, but prior research has also found that regions distal to the ischemic core may be hypoperfused [20–22]. For IWA, this suggests that hypoperfusion may contribute to language impairments that would not otherwise be predicted by structural brain damage alone.

1.2. Hypoperfusion in Aphasia

The majority of research looking at hypoperfusion in aphasia has focused on the acute stages of stroke, with far less work focusing on the impacts of reduced CBF in chronic stroke (>1 year post-onset). Unlike in acute stroke, studies looking at the role of hypoperfusion in chronic stroke have largely focused on study defined perilesional (i.e., penumbra) tissue, with limited work extending beyond those boundaries. The sparse evidence investigating hypoperfusion in left hemisphere regions outside of the core lesion has suggested that it may provide insight into persisting language impairments and functional recovery in chronic aphasia [12,20,22–25].

In a case study investigating the neural source of reading impairment in a participant with chronic aphasia, Love et al. (2002) found hypoperfusion in two brain areas associated with reading, the angular gyrus and supramarginal gyrus. Interestingly, neither of these regions appeared structurally damaged on an MRI scan suggesting that the impairments demonstrated were due to functional rather than structural brain damage [24]. Similarly, Brumm et al. (2010) found areas of regional hypoperfusion in structurally intact regions in their group of chronic IWA and importantly, demonstrated that the inflow curve (the time it takes CBF to perfuse throughout the brain) may be delayed in individuals with chronic aphasia [20]. This timing of CBF is critical when applying methods that rely on measuring the hemodynamic response during particular behavioral tasks and may be the reason for some discrepant findings in the literature. These patterns have been further demonstrated in a recent study by Robson et al. (2017) where the investigators found that hypoperfused regions outside of core lesions were significantly correlated with behavioral language impairment [12]. These studies suggest that functional brain damage can account for language impairments that would not otherwise be predicted on the basis of structural damage alone and this functional disruption likely introduces variability when attempting to model the roles of specific brain areas in language function.

In addition to remote regional hypoperfusion in chronic aphasia, there also seems to be a correlation between language impairment and CBF in the perilesional tissue surrounding the core lesion, as has been found in acute stroke. As we turn our focus to perilesional tissue in chronic aphasia, we must first point out that there is no clear standard on how to define the extent of perilesional tissue. Early evidence has defined perilesional tissue as extending anywhere from 0 to 15 mm beyond the lesion's border. Richardson et al. (2011) found that perilesional tissue between 3 and 8 mm from the lesion's rim was highly susceptible to hypoperfusion [25]. Similarly, Thompson et al. (2017) found a correlation between language impairment and CBF values in perilesional tissue extending 0–6 mm beyond the lesion's border, with lower values indicating greater impairment [22]. However, they did not find a correlation between CBF values in language regions of interest (ROIs) outside of perilesional tissue and behavioral impairments in the chronic stage. In another study by Fridriksson et al. (2012), the authors explored functional activation changes within perilesional tissue before and after an Anomia treatment protocol and found that increased activation in perilesional tissue was related to increased performance in naming abilities [26]. Interestingly, in this study, the authors attempted to define perilesional tissue based on CBF values and determined that in their sample of patients, functional damage extended up to 15 mm beyond the lesion's border.

Across all of these studies that attempt to identify perilesional tissue, hypoperfusion is not defined based on thresholded values, but instead is based on group-level analyses that explore whether there are significant differences between the affected hemisphere and right hemisphere counterparts. When there is a significant change in CBF from one perilesional ring to the next or when perilesional CBF is similar to CBF in the right hemisphere homologue, it is assumed that the difference indicates an overall change in functionality. However, this may be faulty logic. CBF values, especially post-stroke, are known to vary widely among individuals as a result of autoregulatory processes, vascular changes and age [22,27]. While employing group-level analyses to understand how blood flow impacts language behavior is important, this approach may overlook important

individual patterns that can affect the interpretation of how different regions support language function. Below we present an alternative approach in identifying hypoperfused regions of the brain. To foreshadow, by determining individualized thresholds of CBF, we argue that we can better identify functionally compromised tissue, which will allow us to individually map when perilesional tissue becomes “normal” and better account for language behavior in chronic aphasia.

1.3. The Role of Perilesional Tissue in Chronic Stroke

In order to best understand how to characterize tissue in and around the lesion in the chronic stage, we must first look at how affected tissue is defined during the acute stages of stroke. In the acute stage, immediately after the stroke, there are three identifiable regions of affected brain tissue: (1) the ischemic core, or necrotic brain tissue that has been irreversibly damaged; (2) the ischemic penumbra, or tissue surrounding the ischemic core that is susceptible to infarction if reperfusion does not occur within a timely manner; and (3) an area of benign oligemia, the area between the unaffected region and the ischemic penumbra [28,29]. In the subacute stage, during the first three to six months after the ischemic core has resolved, the remaining perilesional tissue surrounding the core lesion becomes prone to cellular changes that promote neurogenesis and ultimately lead to reorganization of function [30]. During this stage, there may be functional changes in brain regions connected to the ischemic core and penumbra (i.e., diaschisis) [31]. However, as blood flow surrounding the lesion increases, areas of remote dysfunction begin to resolve [32]. Thus, in the subacute stage, functional brain changes are highly influenced by CBF in regions both proximal and distal to the lesion [30]. Finally, in the chronic stage, the areas directly affected by the stroke include the ischemic core and the perilesional tissue surrounding it (i.e., the ischemic penumbra). Perilesional tissue has been the subject of many studies aimed at recovery of language in the chronic stage as the tissue is functionally compromised but still remains viable [26,33–36]. Due to the cellular changes and restoration of blood flow that occur in the acute stages of stroke, it is reasonable to believe that the extent of perilesional tissue varies across individuals in the chronic stage and may contribute to variability in behavior.

1.4. The Current Study

In this exploratory investigation, we examined whether determining hypoperfusion based on individual patterns better allows for an understanding of neuronal health and functionality in chronic aphasia by (1) first defining hypoperfusion in each of our participants; (2) then using these individualized metrics to determine the extent of hypoperfused tissue in perilesional bands; and (3) exploring how hypoperfusion in language regions of the brain is related to language behavior in chronic aphasia. In doing so, this will allow us to better define when perilesional tissue (which has been the target of many treatment studies) becomes functionally more “normal” and will help us identify functionally affected, but viable tissue in chronic aphasia. We argue that approaching diagnosis and treatment with information on both structural and functional integrity of the brain’s language network can aid translational researchers in developing novel treatment approaches to language impairment as well as clinicians in identifying treatment approaches that take advantage of intact mechanisms to maximize recovery.

2. Methods

2.1. Participants

All participants were diagnosed with aphasia following a single (first time), left hemisphere ischemic stroke and were in the chronic stage (>4 years post-onset). Participants included 6 individuals with aphasia (IWA; 2 females) with a mean age at testing of 63 years old (range = 55–76 years old). A summary of demographic information is provided in Table 1. There were no reports of pre-morbid neurological or psychiatric disorders, or active or significant drug or alcohol abuse. All participants were native English speakers,

had normal or corrected visual acuity and hearing, and were pre-morbidly right-handed. Participants were recruited from San Diego State University (SDSU) and University of California, San Diego (UCSD) and were compensated for their time. This study was approved under both universities' IRB protocols.

Table 1. Demographic information and language assessment scores.

Participant	Sex/Age/Years Post-Stroke	Education (Years)	Aphasia Subtype ¹	BDAE-3 ² Severity (1 = Severe, 5 = Mild)	BDAE-AC ³ Percentile	WAB-AQ ⁴ Max = 100	WAB-AC ⁵ Percentile
S01	M/55/15	17	Broca's	2	21	67.7	72
S02	M/67/9	20	Broca's	3	65	82.6	91
S03	F/65/7	16	Anomic	4	90	95.8	100
S04	M/59/4	12	Broca's	2	35	28.2 *	80
S05	M/58/5	-	Broca's	2	11	50.8	72
S06	F/76/6	12	Anomic	3	78	88.2	89

¹ Based on WAB-R subtypes. ² BDAE-3: Boston Diagnostic Aphasia Examination—3rd edition severity rating scale (1 = severe, 5 = mild);

³ BDAE-AC: auditory comprehension composite (AC) score based on the BDAE-3 auditory comprehension subtests; ⁴ WAB-AQ: Western Aphasia Battery-Aphasia Quotient, measure of aphasia severity derived from the WAB-Revised (R) assessment (<50 = severe, 51–70 = moderate, >71 = mild); ⁵ WAB-AC: auditory comprehension composite (AC) score based on the WAB-R auditory comprehension subtests. * WAB-AQ score was low due to an inability to perform the repetition and overt naming tasks. Note: Education information was unavailable for S05.

2.2. Behavioral Measures

Aphasia subtype, extent and severity were determined based on clinical consensus and standardized language assessments, including the Boston Diagnostic Aphasia Examination, version 3 (BDAE-3) and the Western Aphasia Battery-Revised (WAB-R) [37,38]. The WAB-R is a standardized assessment comprised of multiple cognitive and linguistic subtests. Aphasia diagnosis and an aphasia severity quotient (AQ) were derived from the WAB-R. Lower AQ scores indicate a more severe language impairment. Additionally, we assessed auditory comprehension through the BDAE-3 and WAB-R subtests (BDAE-AC and WAB-AC, respectively; see Table 1 for scores).

3. Neuroimaging Analysis

3.1. Image Acquisition

High-resolution structural scans were acquired at the UCSD Center for Functional MRI using a General Electric (GE) Discovery MR750 3.0T whole-body scanner equipped with an 8-channel head coil. Anatomical imaging was performed using an inversion prepared fast spoiled gradient-echo (FSPGR) sequence that yielded T₁-weighted images with 1 mm isotropic resolution. Other parameters were as follows: field of view (FOV) = 25 cm, repetition time (TR) = 8.1, echo time (TE) = 3.1 ms, inversion time (TI) = 450 ms, flip angle 12°, 172 sagittal slices, 256 × 128 matrix, total scan time = 7:30 min.

Resting-state cerebral blood flow (CBF) data were acquired using an optimized pseudo-continuous arterial spin labeling sequence (Opt-PCASL). With this method, the magnetization of protons in the blood is inverted using RF pulses. The inverted magnetization is then used as an endogenous tracer to track blood flow throughout the brain [39]. Unlike the conventional PCASL method, which is sensitive to phase tracking errors that can lead to inaccurate CBF estimates, Opt-PCASL employs an additional prescan procedure to determine optimal RF phase and in-plane gradient amplitudes [40]. Scan parameters were as follows: labeling duration = 1.9 s, post-labeling delay = 2.0 s, two background suppression pulses with inversion times of 1570 ms and 390 ms, TE = 3.2 ms, TR = 4.5 s, slices = 20, slice thickness = 6 mm, FOV = 22 cm, matrix size = 64 × 64, total scan time = 9:54 min.

A time-of-flight angiogram was acquired using a 3D spoiled gradient echo sequence to define the optimal tagging plane location for continuous inversion of arterial blood during the Opt-PCASL sequence described above (FOV = 22 cm, TR = 20 ms, TE = 2.7 ms, flip angle 15°, axial slice thickness = 1.0 mm, 0.43 × 0.43 × 1.0 mm³ resolution, total scan

time = 1:55 min). The tagging plane was located by visually examining the angiogram to find where the carotid and vertebral arteries were most parallel to one another and perpendicular to the tagging plane. A proton-density weighted scan was acquired to measure the equilibrium magnetization (M_0), which is used to convert the ASL difference signal into physiological units (i.e., 100 mL of blood/100 g of tissue/min; TR = 4000 ms, TE = 3.3 ms, 9 repetitions with a 90° excitation pulse turned off for the first 8 repetitions, only the 9th image is used; total scan time = 40 s) [41].

3.2. MRI Data Processing

3.2.1. T₁-Weighted Structural Images

For anatomical processing, the T₁-weighted structural images were registered to the ASL data and segmented into gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF). These steps were performed using tools from Analysis of Functional NeuroImages software (AFNI), and FMRI Software Library (FSL), respectively [42,43]. Structural images were then manually skull stripped in AFNI by creating individual, hand-drawn brain masks in native space which were used to exclude any voxels outside of brain tissue. This allowed for more accurate results near areas of lesioned tissue. Individual brain hemisphere masks were also created from the whole-brain masks to determine the total volume of each participant's left and right hemisphere (Table 2). Finally, all structural data were resampled to match the resolution of the ASL data.

Table 2. A summary of lesion information and brain volume for each participant.

Participant	Lesion Location	LH ¹ Brain Volume (cc ³)	RH ² Brain Volume (cc ³)	Lesion Volume (cc ³)	% Lesion in LH
S01	L inferior and posterior frontal lobe w/subcortical extension; anterior, superior and middle temporal lobe; inferior, anterior and posterior parietal lobe	540.90	619.85	172.52	31.90
S02	L inferior and posterior frontal lobe w/subcortical extension; superior and middle temporal lobe; inferior and anterior parietal lobe	557.25	611.24	146.27	26.25
S03	L posterior frontal lobe with subcortical structures	426.01	517.34	23.26	5.46
S04	L medial and posterior frontal lobe; superior and middle temporal lobe; anterior parietal lobe	544.43	580.05	66.03	12.13
S05	L inferior and posterior frontal lobe w/subcortical extension; superior and middle temporal lobe; anterior, posterior, superior and inferior parietal lobe; middle and superior occipital lobe	436.17	487.67	180.60	41.41
S06	L superior temporal lobe	352.06	389.63	12.06	3.43

¹ LH: left hemisphere; ² RH: right hemisphere; cc³: cubic centimeters; percent (%) lesion in LH was calculated by dividing the lesion volume by the LH brain volume.

To allow us to investigate hypoperfusion within different regions of interest (ROIs), the anatomical images were transformed from native space to the Montreal Neurological Institute (MNI) Colin27 brain by first masking out lesioned brain tissue using manually delineated lesion masks, then using FSL FLIRT to perform affine registration, and finally performing an additional non-linear registration using in-house software. Once transformed, ROIs were labeled using the Automated Anatomical Labeling (AAL) atlas [44]. Linear registration was used to align the AAL atlas with the T₁ anatomical and CBF images so that we could extract mean CBF values in our ROIs. All values within the AAL ROIs reflect the remaining CBF in intact tissue, as lesioned brain tissue was removed from the analysis. Finally, all structural data were resampled to match the resolution of the ASL data.

3.2.2. Lesion and Perilesional Masks

To determine the extent of structural brain damage within the left hemisphere, lesion masks were manually created for each participant in native space by delineating damaged brain tissue on the T₁-weighted images using AFNI (see Figure 1 for lesion overlap map). Total lesion volume was calculated in cubic centimeters (cc³) and percent tissue damage in the left hemisphere was calculated by dividing the lesion volume by the total left hemisphere volume (see Table 2). To systematically investigate the perilesional region, four 3-mm (mm) lesion masks were created, one that extended 0–3 mm (3 mm) beyond the lesion's border, one that extended 3–6 mm (6 mm), another that extended 6–9 mm (9 mm) and a final one that extended 9–12 mm (12 mm). Perilesional masks were then resampled to the resolution of the ASL data and only those voxels that were at least 60% occupied by non-zero, positive values were kept to account for partial voluming effects near the lesion. The original lesion masks and the perilesional masks were flipped to the right hemisphere, to create five additional right hemisphere ROIs (right lesion, right 3 mm perilesional band, right 6 mm perilesional band, right 9 mm perilesional band, and right 12 mm perilesional band). Mean CBF within each ROI was then calculated for each participant.

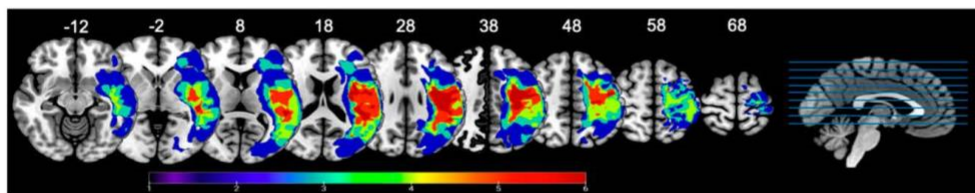


Figure 1. Lesion overlay maps illustrating lesion location and extent in our sample of 6 participants. Heat maps correspond to the number of patients that have a lesion in that area. Lesions are overlaid on labeled axial slices (z-coordinates) from the SPM152 template; SPM: Statistical Parametric Mapping. Images are presented in radiological view (i.e., left hemisphere is on the right side).

3.3. ASL Data

ASL data were processed using code originally developed for the Cerebral Blood Flow Biomedical Informatics Research Network (CBFBIRN) analysis pipeline [45]. This code included several MATLAB scripts for field map correction and quantification of CBF and utilized AFNI for the volume registration and alignment steps. The ASL data were field map corrected and volume registered, while the M₀ data were aligned to the ASL data. Finally, the ASL data were quantified into physiological CBF units via local tissue correction with the aligned M₀ data.

To minimize partial volume effects due to reduced CBF values in white matter or increased volume of CSF within damaged tissue areas [46], we adopted the method described by Johnson et al. (2005) [47]. With this method, CSF is assumed to have a CBF value

of 0, while GM is assumed to have a CBF value that is 2.5 times greater than the value in WM. Therefore, to calculate corrected CBF values, we used the following formula:

$$CBF_{corrected} = CBF_{uncorrected} / (f_{GM} + (0.4 \times f_{WM}))$$

where f_{GM} and f_{WM} denote the partial volume fractions. To make sure there were no spurious CBF values due to noise, the $CBF_{corrected}$ data were then thresholded to remove any CBF values outside of the range of 0–130 mL blood/100 g tissue/min. This range was selected to allow for the possibility of both hypo- and hyper-perfused tissue. The thresholded CBF maps were then overlaid on top of the segmented gray matter images to create gray matter CBF maps. Importantly, any gray matter voxels that overlapped with the left hemisphere lesion mask were removed. This allowed us to exclude the lesion when calculating CBF within specific ROIs, as values of zero within the lesion lead to substantially smaller CBF values. The gray matter CBF maps were then overlaid on top of the AAL atlas to determine the mean CBF within each ROI for each participant. Importantly, since lesioned tissue was excluded in our calculations, any CBF values of zero were likely the result of partial voluming effects between the gray matter CBF maps and the ROIs. Thus, any voxels with a CBF value of zero were excluded from the mean calculation.

4. Results

All analyses were performed using R [48]. For each analysis, areas of lesioned tissue were excluded from the calculations as very low CBF values within the lesion (group level: $M = 10.12$, $SD = 5.79$) would substantially lower the left hemisphere mean value (group level: $M = 46.94$, $SD = 16.14$).

4.1. CBF Comparisons: Left Versus Right Hemisphere

To understand general CBF patterns within gray matter for each participant, we calculated the mean, standard deviation, and median CBF values within the whole brain (global CBF), the left hemisphere (CBF_{LH}), and the right hemisphere (CBF_{RH}). These metrics were calculated at both the group- and individual- levels (the median was to ensure that average CBF_{RH} was not heavily influenced by extreme values; Table 3). To demonstrate the extent of the differences between CBF_{RH} and CBF_{LH} values, a perfusion ratio was also calculated (CBF_{LH}/CBF_{RH}); where values < 1 indicate lower CBF_{LH} , and values > 1 indicate greater CBF_{LH} .

An analysis of variance (ANOVA) showed that at the **group level**, there were significant differences in mean CBF_{LH} ($M = 46.94$, $SD = 16.14$) and mean CBF_{RH} ($M = 54.92$, $SD = 16.14$), $F(1,5) = 17.62$, $p = 0.009$, with the left hemisphere having overall lower CBF (perfusion ratio = 0.85). This pattern was similar to what was seen at the individual level (reported below), but individual analyses allowed for a more fine-grained interpretation of differences in CBF between the two hemispheres.

To determine whether there was a difference in mean CBF values between the two hemispheres at the **individual level**, paired t-tests were conducted. Results showed that there were significant differences between left and right hemisphere CBF for all participants except for S03 (as shown in Table 3). For those who had a significant difference, mean CBF_{LH} was less than mean CBF_{RH} as indicated by the perfusion ratios. For S03, the perfusion ratio was 0.95, which indicates that the left hemisphere was lower than the right on average, but this difference was not statistically significant. When comparing the results from the group analysis to the individual analysis, we see that group analysis did not capture the similarity between CBF in the two hemispheres for S03, whereas individual-level analyses not only captured this difference but allowed for a more comprehensive picture of the integrity of the remaining structurally intact left hemisphere.

Table 3. CBF (mL/100 g tissue/min) values in gray matter for the whole brain, left (CBF_{LH}) and right (CBF_{RH}) hemispheres. Functionally compromised brain tissue (bolded) was calculated based on 1.5 standard deviations (SD) below mean CBF_{RH}. A perfusion ratio was calculated by dividing CBF_{LH} by CBF_{RH} to demonstrate the extent of differences between the two hemispheres. Values < 1 indicate lower CBF_{LH} and values > 1 indicate greater CBF_{LH}. * Indicates a significant difference at $p < 0.05$.

	Group-Level	S01	S02	S03	S04	S05	S06
Whole Brain CBF mean (SD)	50.97 (16.61)	30.06 (10.69)	62.66 (13.73)	44.18 (12.48)	56.44 (11.13)	58.62 (14.45)	54.42 (12.37)
Mean CBF _{LH} (SD)	46.94 (16.14)	24.29 (8.85)	58.36 (13.26)	43.14 (12.51)	54.44 (11.68)	51.18 (11.68)	50.95 (11.88)
Median CBF _{LH}	47.73	23.63	60.46	43.55	57.05	52.1	51.31
Mean CBF _{RH} (SD)	54.92 (16.14)	35.71 (9.29)	66.78 (13.02)	45.23 (12.51)	58.35 (10.35)	65.56 (13.39)	57.90 (11.99)
Median CBF _{RH}	57.04	34.9	68.75	43.91	60.55	67.57	60.11
Functionally compromised CBF (1.5 SD below mean CBF_{RH})	30.71	21.77	47.25	26.46	42.83	45.48	39.91
<i>t</i> -test results: Mean CBF _{LH} versus CBF _{RH}	F(1,5) = 32.03, $p < 0.00001$ *	t(44) = −5.94, $p < 0.00001$ *	t(44) = −3.00, $p < 0.01$ *	t(44) = −0.79, $p > 0.05$	t(44) = −1.66, $p = 0.05$ *	t(44) = −5.29, $p < 0.00001$ *	t(44) = −2.76, $p < 0.01$ *
Perfusion Ratio (CBF _{LH} / CBF _{RH})	0.85	0.68	0.87	0.95	0.93	0.78	0.88

4.2. Lesion Size and CBF

Although there is a relationship between lesion size, lesion location and language recovery in post-stroke individuals with aphasia, a link between lesion size and overall CBF in the remaining intact tissue of the left hemisphere has not been established [9,49,50]. To directly test whether CBF values are influenced by the amount of structural damage within the left hemisphere, we looked for a correlation between CBF in the remaining left hemisphere (without the lesion) and the percent of lesion damage in the left hemisphere at the group level. Results showed no relationship between CBF in the intact left hemisphere and percent damage, $r(4) = -0.19$, $p = 0.72$ (Figure 2). Comparisons using *t*-tests at the individual level illustrate this pattern further. For example, S05, who has the largest lesion in our sample (41.4% lesion damage in the left hemisphere), showed no significant differences in CBF compared to S06 who has the smallest lesion (3.5% lesion damage in the left hemisphere; $t(84) = 0.09$, $p = 0.47$). S04, who has a medium size lesion in our sample (12.1% lesion damage in the left hemisphere), and S02, who has a large lesion (26.3% lesion damage in the left hemisphere), again showed no significant differences in CBF when compared to one another ($t(84) = -1.46$, $p = 0.07$). From our current sample, lesion size does not appear to influence CBF values in the remaining intact left hemisphere; in other words, a small lesion does not imply that the remaining tissue will be functional.

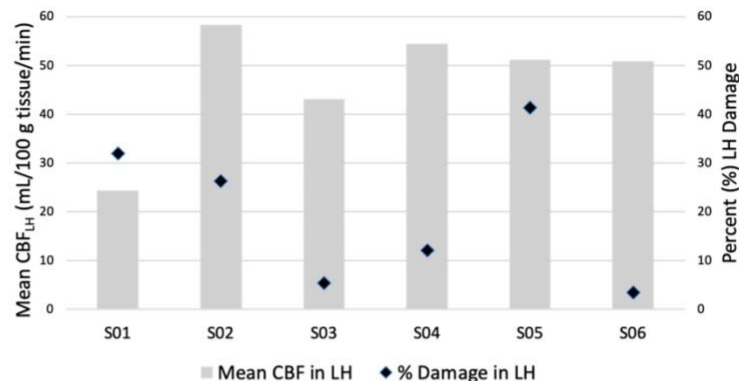


Figure 2. A comparison between mean CBF in remaining intact tissue of the left hemisphere (CBF_{LH}) and percent lesion damage in the left hemisphere (LH). There is no clear relationship between mean CBF_{LH} and lesion size in our sample which suggests that CBF in remaining intact tissue is not influenced by lesion size alone.

Thus far, we have demonstrated that after a stroke, CBF patterns are lower in the remaining tissue of the left hemisphere as compared to the right hemisphere, and this is true at the group level and for the majority of our participants at the individual level. We have also shown that the size of the lesion itself does not impact overall CBF values of the remaining tissue in the left hemisphere. We now turn to the question of how to best define functionally compromised tissue in the remaining intact tissue of the left hemisphere.

4.3. Defining Functionally Compromised Brain Tissue

Recall, one of the goals of this paper was to establish individualized thresholds of CBF in chronic aphasia so we can better identify functionally compromised tissue. To accomplish this, we had to determine what constituted “normal” and “functionally compromised” CBF for each participant. Since our participants have no overt evidence of right hemisphere stroke or injury, we chose to use each participant’s average CBF_{RH} as their normal value. We acknowledge here that evidence in the literature has pointed to right hemisphere engagement in certain behaviors following a left hemisphere stroke [51]. We chose to compare CBF_{LH} to average CBF_{RH} so as to capture comparable regions in the non-lesioned hemisphere. In spite of the potential increase in CBF_{RH} , we believe that this is the correct contrast as: (1) these were resting-state scans, so theoretically there should not have been behaviorally driven increases in CBF; and (2) in addition to the mean, we also calculated each participant’s median and standard deviation in the right hemisphere (see Table 3) and found no significant differences between the mean and median ($t(5) = -1.56, p = 0.09$).

Our next step after establishing a normal CBF value for each participant was to identify hypoperfused tissue. As discussed previously, there are certain physiological requirements needed for neuronal health and function. One aspect that was missing in the previous discussion was how neuronal function is impacted when CBF values are between 25 and 50 mL/100 g tissue/min. According to a more fine-grained description, when CBF is between 25 and 50 mL/100 g tissue/min, cellular and chemical changes in the brain begin to take place, such as a decline in protein synthesis (~ 50 mL/100 g tissue/min) and an increase in glutamate (~ 30 mL/100 g/min), which can trigger the release of destructive enzymes [52,53]. Many of these changes lead to the activation of coordinated activities within the brain to protect the viability of neurons, the vasculature, and other cells and systems [54]. In the chronic stage post-stroke, certain areas of brain tissue may exist within this perpetually compromised state by which tissue remains viable through compensatory mechanisms but is functionally altered. We wish to point out here that there are potential

problems with interpreting functionality based on these strict number scales. For example, one of our participants (S03) has an average CBF value for their intact right hemisphere that falls in this potentially compromised range, but their CBF_{RH} does not link directly to impairment as noted by their low severity indices on the BDAE-3 and WAB-AQ (see Table 1). Using the standard cutoff values to identify functionally compromised tissue in this case demonstrates how incorrect conclusions can be made. We therefore argue that it is critical to calculate individualized CBF thresholds to determine functionally compromised tissue.

In an attempt to better specify hypoperfused tissue, we considered functionally compromised tissue conservatively as being 1.5 standard deviations below average CBF_{RH} for each of our participants (see Table 3 for values). After establishing an individualized threshold for hypoperfusion in each of our participants, we used those CBF thresholds to (1) individually map CBF changes in perilesional tissue (extending outward from 0 mm to 12 mm in 3 mm bands, Section 4.4), (2) examine hypoperfusion in language regions of the left hemisphere (Section 4.5), and (3) link these patterns to language behavior (Section 4.6). For readers who are interested in changes within the perilesional tissue, we provide additional analyses in the Appendix that explores (at both the group- and individual- levels) CBF_{LH} in the four 3 mm perilesional bands compared to homologue (CBF_{RH}) 3 mm bands (Appendix A) as well as individual intrahemispheric (CBF_{LH}) differences across the four perilesional bands (Appendix B).

4.4. Defining Hypoperfusion within Perilesional Rings: Individualized Thresholding

In this section, we individually identified functionally affected brain tissue based on 1.5 standard deviations below each participant's mean CBF_{RH} and compared these values across all four perilesional bands. At the group level, CBF values in the 0–3 mm band did not differ from the calculated threshold of hypoperfusion ($1.5\text{ SD} < \text{mean } CBF_{RH}$, $t(5) = -1.18$, $p = 0.15$). Unsurprisingly, this replicates findings that tissue in the 0–3 mm band is dysfunctional/hypoperfused. This hypoperfused 0–3 mm band is statistically different at the group level from all the other bands (3–6 mm: $t(5) = 6.69$, $p = 0.001$; 6–9 mm: $t(5) = 5.52$, $p = 0.001$; and 9–12 mm: $t(5) = 4.96$, $p = 0.002$).

This landscape changed when looking at **individual patterns** of CBF in each of the perilesional bands. As can be seen in Figure 3, in the 0–3 mm band, CBF values were at or below the cutoff threshold for all participants. As we moved outward from the lesion's rim, CBF values within the perilesional bands increased by different amounts for each participant, but overall, we saw a return toward “normal” blood flow values outside of the 0–3 mm band. We argue that our individualized thresholding provides precision in determining when perilesional tissue approximates “normal” on a case-by-case basis.

4.5. Identifying Hypoperfused Tissue in Language Regions

Recall that the individuals under investigation in this paper are individuals with aphasia (IWA) who have language impairments post-stroke. Throughout this paper, we emphasized the importance of looking at individualized CBF metrics for understanding brain function post-stroke, particularly in a population whose recovery is influenced by a variety of factors that can affect CBF. We demonstrated its importance in defining functionally compromised brain tissue through group versus individual-level and standard versus individualized threshold analyses.

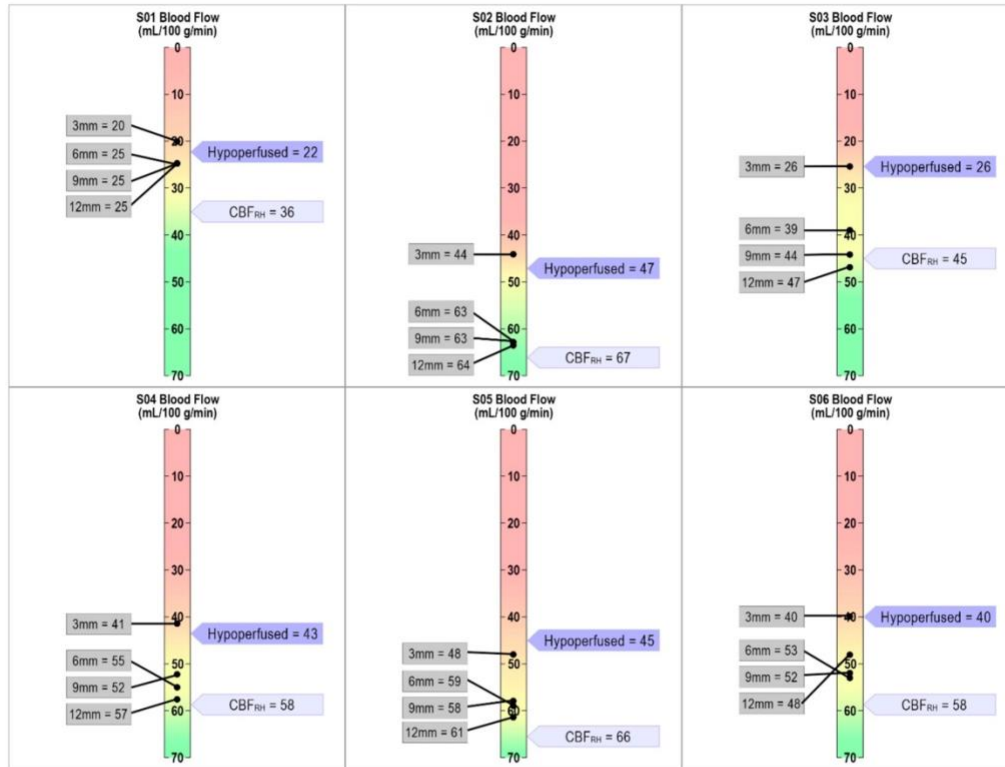


Figure 3. Individualized CBF threshold maps for each participant. The dark purple flag indicates when tissue is hypoperfused based on the individually defined approach of 1.5 SD below CBF_{RH} . The light purple flag indicates average CBF_{RH} . The gray boxes show CBF values for each of the four 3mm perilesional bands. As can be seen in the figure, the 0–3mm band is either at or below the individually defined threshold for hyperfusion for each participant.

In this section, we explore how determining hypoperfused tissue through individual thresholding better aligns with observed language-impaired behavior in IWA, as other approaches are likely to miss compromised brain regions within the left hemisphere language network. We examined mean CBF values in the remaining intact tissue of 11 left hemisphere language ROIs for each participant (see Appendix C, Table A4 for mean CBF values). Table 4 shows the percentage of tissue remaining with hypoperfused values noted in two distinct ways: (1) individual threshold calculations ($1.5 \text{ SD} < CBF_{RH}$), shaded blue and (2) standard value thresholds ($<20 \text{ mL}/100 \text{ g of tissue}/\text{min}$), indicated by red font. In doing so we discovered that individualized thresholding identified more regions of compromised tissue (see Table 4). As expected, language ROIs that had less than 10% of intact tissue remaining were mostly hypoperfused. What we want to focus attention on here is that if we were to use the standard cutoff thresholds, we would miss cases such as those found in S04, where the middle temporal pole has 100% of tissue intact but the CBF value was approximately $32 \text{ mL}/100 \text{ g tissue}/\text{min}$. This value, it turns out, is below this participant's 1.5 SD cutoff of their mean CBF_{RH} , rendering it functionally compromised. This discrepant pattern of amount of tissue remaining and functionality can be seen across participants and ROIs only when using individualized threshold calculations (blue shading in Table 4). This suggests that evidence of structurally viable tissue alone does not translate

to functionality of that region. Individualized thresholding of CBF is the only way to determine whether tissue near or far from the lesion is functionally compromised.

Table 4. A comparison of individualized and standard hypoperfusion approaches in structurally intact brain tissue. Percentages represent the amount of tissue remaining in each ROI after accounting for the lesion. Blue shading = hypoperfused based on 1.5 standard deviations below mean CBF_{RH} . Red text = hypoperfused based on standard threshold values (<20 mL/100 g tissue/min). The total number of ROIs categorized as hypoperfused using each hypoperfusion metric is reported at the bottom of the table.

Language ROI	S01	S02	S03	S04	S05	S06
Pars Opercularis (BA44)	14.3%	27.8%	83.3%	92.2%	97.0%	99.9%
Pars Triangularis (BA45)	59.6%	98.9%	99.6%	100.0%	70.9%	100.0%
Pars Orbitalis (BA47)	85.7%	100.0%	100.0%	100.0%	79.5%	100.0%
Insula	3.1%	53.0%	96.8%	59.3%	70.4%	99.0%
Superior Temporal Lobe (STL)	15.6%	3.7%	100.0%	39.0%	25.9%	74.7%
Superior Temporal Pole (STP)	29.8%	93.3%	100.0%	98.0%	100.0%	100.0%
Middle Temporal Lobe (MTL)	82.1%	30.3%	100.0%	59.7%	41.9%	93.5%
Middle Temporal Pole (MTP)	44.1%	100.0%	100.0%	100.0%	100.0%	100.0%
Supramarginal Gyrus (SMG)	7.6%	30.1%	99.9%	54.6%	2.1%	51.2%
Angular Gyrus (AG)	94.8%	98.2%	100.0%	66.7%	2.9%	91.0%
Inferior Parietal Lobule (IPL)	56.9%	76.4%	100.0%	87.6%	6.4%	95.5%
Number of ROIs hypoperfused with standard cutoffs	3 out of 11	0 out of 11	0 out of 11	0 out of 11	3 out of 11	0 out of 11
Number of ROIs hypoperfused with individualized cutoffs	5 out of 11	4 out of 11	1 out of 11	4 out of 11	6 out of 11	2 out of 11

4.6. Hypoperfusion and Language Behavior

These data, as presented, lay the foundation to raise questions regarding existing attempts in the literature to link brain and language behavior. A recurring issue in the literature is the reproducibility of lesion patterns and language behavior post-stroke. Here, we argue that areas of the brain functionally impacted by stroke are often overlooked when modeling language networks. Furthermore, the way in which functionally compromised

brain tissue is identified has been coarse grained at best. Below we present exploratory analyses (due to the small sample size) that looks at correlations between hypoperfused tissue (defined individually and by standard cutoffs) and language abilities. To do this, we performed two different point-biserial correlations using both our individualized metric and the standard cutoff CBF metric. In these analyses, we included hypoperfusion as a binary variable within all of our language ROIs and compared that to performance on three different language assessments, one measuring overall language severity (WAB-AQ) and two measuring basic auditory comprehension skills (BDAE-AC and WAB-AC; See Table 1 for individual scores and section “2.2. Behavioral Measures” for details on the assessments).

As a check on our language metrics, we found that both auditory comprehension (AC) subtests of the BDAE-3 and WAB-R were correlated with one another ($r(5) = 0.97$, $p = 0.001$). When looking at correlation results using standard cutoff values, the only areas that were correlated with AC language performance were the angular gyrus (AG) and the inferior parietal lobule (IPL) (Table 5). The WAB-AQ did not correlate with any regions of interest. However, when we performed this same analysis using our individualized hypoperfusion metrics, we found a significant relationship between multiple temporal and parietal regions and our language measures.

Table 5. A comparison of significant correlations between frontal, parietal and temporal ROIs and language measures using individual versus standard (<20 mL/100 g of tissue/min) hypoperfusion metrics. Gray shading represents significant correlations using the individualized approach not apparent with standard cutoffs. ¹ WAB-AQ: Western Aphasia Battery-Aphasia Quotient; ² WAB-AC: auditory comprehension composite (AC) score; ³ BDAE-AC: auditory comprehension (AC) composite score; * $p < 0.05$; ** $p < 0.01$; + $p < 0.06$; - no hypoperfusion found for any of the participants.

	Individual Cutoffs			Standard Cutoffs		
	WAB-AQ ¹	WAB-AC ²	BDAE-AC ³	WAB-AQ ¹	WAB-AC ²	BDAE-AC ³
WAB-AQ ¹	1			1		
WAB-AC ²	0.71 +	1		0.71 +	1	
BDAE-AC ³	0.77 *	0.97 **	1	0.77 *	0.97 **	1
Pars Opercularis (BA44)	−0.26	−0.31	−0.23	−0.26	−0.31	−0.23
Pars Triangularis (BA45)	−	−	−	−	−	−
Pars Orbitalis (BA47)	−	−	−	−	−	−
Insula	−0.39	−0.14	−0.13	0.02	0.52	0.44
Superior Temporal Lobe (STL)	0.64	0.29	0.44	0	0	0
Superior Temporal Pole (STP)	0.39	0.14	0.13	−0.37	−0.22	−0.43
Middle Temporal Lobe (MTL)	0.29	0.83 *	0.82 *	0.023	0.52	0.44
Middle Temporal Pole (MTP)	0.14	0.14	0.01	0.02	0.52	0.44
Supramarginal Gyrus (SMG)	0.89 **	0.55	0.65	0.34	0.52	0.59
Angular Gyrus (AG)	0.29	0.83 *	0.82 *	0.29	0.83 *	0.82 *
Inferior Parietal Lobule (IPL)	0.29	0.83 *	0.82 *	0.29	0.83 *	0.82 *

With the standard cutoff approach, we expected a relationship to be revealed in temporal regions since they have been implicated in auditory comprehension but did not find one [55–57]. The pattern in the temporal lobe did emerge when we used individualized thresholding to define hypoperfused tissue which is more in line with the literature linking auditory comprehension to regions within the temporal lobe. These patterns of results are indicative of how using individualized metrics of tissue function can provide insight into disruptions of language behavior in chronic aphasia.

As a follow up to the significant correlations seen in the MTL, IPL and AG, we examined these results at the individual level (Figure 4). Interestingly, we found that the two individuals with Broca's aphasia who performed the worst on both the BDAE-AC and the WAB-AC (S01 and S05) showed structural and functional damage in all three of these ROIs. The two individuals with Anomic aphasia who performed well on both auditory comprehension subtests (S03 and S06) showed no involvement of any of these ROIs. What we believe to be quite intriguing was that the two individuals with Broca's aphasia (S02 and S04) who showed poor performance only on the BDAE-AC (which has a subtest that taps into semantic-conceptual knowledge, unlike the WAB-R), had structural but not functional damage in a subset of these three ROIs. While there is not enough data to interpret this pattern, it demonstrates that further investigation is warranted. Overall, these results suggest that information about both the structural and functional integrity of brain regions is important to consider for explaining language behavior outcomes.

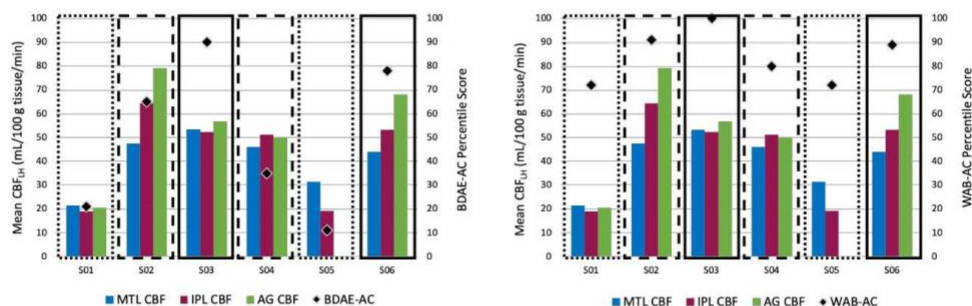


Figure 4. Individual CBF patterns in ROIs that were significantly correlated with the BDAE-AC (left) and the WAB-AC (right) and percentile scores. Dotted boxes represent individuals with Broca's aphasia who performed the worst on the two auditory comprehension measures. Dashed boxes represent individuals with Broca's aphasia who performed poorly on the BDAE-AC but not the WAB-AC. Solid boxes represent individuals with Anomic aphasia who performed well on the two auditory comprehension measures. MTL: medial temporal lobe; IPL: inferior parietal lobe; AG: angular gyrus. *Note:* S05 had a CBF value near zero in the AG, likely due to a small number of voxels not included in the lesion mask.

Though the results presented in this section are only exploratory given our sample size, they do show the utility of investigating how individualized CBF metrics relate to language behavior. They also have implications for language treatment techniques, such as non-invasive brain stimulation (NIBS), that target regions of the brain that will likely respond to treatment. By using an individualized approach for defining hypoperfused tissue, both the structural and functional integrity of brain regions can be considered, which may enhance the accuracy of treatment protocols.

5. Discussion

The aim of the current study was to explore an alternative approach to investigating functional integrity of brain regions in chronic aphasia. In this study, we measured cerebral blood flow (CBF) in six individuals using a resting-state perfusion imaging scan protocol. With these data, we compared mean CBF in the left (CBF_{LH}) and right hemispheres (CBF_{RH}) at both the group and individual levels, revealing overall lower CBF values in the left compared to the right hemisphere. We also showed that lesion size alone does not determine the level of CBF found in the remaining intact tissue in the left hemisphere. In service of our goal of identifying a better way to determine whether structurally intact tissue is functionally operational, we contrasted two approaches across our participants (standard cutoff and individualized thresholds). We argued that an individualized approach provides a more accurate representation for participants when mapping out functionally compromised tissue across four different 3 mm perilesional bands. Finally, we provided preliminary

evidence that this individualized approach better links brain function to language behavior by analyzing CBF values in 11 different language regions of interest (ROIs).

Hypoperfusion, or reduced CBF, is often considered to be limited to the regions within and directly surrounding the lesion in chronic aphasia, but prior research has demonstrated that regions both near and remote from the lesion can be affected by the stroke. Given the close relationship between neuronal function and CBF, disruptions of CBF can have downstream effects on behavior. In regard to aphasia, these disruptions generally occur within the language network and can adversely affect language abilities. Yet, when considering the impact of a stroke on language behavior, many research studies focus solely on relating structural damage to language impairment. However, we know that certain areas of the brain, such as perilesional tissue, can be functionally compromised despite not having any obvious structural damage. Regions such as these may contribute to language impairments that would not otherwise be predicted on the basis of structural damage alone.

Across the aphasia literature, there is a lack of clear criteria for defining perilesional tissue or defining when tissue becomes functionally compromised. Studies that investigate these factors most commonly conduct analyses at the group level, which means that important individual differences may be overshadowed by group effects. What constitutes hypoperfusion for one participant may not be as accurate for another, as CBF is moderated by many factors. While informative, these group-level analyses tend to base functionality off of whether there are significant differences between an affected region of interest and another unaffected region, often in the right hemisphere. As this may overshadow important differences at the individual level, we advocate for using an individualized approach. Additionally, standard threshold values for defining hypoperfused tissue (50–60 mL/100 g/min = normal; 12–20 mL/100 g/min = hypoperfused; <12 mL/100 g/min = necrotic) may over- or underestimate functionality. Between 25 and 50 mL/100 g/min a number of cellular changes occur that could impact function. The brain has built-in compensatory mechanisms to try to mitigate these effects, but it is possible that when CBF is within this range, brain function is altered.

Therefore, in this study, in an effort to explore individual differences in brain tissue functionality, we first compared CBF_{LH} to CBF_{RH} . We saw similar patterns at both the group- and individual- level, where, unsurprisingly, CBF_{LH} was lower than CBF_{RH} . Our next question was whether CBF in the remaining intact left hemisphere was impacted by lesion size. The results showed no clear relationship between lesion size and CBF, suggesting that additional factors beyond lesion size may influence CBF values in the intact left hemisphere in chronic aphasia.

After investigating overall differences between CBF_{LH} and CBF_{RH} , we defined normal and hypoperfused tissue for each of our participants (see Appendices A and B for additional comparisons). To do this, we used each participant's CBF_{RH} to determine "normal" tissue function. We then identified hypoperfused tissue by calculating 1.5 standard deviations (SD) below each participant's mean CBF_{RH} . By using the mean CBF_{RH} , it allowed us to consider CBF across a wider cortical network of regions rather than just one particular region. Our individualized approach revealed that the perilesional tissue 0–3 mm from the lesion's rim approximated 1.5 SD below mean CBF_{RH} , the threshold we determined to define hypoperfused tissue. As we expanded these bands outwards, the CBF values increased in different ways across our participants but never quite reached CBF_{RH} (except for 1 participant). These differing patterns indicated that for some, tissue as close as 3–6 mm from the lesion's border began to approximate 'normal' CBF function.

All of these results underscore the necessity of identifying the structural and functional integrity of brain regions when attempting to link brain and behavior. Structural lesion mapping techniques have provided important insights into this link but variability amongst participants often clouds this picture. The addition of functional integrity measures may help account for some of this variability. By individually mapping out functionally compromised brain tissue we can begin to understand how it may uniquely

contribute to behavior. To zero in on this in terms of language function, we identified hypoperfusion in our 11 language ROIs based on both our individualized hypoperfusion metric as well as the standard hypoperfusion metric ($<20 \text{ mL}/100 \text{ g}/\text{min}$). Our goal was to compare the number of ROIs that emerged as hypoperfused, so we could understand the sensitivity of these two approaches. When we looked at hypoperfusion at the group level with both individualized and standard cutoff values, none of the ROIs emerged as being compromised. However, at the individual level, our individualized thresholding approach classified more ROI tissue as hypoperfused. This means that analyses at the group level would have missed multiple language regions that are functionally compromised, while standard cutoff values would have underestimated the extent of functional damage.

Exploratory correlational analyses were conducted to gauge links between hypoperfusion in language related ROIs and behavioral language patterns, as it is argued that discrepancies in the literature may be driven by a lack of consideration for how functionally compromised brain regions impact behavior. To provide assurance in our analyses, we found that all our language measures were significantly correlated with one another. When we explored the link between language and CBF patterns, we found a discrepant pattern between the two different approaches for defining hypoperfused tissue. While both approaches found links between auditory comprehension and the inferior parietal lobe and angular gyrus, only the individualized thresholding revealed links to the middle temporal lobe. These results are promising as temporal lobe damage has been strongly linked to comprehension impairments in aphasia. Here, we were looking at pure functional damage rather than structural which means that information about the functional integrity of brain regions can potentially help explain language impairment and can account for differences reported in the literature. This first step in defining functionally compromised tissue lays the groundwork for future studies to investigate structure-function relationships in language impairment and more broadly, other cognitive deficits.

6. Limitations of the Current Study

The goal of this exploratory study was to define an individualized metric for determining hypoperfusion in chronic aphasia and to investigate whether this metric better accounted for language impairments post-stroke. Within the aphasia literature, individual-level analyses are less common than group-level analyses. As such we provided preliminary evidence from a small sample of six individuals with chronic aphasia to advocate for the necessity of individual-level studies. Moving forward, future studies would benefit from larger sample sizes to allow for the use of more robust statistical measures that link patterns of hypoperfusion to language impairment. Additionally, in this study, our participants ranged in lesion size and aphasia severity. From our results we showed that lesion size was not related to CBF in the left hemisphere and that patterns of hypoperfusion using our individualized metric seemed to correlate with language behavior, but again because of our small sample size, it is difficult to generalize.

Finally, we acknowledge that without T2 FLAIR imaging, we are unable to confirm whether or not there are microvascular changes in the right hemisphere. Nevertheless, we do not believe that this impacts our interpretation of the performance of regions in the left hemisphere compared to the right. Recall that individualized thresholding was based on measuring whether or not CBF values fell 1.5 SD outside of mean CBF_{RH} . Microvascular changes would introduce more variability which would have ultimately reduced our ability to identify areas as hypoperfused.

7. Conclusions

Overall, results from this study revealed important individual differences in CBF values that should be considered when mapping out functionally compromised brain tissue. These individual differences are often lost at the group level but may actually help in modeling structure-function relationships in the brain. When trying to predict language function based on structural damage alone, certain behaviors may be falsely attributed

to patterns of structural damage or may be overlooked all together. In this paper, we argued the importance of uniquely defining functional impairment for every participant. Though this work can be time consuming with large sample sizes, it may better account for the variability in CBF patterns across individuals and may link to behavioral changes post-stroke. Given that numerous investigative (e.g., VLSM) and intervention (e.g., NIBS) techniques rely on the identification of intact (or impaired) brain regions, we believe that this approach can have widespread implications for theoretical modeling. Furthermore, approaching diagnosis and treatment with information about both the functional and structural integrity of the language network can help with bootstrapping recovery and developing novel approaches to treatment.

Author Contributions: Conceptualization, N.T.A., C.J.B. and T.E.L.; methodology, N.T.A., C.J.B., C.C., T.T.L. and T.E.L.; formal analysis, N.T.A., C.J.B. and C.C.; investigation, T.E.L.; writing—original draft preparation, N.T.A.; writing—review and editing, N.T.A., C.J.B., C.C., T.T.L. and T.E.L.; supervision, N.T.A. and T.E.L.; visualization, N.T.A., C.J.B. and T.E.L.; funding acquisition, N.T.A. and T.E.L. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by NIH NIDCD award numbers T32 DC007361 (PI T.E.L., trainee N.T.A.), R21 DC015263 (T.E.L.), and R01 DC009272 (T.E.L.).

Institutional Review Board Statement: This study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Institutional Review Board of the University of California, San Diego and San Diego State University (IRB number: 171023, continuous approval since 06-03-2015).

Informed Consent Statement: Informed consent was obtained from all subjects involved in this study.

Data Availability Statement: The data used to support the findings of this publication can be requested from the corresponding author upon request.

Acknowledgments: We thank Natalie Sullivan, David Shin, Frank Haist, Peter Pieperhoff, and Katrin Amunts for their assistance during various stages of data collection and processing, and all of our participants, their families, and our funding agencies for supporting this work.

Conflicts of Interest: The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

Appendix A. Perilesional Masks: Left Hemisphere Versus Right Hemisphere

We tested overall CBF differences at the group level in each perilesional band across the two hemispheres. We conducted a 2 (hemisphere: left versus right) $\times$ 4 (perilesional bands: 3 mm, 6 mm, 9 mm, and 12 mm) ANOVA. As expected, results showed a main effect of hemisphere ($F(1, 40) = 6.31, p = 0.02$), indicating greater CBF_{RH} ($M = 55.16, SD = 10.93$) than CBF_{LH} ($M = 46.11, SD = 13.74$). There were no significant main effects for the perilesional bands ($F(3, 40) = 0.43, p = 0.74$) or the hemisphere $\times$ perilesional bands interaction ($F(3, 40) = 1.42, p = 0.25$).

This landscape changed when looking at **individual patterns** of CBF within the perilesional bands across the two hemispheres. T-test were conducted for each participant to compare each perilesional band to its right hemisphere homologue (Bonferroni corrected for multiple (4) comparisons; see Table A1 for a full list of t-statistics and p -values). To get a better sense of the extent of differences between each hemisphere, we also calculated a perfusion ratio (CBF_{LH}/CBF_{RH}). Individual results revealed different patterns as to when perilesional tissue had CBF values in the left hemisphere that were similar to the right hemisphere. Within the 3 mm perilesional band, each participant had significant differences in left versus right CBF. As we moved outward, we saw differences across participants as to *if* and *when* CBF became comparable to the right hemisphere homologue band; again, a nonsignificant difference with the right hemisphere is a measure we take to reflect functionally spared tissue. Significant differences between the left and right homologue bands persisted in the 3–6 mm band in all but 1 participant (S03, though see

note for S04). Moving outward to the 6–9 mm band, differences persisted for 4 of the 6 participants. In the 9–12 mm band, differences remained for only 3 of the participants (S01, S05, S06; though see the note for S05). We note that these participants have different scaled lesions—the former two having the largest lesions of the group and the latter having the smallest lesion of the group, indicating again that lesion size does not seem to impact CBF in the intact left hemisphere.

Table A1. Mean CBF (mL/100 g tissue/min) values in the four left hemisphere (CBF_{LH}) and four right hemisphere (CBF_{RH}) perilesional bands. Paired t-test results are given for CBF_{LH} versus CBF_{RH} differences. A perfusion ratio was calculated by dividing CBF_{LH} by CBF_{RH} to demonstrate the extent of differences within perilesional bands between the two hemispheres. Values < 1 indicate lower CBF_{LH}, and values > 1 indicate greater CBF_{LH}. Bold values indicate that there was a significant difference in CBF values between the two hemispheres at $p < 0.05$. * indicates that the p -value survived Bonferroni correction at $p < 0.0125$.

	S01	S02	S03	S04	S05	S06
Perilesion: 0–3 mm						
Mean CBF _{LH} (SD)	20.04 (19.41)	44.47 (28.36)	25.71 (19.66)	41.30 (22.24)	47.53 (21.68)	40.22 (22.70)
Mean CBF _{RH} (SD)	41.81 (23.56)	68.00 (24.90)	49.81 (23.81)	62.83 (21.72)	64.07 (25.00)	61.23 (22.38)
t-test: CBF _{LH} vs. CBF _{RH}	t(826) = −14.59, $p < 0.00001$ *	t(880) = −13.11, $p < 0.00001$ *	t(297) = −10.50, $p < 0.00001$ *	t(138) = −8.30, $p < 0.00001$ *	t(650) = −10.42, $p < 0.00001$ *	t(307) = −8.45, $p < 0.00001$ *
CBF _{LH} /CBF _{RH} ratio	0.48	0.65	0.52	0.66	0.74	0.66
Perilesion: 3–6 mm						
Mean CBF _{LH} (SD)	25.21 (21.28)	62.51 (28.19)	38.86 (22.52)	55.38 (23.46)	59.24 (22.75)	53.02 (26.57)
Mean CBF _{RH} (SD)	39.13 (24.47)	67.99 (25.61)	41.00 (24.48)	59.10 (22.11)	65.32 (25.36)	63.90 (24.83)
t-test: CBF _{LH} vs. CBF _{RH}	t(768) = −8.47, $p < 0.00001$ *	t(612) = −2.70, $p = 0.004$ *	t(273) = −0.83, $p = 0.20$	t(408) = −1.68, $p = 0.05$	t(644) = −3.28, $p = 0.0005$ *	t(247) = −3.35, $p = 0.0005$ *
CBF _{LH} /CBF _{RH} ratio	0.64	0.92	0.95	0.94	0.91	0.83
Perilesion: 6–9 mm						
Mean CBF _{LH} (SD)	24.70 (18.75)	62.67 (26.97)	43.73 (23.87)	51.97 (21.40)	57.83 (20.71)	52.38 (27.69)
Mean CBF _{RH} (SD)	35.74 (21.92)	64.82 (29.21)	44.75 (23.90)	58.63 (23.69)	62.40 (24.31)	60.10 (25.54)
t-test: CBF _{LH} vs. CBF _{RH}	t(754) = −7.48, $p < 0.00001$ *	t(570) = −0.91, $p = 0.18$	t(347) = −0.41, $p = 0.34$	t(451) = −3.15, $p = 0.0009$ *	t(601) = −2.52, $p = 0.006$ *	t(294) = −2.53, $p = 0.006$ *
CBF _{LH} /CBF _{RH} ratio	0.69	0.97	0.98	0.89	0.93	0.87

Table A1. Cont.

	S01	S02	S03	S04	S05	S06
Perilesion: 9–12 mm						
Mean CBF _{LH} (SD)	24.66 (17.72)	64.10 (27.37)	46.45 (22.87)	57.11 (22.40)	61.17 (25.37)	47.99 (21.52)
Mean CBF _{RH} (SD)	32.96 (21.49)	62.20 (29.14)	44.01 (25.63)	58.09 (23.93)	56.61 (24.05)	59.47 (25.03)
<i>t</i> -test: CBF _{LH} vs. CBF _{RH}	<i>t</i> (768) = −5.90, <i>p</i> < 0.00001 *	<i>t</i> (589) = 0.81, <i>p</i> = 0.21	<i>t</i> (348) = 0.94, <i>p</i> = 0.17	<i>t</i> (496) = −0.47, <i>p</i> = 0.32	<i>t</i> (526) = 2.13, <i>p</i> = 0.02	<i>t</i> (420) = −5.10, <i>p</i> < 0.00001 *
CBF _{LH} / CBF _{RH} ratio	0.75	1.03	1.06	0.98	1.08	0.81

As demonstrated by the perfusion ratios in Table A1, the greatest differences between CBF_{LH} and CBF_{RH} were in the 3 mm perilesional band, where CBF_{LH} was significantly lower than CBF_{RH}. As perilesional bands expanded out to 6 mm and 9 mm, the perfusion ratios between left and right CBF increased such that CBF_{LH} was closer to the level of CBF_{RH}. By the 12 mm band, three participants (S02, S03, and S05) had greater CBF_{LH} than CBF_{RH}; this difference was only significant for S05. In summary, as the perilesional rings extended outward from the lesion's rim, we saw variability when participants showed CBF_{LH} values that were comparable to CBF_{RH} values in the homologue region, if they did at all. This variability was not linked to lesion size as some with larger lesions showed a return to CBF_{RH} levels earlier than those with smaller lesions (e.g., S02 vs. S06).

Appendix B. Left Hemisphere Perilesional Bands

To better understand how CBF in perilesional bands within the left hemisphere changes at the group level, we looked at the six planned comparisons shown in Table A2 (Bonferroni corrected for multiple comparisons).

Table A2. An illustration of the six planned comparisons across the perilesional bands.

	Planned Comparisons		
	3–6 mm	6–9 mm	9–12 mm
0–3 mm	X	X	X
3–6 mm		X	X
6–9 mm			X

As shown in Table A3, only the comparison between the 0–3 mm and 9–12 mm perilesional bands yielded significant results (*t* (10) = −1.8, *p* = 0.047), indicating that CBF in the 9–12 mm band (*M* = 48.89, *SD* = 27.31) was significantly greater than CBF in the 0–3 mm band (*M* = 37.02, *SD* = 25.87), but this comparison did not survive multiple comparisons correction.

Table A3. Comparisons of CBF patterns at each perilesional band for group and individual levels. ¹ Group-level analyses were conducted with mean CBF values across all participants. Underlined *p*-values reflect trends at the *p* < 0.06 level. Bolded values are significant at *p* < 0.05. * indicates that the *p*-value survived Bonferroni correction at *p* < 0.0083.

Perilesional Bands	Group Level ¹	S01	S02	S03	S04	S05	S06
0–3 mm to 3–6 mm	$t(10) = -1.69$, <u>$p = 0.06$</u>	$t(692) = -3.40$, $p = 0.0004$ *	$t(656) = -8.71$, $p < 0.00001$ *	$t(244) = -4.92$, $p < 0.00001$ *	$t(186) = -4.91$, $p < 0.00001$ *	$t(573) = -6.33$, $p < 0.00001$ *	$t(233) = -4.46$, $p < 0.00001$ *
0–3 mm to 6–9 mm	$t(10) = -1.74$, <u>$p = 0.06$</u>	$t(703) = -3.27$, $p = 0.0006$ *	$t(598) = -8.74$, $p < 0.00001$ *	$t(287) = -7.03$, $p < 0.00001$ *	$t(162) = -3.91$, $p = 0.00008$ *	$t(550) = -5.72$, $p < 0.00001$ *	$t(270) = -4.30$, $p = 0.00001$ *
0–3 mm to 9–12 mm	$t(10) = -1.85$, $p = 0.05$	$t(731) = -3.41$, $p = 0.0003$ *	$t(609) = -9.40$, $p < 0.00001$ *	$t(283) = -8.23$, $p < 0.00001$ *	$t(160) = -5.83$, $p < 0.00001$ *	$t(513) = -6.76$, $p < 0.00001$ *	$t(387) = -3.48$, $p = 0.0003$ *
3–6 mm to 6–9 mm	$t(10) = 0.01$, $p = 0.50$	$t(673) = 0.33$, $p = 0.37$	$t(579) = -0.07$, $p = 0.47$	$t(274) = -1.77$, $p = 0.04$	$t(402) = 1.56$, $p = 0.06$	$t(540) = 0.75$, $p = 0.23$	$t(263) = 0.19$, $p = 0.42$
3–6 mm to 9–12 mm	$t(10) = -0.15$, $p = 0.44$	$t(670) = 0.37$, $p = 0.36$	$t(586) = -0.69$, $p = 0.25$	$t(268) = -2.80$, $p = 0.003$ *	$t(414) = -0.80$, $p = 0.21$	$t(522) = -0.93$, $p = 0.18$	$t(222) = 1.79$, $p = 0.04$
6–9 mm to 9–12 mm	$t(10) = -0.17$, $p = 0.44$	$t(695) = 0.03$, $p = 0.49$	$t(557) = -0.62$, $p = 0.27$	$t(321) = -1.04$, $p = 0.15$	$t(485) = -2.60$, $p = 0.005$ *	$t(498) = -1.64$, $p = 0.05$	$t(258) = 1.59$, <u>$p = 0.06$</u>

Similar to the **group level**, the same planned comparisons (Bonferroni corrected for six comparisons) were conducted at the **individual level** to compare adjacent bands to one another within the left hemisphere. All participants showed significant differences between the 0–3 mm band and all the other bands (3–6 mm, 6–9 mm, and 9–12 mm; see Table A3 for a list of *t*-statistics and *p*-values). Clearly, all participants have dysfunctional tissue adjacent to the lesion. Patterns began to diverge across participants as we moved outwards from the 0–3 mm band (see Figure 3 in main text). Specifically, only S03 began to show differentiation between the 3–6 mm and 6–9 mm bands. This continued to the outermost (9–12 mm) band, where we identified “normal” tissue by 9 mm outside of the lesion rim. Other participants showed different patterns. For example, S04 showed differentiation as early as the second band (3–6 mm). From these results and the group-level analyses, it is clear that participants show variable patterns of CBF within the perilesional bands, as well as across the two hemispheres. At the group level, some important patterns were detected, but when exploring the same comparisons at the individual level, more regional differences were illuminated. These differences may be important when using perilesional tissue information in designing individual treatment plans.

Summary

To better understand CBF values surrounding the lesion, we looked at CBF in perilesional tissue. Based on prior research, we divided the tissue into four different 3 mm bands that extended 0–12 mm outside of the lesion’s border (0–3 mm, 3–6 mm, 6–9 mm, and 9–12 mm) and looked at differences in the perilesional bands between the left and right hemispheres. At the group level, there was a significant effect of hemisphere, indicating that CBF in right hemisphere perilesional bands was higher than CBF in left hemisphere perilesional bands, but there were no other significant effects or interactions. However, at the individual level, this pattern changed. There were significant differences between CBF_{LH} and CBF_{RH} for each participant in the 0–3 mm band. Within the other bands, results varied across participants, for some there were significant differences between left and right while for others there were not.

We also explored individual patterns within the left hemisphere by comparing CBF values across each perilesional band. Once again, at the group level, we found an underestimation of differences as only one comparison between the closest band to the lesion's rim (0–3 mm) and the farthest band (9–12 mm) was found to be significantly different, though they did not survive multiple comparisons correction. As we probed these effects at the individual level, we found different patterns across participants. These differences are important to understand because they potentially indicate different patterns of neuronal function outside of lesioned tissue. All participants seemed to have reduced CBF just outside of the lesion (within the 0–3 mm band), but this landscape changed for each participant in unique ways as the perilesional band expanded further out. These patterns can help inform the extent of functional damage in intact brain tissue outside of the lesion and may implicate different regions that would not otherwise be detected when modeling brain and behavior.

Appendix C

Table A4. A comparison of hypoperfused ROIs based on individualized (blue shading) and standard (red font) threshold values at both the group and individual level. The numbers in the table represent mean CBF (mL/100 g tissue/min) in that left hemisphere (LH) ROI. * values of 0 likely reflect a small number of voxels that were not captured in the original lesion mask due to their proximity to large sulci.

Language ROI (LH)	Group	S01	S02	S03	S04	S05	S06
Functionally compromised CBF (1.5 SD below mean CBF _{RH})	30.71	21.77	47.25	26.46	42.83	45.48	39.91
Pars Opercularis (BA44)	46.12	30.64	40.79	30.27	57.12	70.49	47.43
Pars Triangularis (BA45)	54.77	22.31	76.19	50.10	67.64	55.08	57.32
Pars Orbitalis (BA47)	52.38	25.98	67.44	39.85	61.50	56.79	62.75
Insula	41.36	16.55	56.07	25.27	48.78	52.07	49.46
Superior Temporal Lobe (STL)	42.89	44.20	40.35	48.72	29.94	45.00	49.13
Superior Temporal Pole (STP)	34.74	21.83	43.98	43.55	32.93	44.43	21.71
Middle Temporal Lobe (MTL)	40.70	21.62	47.57	53.40	46.18	31.45	44.00
Middle Temporal Pole (MTP)	32.65	15.64	43.12	35.06	31.82	46.67	23.58
Supramarginal Gyrus (SMG)	31.86	25.21	49.90	39.45	36.28	0.00 *	40.34
Angular Gyrus (AG)	45.78	20.65	79.13	56.83	49.95	0.00 *	68.15
Inferior Parietal Lobule (IPL)	43.22	19.00	64.30	52.26	51.19	19.25	53.31
Number of ROIs hypoperfused with standard cutoffs	0 out of 11	3 out of 11	0 out of 11	0 out of 11	0 out of 11	3 out of 11	0 out of 11
Number of ROIs hypoperfused with individualized cutoffs	0 out of 11	5 out of 11	4 out of 11	1 out of 11	4 out of 11	6 out of 11	2 out of 11

References

1. National Aphasia Association. Aphasia Statistics. 2016. Available online: <https://www.aphasia.org/aphasia-resources/aphasia-statistics/> (accessed on 13 December 2020).
2. Spaccavento, S.; Craca, A.; del Prete, M.; Falcone, R.; Colucci, A.; di Palma, A.; Loverre, A. Quality of life measurement and outcome in aphasia. *Neuropsychiatr. Dis. Treat.* **2014**, *10*, 27. [CrossRef]
3. Bakas, T.; Kroenke, K.; Plue, L.D.; Perkins, S.M.; Williams, L.S. Outcomes among family caregivers of aphasic versus nonaphasic stroke survivors. *Rehabil. Nurs.* **2006**, *31*, 33–42. [CrossRef]
4. Duncan, E.S.; Small, S.L. Increased modularity of resting state networks supports improved narrative production in aphasia recovery. *Brain Connect.* **2016**, *6*, 524–529. [CrossRef] [PubMed]
5. Lazar, R.M.; Speizer, A.E.; Festa, J.R.; Krakauer, J.W.; Marshall, R.S. Variability in language recovery after first-time stroke. *J. Neurol. Neurosurg. Psychiatry* **2008**, *79*, 530–534. [CrossRef] [PubMed]
6. Bates, E.; Wilson, S.M.; Saygin, A.P.; Dick, F.; Sereno, M.I.; Knight, R.T.; Dronkers, N.F. Voxel-based lesion–symptom mapping. *Nature Neurosci.* **2003**, *6*, 448–450. [CrossRef] [PubMed]

7. Kiran, S.; Thompson, C.K. Neuroplasticity of language networks in aphasia: Advances, updates, and future challenges. *Front. Neurol.* **2019**, *10*, 295. [\[CrossRef\]](#)
8. Skipper-Kallal, L.M.; Lacey, E.H.; Xing, S.; Turkeltaub, P.E. Right Hemisphere Remapping of Naming Functions Depends on Lesion Size and Location in Poststroke Aphasia. *Neural Plast.* **2017**, *2017*, 8740353. [\[CrossRef\]](#) [\[PubMed\]](#)
9. Thyé, M.; Mirman, D. Relative contributions of lesion location and lesion size to predictions of varied language deficits in post-stroke aphasia. *Neuroimage Clin.* **2018**, *20*, 1129–1138. [\[CrossRef\]](#)
10. Crinion, J.; Holland, A.L.; Copland, D.A.; Thompson, C.K.; Hillis, A.E. Neuroimaging in aphasia treatment research: Quantifying brain lesions after stroke. *Neuroimage* **2013**, *73*, 208–214. [\[CrossRef\]](#)
11. Hillis, A.E.; Heidler, J. Mechanisms of early aphasia recovery. *Aphasiology* **2002**, *16*, 885–895. [\[CrossRef\]](#)
12. Robson, H.; Specht, K.; Beaumont, H.; Parkes, L.M.; Sage, K.; Ralph, M.A.L.; Zahn, R. Arterial spin labelling shows functional depression of non-lesion tissue in chronic Wernicke's aphasia. *Cortex* **2017**, *92*, 249–260. [\[CrossRef\]](#) [\[PubMed\]](#)
13. Sorensen, A.G.; Reimer, P. *Cerebral MR Perfusion Imaging: Principles and Current Applications*; Thieme: Stuttgart, Germany, 2000.
14. Girouard, H.; Iadecola, C. Neurovascular coupling in the normal brain and in hypertension, stroke, and Alzheimer disease. *J. Appl. Physiol.* **2006**, *100*, 328–335. [\[CrossRef\]](#) [\[PubMed\]](#)
15. Biagi, L.; Abbruzzese, A.; Bianchi, M.C.; Alsop, D.C.; del Guerra, A.; Tosetti, M. Age dependence of cerebral perfusion assessed by magnetic resonance continuous arterial spin labeling. *J. Magn. Reson. Imaging Off. J. Int. Soc. Magn. Reson. Med.* **2007**, *25*, 696–702. [\[CrossRef\]](#)
16. Fantini, S.; Sassaroli, A.; Tgavalekos, K.T.; Kombluth, J. Cerebral blood flow and autoregulation: Current measurement techniques and prospects for noninvasive optical methods. *Neurophotonics* **2016**, *3*, 031411. [\[CrossRef\]](#) [\[PubMed\]](#)
17. Haller, S.; Zaharchuk, G.; Thomas, D.L.; Lovblad, K.O.; Barkhof, F.; Golay, X. Arterial spin labeling perfusion of the brain: Emerging clinical applications. *Radiology* **2016**, *281*, 337–356. [\[CrossRef\]](#) [\[PubMed\]](#)
18. Baron, J.C. Perfusion thresholds in human cerebral ischemia: Historical perspective and therapeutic implications. *Cerebrovasc. Dis.* **2001**, *11*, 2–8. [\[CrossRef\]](#)
19. Botteri, M.; Bandera, E.; Minelli, C.; Latronico, N. Cerebral blood flow thresholds for cerebral ischemia in traumatic brain injury: A systematic review. *Crit. Care Med.* **2008**, *36*, 3089–3092. [\[CrossRef\]](#) [\[PubMed\]](#)
20. Brumm, K.; Gravier, M.; Shapiro, L.; Love, T. Variability in Aphasia: A Neurophysiological Perspective. *Proced. Soc. Behav. Sci.* **2010**, *6*, 98–100. [\[CrossRef\]](#)
21. Hillis, A.E.; Baron, J.C. The ischemic penumbra: Still the target for stroke therapies? *Front. Neurol.* **2015**, *6*, 85. [\[CrossRef\]](#)
22. Thompson, C.K.; Walenski, M.; Chen, Y.; Caplan, D.; Kiran, S.; Rapp, B.; Parrish, T.B. Intrahemispheric perfusion in chronic stroke-induced aphasia. *Neural Plast.* **2017**. [\[CrossRef\]](#)
23. Fridriksson, J.; Rorden, C.; Morgan, P.S.; Leigh Morrow, K.; Baylis, G.C. Measuring the hemodynamic response in chronic hypoperfusion. *Neurocase* **2006**, *12*, 146–150. [\[CrossRef\]](#)
24. Love, T.; Swinney, D.; Wong, E.; Buxton, R. Perfusion imaging and stroke: A more sensitive measure of the brain bases of cognitive deficits. *Aphasiology* **2002**, *16*, 873–883. [\[CrossRef\]](#)
25. Richardson, J.D.; Baker, J.M.; Morgan, P.S.; Rorden, C.; Bonilha, L.; Fridriksson, J. Cerebral perfusion in chronic stroke: Implications for lesion-symptom mapping and functional MRI. *Behav. Neurol.* **2011**, *24*, 117–122. [\[CrossRef\]](#)
26. Fridriksson, J.; Richardson, J.D.; Fillmore, P.; Cai, B. Left hemisphere plasticity and aphasia recovery. *Neuroimage* **2012**, *60*, 854–863. [\[CrossRef\]](#)
27. Bertsch, K.; Hagemann, D.; Hermes, M.; Walter, C.; Khan, R.; Naumann, E. Resting cerebral blood flow, attention, and aging. *Brain Res.* **2009**, *1267*, 77–88. [\[CrossRef\]](#)
28. Gauberti, M.; de Lizarondo, S.M.; Vivien, D. The “inflammatory penumbra” in ischemic stroke: From clinical data to experimental evidence. *Eur. Stroke J.* **2016**, *1*, 20–27. [\[CrossRef\]](#) [\[PubMed\]](#)
29. Manning, N.W.; Campbell, B.C.; Oxley, T.J.; Chapot, R. Acute ischemic stroke: Time, penumbra, and reperfusion. *Stroke* **2014**, *45*, 640–644. [\[CrossRef\]](#)
30. Kiran, S. What is the nature of poststroke language recovery and reorganization? *Int. Sch. Res. Not.* **2012**. [\[CrossRef\]](#) [\[PubMed\]](#)
31. Saur, D.; Lange, R.; Baumgaertner, A.; Schraknepper, V.; Willmes, K.; Rijntjes, M.; Weiller, C. Dynamics of language reorganization after stroke. *Brain* **2006**, *129*, 1371–1384. [\[CrossRef\]](#)
32. Cappa, S.F.; Perani, D.; Grassi, F.; Bressi, F.; Alberoni, M.; Franceschi, M.; Fazio, M. A PET follow-up study of recovery after stroke in acute aphasics. *Brain Lang.* **1997**, *56*, 55–67. [\[CrossRef\]](#) [\[PubMed\]](#)
33. Leger, A.; Demonet, J.F.; Ruff, S.; Aithamon, B.; Touyeras, B.; Puel, M.; Cardebat, D. Neural substrates of spoken language rehabilitation in an aphasic patient: An fMRI study. *Neuroimage* **2002**, *17*, 174–183. [\[CrossRef\]](#) [\[PubMed\]](#)
34. Meinzer, M.; Flaisch, T.; Breitenstein, C.; Wienbruch, C.; Elbert, T.; Rockstroh, B. Functional re-recruitment of dysfunctional brain areas predicts language recovery in chronic aphasia. *Neuroimage* **2008**, *39*, 2038–2046. [\[CrossRef\]](#) [\[PubMed\]](#)
35. Turkeltaub, P.E.; Messing, S.; Norise, C.; Hamilton, R.H. Are networks for residual language function and recovery consistent across aphasic patients? *Neurology* **2011**, *76*, 1726–1734. [\[CrossRef\]](#) [\[PubMed\]](#)
36. Vitali, P.; Abutalebi, J.; Tettamanti, M.; Danna, M.; Ansaldo, A.I.; Perani, D.; Cappa, S.F. Training-induced brain remapping in chronic aphasia: A pilot study. *Neurorehabil. Neural Repair* **2007**, *21*, 152–160. [\[CrossRef\]](#) [\[PubMed\]](#)
37. Goodglass, H.; Kaplan, E.; Barresi, B. *BDAE-3: Boston Diagnostic Aphasia Examination*, 3rd ed.; Lippincott Williams & Wilkins: Philadelphia, PA, USA, 2001.

38. Kertesz, A. *Western Aphasia Battery (Revised)*; The Psychological Corporation: San Antonio, TX, USA, 2007.
39. Dai, W.; Garcia, D.; de Bazelaire, C.; Alsop, D.C. Continuous flow-driven inversion for arterial spin labeling using pulsed radio frequency and gradient fields. *Magn. Reson. Med. Off. J. Int. Soc. Magn. Reson. Med.* **2008**, *60*, 1488–1497. [\[CrossRef\]](#) [\[PubMed\]](#)
40. Shin, D.D.; Liu, T.T.; Wong, E.C.; Shankaranarayanan, A.; Jung, Y. Pseudocontinuous arterial spin labeling with optimized tagging efficiency. *Magn. Reson. Med.* **2012**, *68*, 1135–1144. [\[CrossRef\]](#) [\[PubMed\]](#)
41. Alsop, D.C.; Detre, J.A.; Golay, X.; Günther, M.; Hendrikse, J.; Hernandez-Garcia, L.; Zaharchuk, G. Recommended implementation of arterial spin-labeled perfusion MRI for clinical applications: A consensus of the ISMRM perfusion study group and the European consortium for ASL in dementia. *Magn. Reson. Med.* **2015**, *73*, 102–116. [\[CrossRef\]](#)
42. Cox, R.W. AFNI: Software for analysis and visualization of functional magnetic resonance neuroimages. *Comput. Biomed. Res.* **1996**, *29*, 162–173. [\[CrossRef\]](#)
43. Smith, S.M.; Jenkinson, M.; Woolrich, M.W.; Beckmann, C.F.; Behrens, T.E.; Johansen-Berg, H.; Matthews, P.M. Advances in functional and structural MR image analysis and implementation as FSL. *Neuroimage* **2004**, *23*, S208–S219. [\[CrossRef\]](#)
44. Tzourio-Mazoyer, N.; Landeau, B.; Papathanassiou, D.; Crivello, F.; Etard, O.; Delcroix, N.; Joliot, M. Automated Anatomical Labeling of Activations in SPM Using a Macroscopic Anatomical Parcellation of the MNI MRI Single-Subject Brain. *Neuroimage* **2002**, *15*, 273–289. [\[CrossRef\]](#)
45. Shin, D.D.; Ozyurt, I.B.; Liu, T.T. The Cerebral Blood Flow Biomedical Informatics Research Network (CBFBIRN) database and analysis pipeline for arterial spin labeling MRI data. *Front. Neuroinform.* **2013**, *7*, 21. [\[CrossRef\]](#) [\[PubMed\]](#)
46. Parkes, L.M.; Rashid, W.; Chard, D.T.; Tofts, P.S. Normal cerebral perfusion measurements using arterial spin labeling: Reproducibility, stability, and age and gender effects. *Magn. Reson. Med. Off. J. Int. Soc. Magn. Reson. Med.* **2004**, *51*, 736–743. [\[CrossRef\]](#) [\[PubMed\]](#)
47. Johnson, N.A.; Jahng, G.H.; Weiner, M.W.; Miller, B.L.; Chui, H.C.; Jagust, W.J.; Schuff, N. Pattern of cerebral hypoperfusion in Alzheimer disease and mild cognitive impairment measured with arterial spin-labeling MR imaging: Initial experience. *Radiology* **2005**, *234*, 851–859. [\[CrossRef\]](#) [\[PubMed\]](#)
48. R Core Team. *R: A Language and Environment for Statistical Computing*; R Foundation for Statistical Computing: Vienna, Austria, 2020; Available online: <https://www.R-project.org/> (accessed on 17 September 2020).
49. Meier, E.L.; Johnson, J.P.; Pan, Y.; Kiran, S. A lesion and connectivity-based hierarchical model of chronic aphasia recovery dissociates patients and healthy controls. *NeuroImage Clin.* **2019**, *23*, 101919. [\[CrossRef\]](#) [\[PubMed\]](#)
50. Plowman, E.; Hentz, B.; Ellis, C. Post-stroke aphasia prognosis: A review of patient-related and stroke-related factors. *J. Eval. Clin. Pract.* **2012**, *18*, 689–694. [\[CrossRef\]](#)
51. Harvey, D.Y.; Podell, J.; Turkeltaub, P.E.; Faseyitan, O.; Coslett, H.B.; Hamilton, R.H. Functional reorganization of right prefrontal cortex underlies sustained naming improvements in chronic aphasia via repetitive transcranial magnetic stimulation. *Cognit. Behav. Neurol. Off. J. Soc. Behav. Cognit. Neurol.* **2017**, *30*, 133. [\[CrossRef\]](#)
52. Hossmann, K.A. Viability thresholds and the penumbra of focal ischemia. *Ann. Neurol. Off. J. Am. Neurol. Assoc. Child Neurol. Soc.* **1994**, *36*, 557–565. [\[CrossRef\]](#)
53. Markus, H.S. Cerebral perfusion and stroke. *J. Neurol. Neurosurg. Psychiatry* **2004**, *75*, 353–361. [\[CrossRef\]](#)
54. Iadecola, C.; Anrather, J. Stroke research at a crossroad: Asking the brain for directions. *Nature Neurosci.* **2011**, *14*, 1363. [\[CrossRef\]](#)
55. Crinion, J.T.; Lambon-Ralph, M.A.; Warburton, E.A.; Howard, D.; Wise, R.J. Temporal lobe regions engaged during normal speech comprehension. *Brain* **2003**, *126*, 1193–1201. [\[CrossRef\]](#)
56. Dronkers, N.F.; Wilkins, D.P.; van Valin, R.D., Jr.; Redfern, B.B.; Jaeger, J.J. Lesion analysis of the brain areas involved in language comprehension. *Cognition* **2004**, *92*, 145–177. [\[CrossRef\]](#) [\[PubMed\]](#)
57. Bonilha, L.; Hillis, A.E.; Hickok, G.; den Ouden, D.B.; Rorden, C.; Fridriksson, J. Temporal lobe networks supporting the comprehension of spoken words. *Brain* **2017**, *140*, 2370–2380. [\[CrossRef\]](#) [\[PubMed\]](#)

Acknowledgements

Chapter 1, in full, is a reprint of the material as it appears in Abbott, N. T., Baker, C. J., Chen, C., Liu, T. T., & Love, T. E. (2021). Defining hypoperfusion in chronic aphasia: An individualized thresholding approach. *Brain Sciences*, 11(4), 491. The dissertation author was the primary investigator and author of this paper.

Chapter 2
**BRIDGING THE DIVIDE: BRAIN AND BEHAVIOR IN DEVELOPMENTAL LANGUAGE
DISORDER**

Preface

Chapter 1 demonstrated that people with aphasia (PWA) have alterations in cerebral blood flow (CBF) within structurally intact brain regions (i.e., functional lesions) that contribute to observed language behavior. The chapter outlined the importance of properly characterizing the underlying properties that support brain function. For PWA, altered brain structure and function is expected given the overt damage to the brain. However, children with DLD do not have overt damage to the brain, yet they also demonstrate language deficits, suggesting that they may have functional aberrancies within the neural system. Thus, in **Chapter 2**, we first synthesize neuroimaging studies and theoretical accounts of DLD. We then attempt to link them together to create a clearer connection between brain and behavior. Through this work, we identified a small number of brain regions that have been consistently implicated in DLD. Based on these findings, we suggest future directions of research for the field. This includes examining underlying properties that support brain function in DLD, namely CBF and functional connectivity. In **Chapter 3**, we explore these metrics and their relationship to language impairment in typically developing (TD) children and a small subset of children with DLD.

Review

Bridging the Divide: Brain and Behavior in Developmental Language Disorder

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Abstract: Developmental language disorder (DLD) is a heterogeneous neurodevelopmental disorder that affects a child's ability to comprehend and/or produce spoken and/or written language, yet it cannot be attributed to hearing loss or overt neurological damage. It is widely believed that some combination of genetic, biological, and environmental factors influences brain and language development in this population, but it has been difficult to bridge theoretical accounts of DLD with neuroimaging findings, due to heterogeneity in language impairment profiles across individuals and inconsistent neuroimaging findings. Therefore, the purpose of this overview is two-fold: (1) to summarize the neuroimaging literature (while drawing on findings from other language-impaired populations, where appropriate); and (2) to briefly review the theoretical accounts of language impairment patterns in DLD, with the goal of bridging the disparate findings. As will be demonstrated with this overview, the current state of the field suggests that children with DLD have atypical brain volume, laterality, and activation/connectivity patterns in key language regions that likely contribute to language difficulties. However, the precise nature of these differences and the underlying neural mechanisms contributing to them remain an open area of investigation.

Keywords: developmental language disorder; child language disorders; language processing; neuroimaging; MRI; brain-behavior relationship; theoretical accounts



Citation: Abbott, N.; Love, T.

Bridging the Divide: Brain and Behavior in Developmental Language Disorder. *Brain Sci.* **2023**, *13*, 1606. <https://doi.org/10.3390/brainsci13111606>

Academic Editor: Jayanthi Sasisekaran

Received: 15 September 2023

Revised: 14 November 2023

Accepted: 16 November 2023

Published: 19 November 2023



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1. Introduction

Developmental language disorder (DLD) is a heterogeneous neurodevelopmental disorder that affects a child's ability to comprehend and/or produce spoken and/or written language but cannot be attributed to hearing loss or overt neurological damage (coded in the ICD-11 §6A01.2). In recognition of the growing preference for the term DLD, we have chosen to use it for this review instead of specific language impairment (SLI) or developmental dysphasia, though the research referenced throughout includes publications that use both terms. DLD affects around 7% of children in the US making it more prevalent than other neurodevelopmental disorders, such as autism spectrum disorders (ASD) and dyslexia [1–4]. Moreover, adults who were diagnosed with DLD as children often experience anxiety and depression and tend to struggle with social relationships, preferring environments and vocations that do not require strong language and literacy skills [5,6]. Despite the prevalence and profound life-long impact DLD can have on a person, little is understood about the neurological basis or etiology of the disorder or how observed language impairments arise.

DLD is typically diagnosed after the age of 4 (around the time a child enters into preschool), when it becomes clear that the child has fallen behind their same age peers in terms of receptive and expressive language skills [7]. Yet, it is likely that the neural substrates underlying the disorder are in place prior to receiving a diagnosis. Current research

suggests that some combination of genetic and environmental factors influence neural development in this population, but it is unclear if aberrant brain pathology causes DLD or if DLD leads to altered brain structure and function [8]. Further, there is significant debate regarding theoretical accounts of language impairment patterns observed in children with DLD. To date, none of the neurological or theoretical explanations of DLD fully account for the range of symptoms across individuals or the differing results across research studies [9]. This disconnect has resulted in some researchers defining DLD as a heterogeneous disorder that may actually be a spectrum disorder with different phenotypes, like ASD, or may even exist on the same continuum as ASD [10–12].

Core to this paper is the notion that the term heterogeneity is oftentimes misused to describe the differences found across studies that are better attributed to differences in research design (population identification, task demands, etc.). For example, if a study uses an assessment that poorly identifies children who have DLD (i.e., low sensitivity) compared to those who do not (i.e., low specificity), that could lead to the DLD group appearing to have more variability in measured behaviors [13,14]. Task demands may also influence how heterogeneous the DLD group appears, especially if the comparison group is poorly matched on age or other criteria. When studies accurately measure known areas of difficulty for children with DLD, such as morphosyntax, they in fact often perform similarly to one another (i.e., heterogeneity is reduced) [14]. In this overview, we broach the topic of heterogeneity briefly to suggest that children with DLD struggle with a range of linguistic and non-linguistic behaviors, but we do so with the knowledge that within specific domains of language they show more consistent impairment patterns than their typically developing peers. Table 1 outlines language problems commonly reported in children with DLD.

Table 1. Language problems commonly reported in children with DLD. Linguistic categories and descriptions provided are based on the principal dimensions of language difficulty outlined in the CATALISE-2 report [15]. Children with DLD can present with a range of these characteristics, though difficulties with syntax and morphology are ubiquitous in DLD.

Phonology	Syntax/Morphology	Word Finding/ Semantics	Pragmatics/Language Use	Discourse	Verbal Learning/Memory
- Linguistic (not motor) difficulties with phonology - Phoneme substitutions and deletions - Poor phonological awareness	- Difficulty using grammatical features of language (e.g., subject–verb agreement) to convey meaning - Difficulty interpreting meaning conveyed by grammatical markers (e.g., past tense -ed in English)	- Word finding difficulties (may use non-specific words, substitutions, circumlocutions, or avoid topics) - Limited vocabulary use and knowledge of word meanings	- Literal interpretations and difficulty with abstract concepts - Insufficient contextual information when conversing - Less aware of social cues - Prosodic aberrancies in intonation and stress	- Disjointed utterances - Difficulty linking sentences and understanding broader topics	- Reductions in verbal short-term memory capacity - Difficulty with statistical pattern recognition

Purpose

The careful characterization of heterogeneity in DLD is important to note because differing patterns of results for both behavioral and neuroimaging studies have obscured what may otherwise be true differences between children with DLD and TD children. As a result, findings have not been synthesized in a way that moves the field forward. As such, though we recognize that there are differences in outcomes across studies, here the aim of this overview is to shift the focus away from addressing outcome differences across studies to identifying converging evidence, so that we can begin to bridge the theoretical and imaging fields. While a few other overviews exist (see [16–18]), none that we are aware

of link neuroimaging patterns with various theoretical approaches that attempt to capture the range of language impairment patterns found in DLD.

We approach this by first reviewing the underlying neuroimaging patterns to date in DLD (structural (Section 2) and functional (Section 3)). We then summarize a subset of common theoretical accounts of language impairment patterns (across production and comprehension) while attempting to bridge the gap between neuroimaging literature and theory to elucidate brain behavior connections in DLD (Sections 5 and 6). As will become clear from this overview, the link between theoretical accounts of DLD and findings from neuroimaging research is based on limited evidence; therefore, we will conclude by proposing future directions for neuroimaging research to better understand how aberrant brain structure and function relates to observed language impairments in DLD (Section 7).

2. Structural Neuroimaging Findings in DLD

In this section and in Section 3 below, we describe the structural and functional outcomes of neuroimaging studies as a way to set up the integration of neuroimaging findings in support of theoretical models of language in DLD (Section 5, below).

The link between brain development and language outcomes in children with DLD is unclear, and this lack of connection is apparent when reviewing the DLD neuroimaging literature. Over the past 50 years, there have been fewer than 60 neuroimaging studies (excluding EEG studies) with children diagnosed with DLD. The majority of these studies have focused on structural brain differences when compared to language-unimpaired (neurotypical) children or children with other neurodevelopmental language disorders, such as children diagnosed with ASD and concomitant language impairment. Though there are some consistencies that will be discussed below, it is important to note that the picture portrayed here is tenuous at best due to the limited number of studies that confirm these consistent findings as compared to the larger number of studies that have contrasting results. In this paper, we determined that differences in participant selection and inclusion, diagnostic criteria, methodology, and analyses used underlie the disparate findings to date (see Appendix A, Table A1). As such, comparing the results across studies and evaluating how structural and functional brain abnormalities contribute to language impairment in children with DLD is challenging. Nonetheless, in this section and in Section 3 below, we provide a general overview of structural and functional neuroimaging findings in DLD and highlight consistent patterns of results. Additionally, when appropriate, we link findings to patterns found with other language-impaired populations to provide credence to the structural and functional patterns found in DLD.

2.1. Structural Brain Differences

Across development, the human brain undergoes a wide variety of structural changes in order to support increasing cognitive demands and the acquisition of new skills [19]. The emergence of white matter pathways in the brain begins in utero following formation of the neural tube and production and migration of neurons [20,21]. The brain then continues to differentiate and refine following birth. Infancy and early childhood are periods of rapid brain development, where the myelination of axons and synaptic reorganization and pruning are abundant in order to strengthen neuronal populations that frequently fire together as well as support those neuronal networks associated with new skills [20,21]. As a result of these changes, the gross structure of the brain continues to visibly change within the first few years of life, with subtle decreases in gray matter volume and increases in white matter volume up until early adulthood [22]. Thus, changes in individual neurons as well as neural networks impact gross brain structure across development.

Any perturbations to the tightly orchestrated processes that contribute to brain development can contribute to a range of developmental disorders [23]. In fact, across different neurodevelopmental disorders, there is widespread evidence of volumetric brain differences compared to neurotypical peers [24–29]. For example, individuals with ASD have been shown to have whole and regional brain volume differences when compared to age-

matched control children. Lange et al. (2015) found that young children with ASD had larger overall brain volumes than their typically developing peers but as they aged, they showed atypical regional volume decreases [30]. Findings such as these underscore the importance of investigating brain differences between typically and atypically developing populations, so that we can begin to uncover how structural (and functional) alterations contribute to language impairment. In the sections that follow, we provide an overview of structural brain differences in DLD starting with global brain volume, moving to a discussion of gray and white matter volume and integrity. It should be noted that the structure of this overview should not be viewed as an annotated summary of findings, but instead presents thematically related information based on the broader categories that were just described.

2.1.1. Global Brain Volume

Studies investigating measurements of global brain volume (i.e., the whole brain, the hemispheres, and the cerebral lobes) in children with DLD have found differences when compared to neurotypically developing (TD) children, suggesting that like other neurodivergent populations, there are abnormalities in brain structure that are associated with the disorder. In typical development, total cerebrum volume and surface area increases from birth until reaching its peak at around 11–12 years of age [31]. The few studies that have reported on these metrics in DLD point to children with DLD having smaller overall brain volumes, hemispheres, and cerebral lobes than typically developing children [32–35]. However, other studies, such as Herbert et al. (2003), have found contrasting results (e.g., larger brain volumes compared to TD children) [36]. These discrepant findings may be due to differences in methodological choices (e.g., voxel-based vs. semi-automatic brain morphometry). Another possibility to account for differences reported here, as well as throughout this paper, is that children with DLD may have different brain volumes relative to their TD peers at different stages across development, since DLD is indeed a developmental disorder. Therefore, studies aimed at measuring longitudinal changes in DLD (similarly to Lange et al.'s 2015 [30] approach with ASD) are needed as they will help elucidate differences in measures of global brain volume across development.

2.1.2. Total Gray Matter Volume

Across the human lifespan, total gray matter volume increases in utero until its peak around 6 years of age followed by a non-uniform decrease from late childhood to late adulthood [31]. Like with overall brain volume, studies investigating total gray matter volume in children with DLD have inconsistent findings because they employ different methods (e.g., volume-based vs. surface-based analysis) and their participant groups (for both DLD and TD children) rarely overlap in age, demographics, and inclusionary/exclusionary criteria (e.g., prior neurological history, assessment scores, etc.). As we focus this paper on converging findings, one common pattern is that reductions in overall gray matter volume (compared to TD children) are evident in younger children with DLD but diminish as they age. Soriano-Mas et al. (2009) used voxel-based morphometry (VBM) to examine gray matter differences in two groups of children with DLD, younger children under 12 years of age ($n = 19$), and older children over 12 years of age ($n = 17$) [37]. They found that when looking at the DLD group as a whole, they had greater global gray matter volumes than TD age-matched controls, but when they separated participants by age group, the younger children with DLD had greater gray matter volumes than control children of the same age, while the older children with DLD showed no differences in gray matter volume compared to their neurotypical peers. Consistent with Soriano Mas et al.'s findings that morphological differences in DLD diminish with age, Badcock et al. (2012) found no differences in overall gray matter volume between older TD children and age-matched children with DLD (mean age: 13.5) [38]. Typically, total cerebrum volume, surface volume, and subcortical volume reach their peaks around twelve years of age, with total gray matter volume peaking earlier, followed by a slow decline [31]. It may be the case that the proportion of gray matter in

TD children after six years of age decreases enough to match that of children with DLD at twelve years of age, while overall brain volume differences remain detectable between groups across late childhood and adolescence. These findings align well with the literature from other neurodevelopmental disorders, such as ASD, that report amplified volumetric differences in younger age groups that eventually diminish around 9–11.5 years of age [39].

As described above, maturational differences underscore the importance of carefully considering the age range of participants included, but other methodological differences, such as not accounting for overall brain size within participants, can also impact results. Larger brains have more brain tissue and can give the appearance of increased gray matter, when in reality, the amount of gray matter may be proportional to overall brain size. To account for proportional differences in gray matter volume, Girbau-Massana et al. (2014) included intracranial volume (ICV) as a covariate in their analyses [33]. Unlike Soriano-Mas et al.'s (2009) study [37], which found that younger children with DLD had larger gray matter volumes, Girbau-Massana et al. (2014) [33] found that the young children with DLD had *lower* overall gray matter volumes than their TD peers. The discrepant findings again may be related to accounting for ICV or they could be due to the fact that 6 of the 10 children with DLD in their study were also diagnosed with a concomitant reading disorder. Regardless of the inconsistent findings, there is limited evidence indicating that children with DLD as a whole have abnormalities in gray matter volume. What remains unclear is the source of gray matter differences; that is, does it represent a difference in the overall surface area or is it due to differences in cortical thickness? Both cortical thickness and surface area follow different developmental trajectories, suggesting that they are driven by partially distinct processes [40]. In the only large-scale study investigating these metrics in DLD, Bahar and colleagues (2023) found that children with DLD (ages 10–16 years old) had lower measures of surface area and, to a lesser extent, volume, but not cortical thickness, when compared to their TD peers [41]. Changes in the surface area of the brain are associated with gyrification (or the folding of brain tissue), which is related to more efficient neural processing [42]. Based on these findings, it is possible that differences in gray matter volume may be related to less efficient neural networks (as indexed by decreased surface area) within language-related brain regions in children with DLD.

In the next section of this paper, we summarize regional gray matter volume differences for areas linked to language function to explore how differences in gray matter volume within language-related brain regions can impact language abilities [43–46]. We also discuss differences in regional asymmetries as they are a common feature of typically developing brains that support growing functional specializations between the two hemispheres.

2.2. Regional Brain Differences

One of the most consistent findings in children with DLD is anomalous gray matter volume and symmetry within the perisylvian language zone. Though across the DLD literature a number of regions within this zone have been discussed [16,17], this section highlights three specific regions which have consistently been shown to have different characteristics in children with DLD as compared to TD children, namely the planum temporale and inferior frontal gyrus (Figure 1a). In addition to these standard language regions, the other region that will be discussed is the caudate nucleus, as it has been theorized to support speech and language processes (Figure 1b).

2.2.1. Planum Temporale

Perception and processing of speech sounds requires the ability to attend to rapidly changing auditory stimuli. The planum temporale is thought to play a key role in this process and has been posited to be a factor in the left hemisphere's dominance for language [47]. Prior research has indicated that the left planum temporale is comprised of densely packed cortical columns that facilitate processing at higher temporal resolutions [48]. As a result of this left hemisphere specialization, the planum temporale is generally larger on the left

than the right in typically developing populations [49–51]. However, children with DLD, as well as children from other language-impaired populations, such as those with ASD with language impairment [52] and dyslexia [53], do not exhibit this pattern, suggesting that there is a connection between language impairment and alterations in volume of the planum temporale.

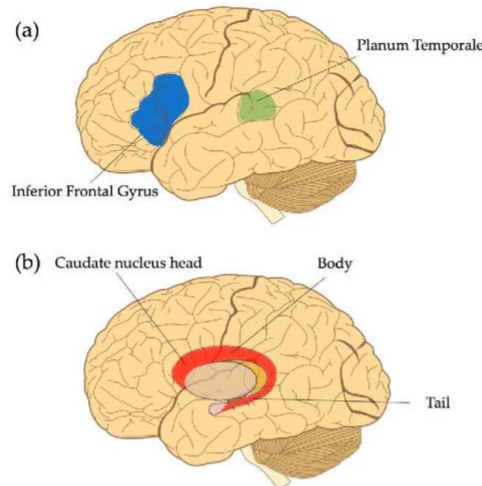


Figure 1. Commonly reported regions of interest in studies investigating structural gray matter differences in DLD. (a) The inferior frontal gyrus and the planum temporale. Note that the transparency of the planum temporale is meant to indicate that it is not visible on the lateral surface of the brain. (b) The caudate nucleus located subcortically. Note that it can be further subdivided into the head, body, and tail, but will be discussed as a whole in the text. Figure adapted from Hugh Guiney, CC BY-SA 3.0, via Wikimedia Commons <https://en.m.wikipedia.org/wiki/File:Human-brain.SVG> (accessed on 12 September 2023).

In children with DLD, the exact nature of these differences is unclear as some studies have demonstrated that they have larger planum temporale in the right hemisphere [22,32,54], while others have found that when compared to controls, the planum temporale size is reduced in the left hemisphere [55–57], or equal in size [58]. Differences in methodological approaches in the segmentation of the planum temporale may have contributed to the conflicting outcomes. For example, in a study by De Fossé et al. (2004), the authors noted that they included broader regions (the horizontal and posterior ascending portions) of the planum temporale in their measurements (delineated by a trained technician using anatomical landmarks), whereas other studies only included surface volume measurements based on automatic parcellation methods [59]. Though the studies referenced here contrast in terms of the directionality of differences (likely due to methodological differences), both indicate a potential link between abnormal planum temporale asymmetry and language impairment.

2.2.2. Inferior Frontal Gyrus

Another commonly implicated region in children with DLD is the inferior frontal gyrus (IFG). The IFG is comprised of three functional regions, the pars triangularis, the pars opercularis, and the pars orbitalis, though the pars opercularis is sometimes further subdivided into dorsal and ventral regions (Figure 2) [46]. This distinction is important as it can impact structural and functional comparisons across studies, yet studies often report results for the entire IFG or for the region known as Broca's area (pars opercularis and pars triangularis) rather than the individual components. The functional role of left IFG regions

has been a long-standing source of debate amongst researchers (see summary by Rogalsky et al., 2008) [60–62]. Though theories differ, they seem to converge on Broca's area being a language support region and the left pars orbitalis playing a role in covert articulation and semantic processing [63].

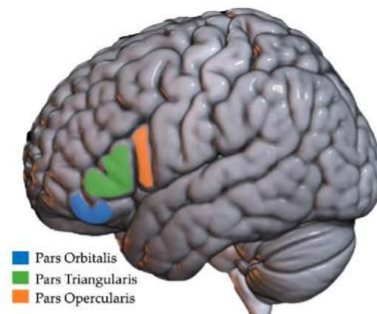


Figure 2. The three subdivisions of the inferior frontal gyrus shown in the left hemisphere.

In typically developing individuals, the left IFG tends to be larger in the left hemisphere than in the right, which is thought again to reflect left hemisphere language dominance [59]. In children with DLD, the regions within the left IFG have been shown to lack this pattern with some studies reporting that they have more gray matter in this region [38,64,65] and other studies reporting that the left IFG is smaller in children with DLD compared to controls [32,59,66]. Interestingly, of the studies reporting overall smaller left IFG volumes in DLD, some pointed to a group correlation between a smaller left pars triangularis and worse observed language outcomes [32,66]. However, as has been emphasized throughout this paper, the interpretation of findings should be approached with caution as results are often affected by research design. For example, Plante et al. (1991) found that the size and symmetry pattern of the IFG in children with DLD did not differ from age-matched peers as a group, but when looking at individual patterns of symmetry within the IFG, results varied from child to child, with some demonstrating reversed asymmetry while others did not [54]. Plante et al.'s results may be due to maturational effects, given that the participants varied in age from 4 years to almost 10 years of age. Another possibility is that there may be a tradeoff between abnormal development of the left IFG early in life and compensation of other structures in the brain. In support of the latter possibility, Lee et al. (2020) reported individual differences in the size of the left IFG with some children with DLD in their study having increased volume in the right pars orbitalis, which may indicate compensation of the right IFG in those who had abnormal left IFG volumes [64]. More research is clearly needed to understand differences in the left IFG volume and symmetry in children with DLD as well as the functional and structural connection between left and right homologue regions. As pointed out in the planum temporal section above, results converge on a similar theme; abnormal brain patterns in DLD can be linked to observed language impairment.

2.2.3. Caudate Nucleus

Other subcortical regions outside of the cortex, such as the basal ganglia and thalamus, have also received attention in children with DLD, as they connect to other language regions and are thought to play a supportive role in certain aspects of language such as complex syntactic processing, semantic processing, phonological processing, word generation, and more generally, attentional resource allocation [67–71]. Focusing in on one of the structures within the basal ganglia, the caudate nucleus (also referred to as the caudate), some studies have found that it tends to be larger in the left hemisphere than in the right in typically developing individuals and it has projections to other cortical

regions involved in verbal working memory, language comprehension and production, and procedural learning [69,72,73]. However, in children with DLD, studies have reported a bilateral reduction in gray matter volume of the caudate, with the exception of Soriano-Mas et al. (2008), who reported an increase in caudate volume in younger children that was not present in older children [35–38].

The caudate has also been implicated in the neuropathology of the famous KE family, known for their genetic mutation of the FOXP2 gene which, it has been argued, has rendered the language/speech of over half the family members agrammatic (i.e., lacking grammatical features) and unintelligible. In a study specifically looking at the relationship between language impairment and the caudate in this family, Watkins et al. (2002) found that the affected family members had smaller caudate volumes than unaffected family members or age-matched controls, and that the size correlated with nonword repetition abilities [65]. Interestingly, in a study by Krishnan et al. (2022) investigating the macromolecular content of gray matter in the caudate in DLD, they found a reduction in myelin content in the caudate nucleus (as well as the inferior frontal gyrus) when compared to controls and this reduction was related to lower language proficiency [74]. During childhood and adolescence, myelin content increases across cortical gray matter regions, while subcortical regions see less pronounced changes [75]. Further, brain regions associated with higher-order cognitive functions, such as language, require longer periods of myelination and are impacted by not just genes but also the environment [76]. It may be the case that the corticostriatal circuit, connecting regions of the caudate to the frontal lobe, associated with learning, is aberrant in DLD. Though more studies are needed, novel findings about the underlying architecture of commonly implicated brain regions in DLD may reveal important insights into DLD pathology. Given that brain regions do not function in isolation, we now turn our discussion to the white matter pathways that support structural connections between these commonly implicated gray matter regions.

2.3. White Matter Pathways

Historically, investigations into brain function have focused on the size and engagement of cortical and subcortical gray matter regions of the brain. However, a missing piece of those investigations are the connections that allow gray matter regions to coordinate activity. Since we know brain regions do not operate in silos, recent technological advances have provided scientists a way to measure the important connections that exist between gray matter regions, known as white matter, which comprises the structural wiring of the brain (Figure 3). Due to the early development of the brain, white matter pathways are already present by 30 weeks of gestation [77]. However, between birth and two years of age, children undergo a period of rapid brain development, highly influenced by genes and the environment, that helps further shape the neural architecture of the brain [20,78]. As children continue to develop, white matter volume continues to increase until around the fourth decade of life to support improvements in cognitive skills [19,79,80].

There is a strong relationship between neural activity associated with new skills and the formation of efficient, myelinated white matter pathways that connect gray matter regions throughout the brain [19]. As a result of this critical interaction, any deviation in the typical formation of white matter pathways will likely contribute to functional impairments [20]. Prior research has demonstrated a link between white matter alterations and language impairment in children with a range of neurodevelopmental disorders, including autism spectrum disorder, dyslexia and other reading disorders, and epilepsy [81–84]. While research on white matter connectivity in children with DLD is limited, like other neurodevelopmental populations, there seems to be a connection between language impairment and altered white matter volume and diffusivity (movement of water molecules along white matter pathways). Here, we provide an overview of these findings starting with white matter volume changes in DLD as compared to TD and then we turn attention to the diffusivity of white matter tracts involved in language processing within dorsal and ventral regions.

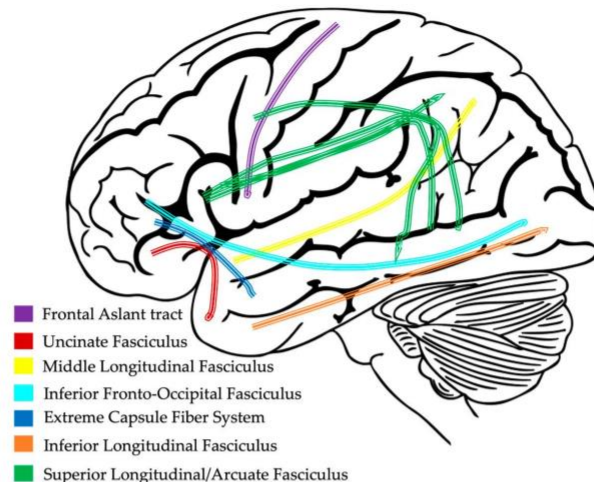


Figure 3. Example of white matter pathways connecting gray matter regions in the left hemisphere.

2.3.1. White Matter Volume

The findings from studies investigating overall white matter volume in children with DLD parallel the findings reported earlier in this paper for gray matter volume, in that results are varied due to differences in methodology and age of participants. However, there is some consistent evidence for children with DLD having overall increased white matter volume [34,36,37]. Similar to the gray matter pattern discovered by Soriano-Mas and colleagues (2009), these researchers discovered that an increase in white matter may be mediated by age. In their 2009 paper, Soriano-Mas and colleagues found that younger children (<12 years of age) with DLD showed an increase in white matter volume, while older children (>12 years of age) did not [33,37]. In contrast to these results, Girbau-Massana et al. (2014) did not find significant differences in white matter volume from their sample of younger children (mean age: 9.4 years) when compared to controls [33]. These difference in findings may be attributed to different methodological approaches. Unlike Soriano-Mas (2009) [37], Girbau-Massana et al. (2014) [33] included measures of intracranial volume in their analysis, which as noted previously, is an important consideration when calculating measures of brain volume. At first glance, the results from Soriano-Mas that link an increase in white matter volume to language impairment in DLD are surprising, since increases in white matter volume have been interpreted as improved cognitive skills across development [80]. In this case, a different interpretation is warranted. Findings of abnormally increased white matter volume in children with DLD may indicate that the underlying microstructure is impacted, which could result in poor connectivity across networks. Thus, in the next section, we turn to the literature investigating white matter integrity using diffusion MRI.

2.3.2. White Matter Diffusivity in Child Language-Impaired Populations

If the transmission of signals between different neural regions is impaired or slowed in any way, it could lead to disruptions of the tightly orchestrated processes needed for successful language processing and production, such as early auditory processing or the production of appropriate grammatical morphemes. Further, it can impact the strength and efficiency of language networks, which could lead to changes in connectivity as well as white and gray matter volume. Diffusion MRI (dMRI; described in more detail in Appendix B, Table A2) is an imaging method that can be used to reveal details about the integrity of white matter pathways by measuring the diffusion of water molecules in

brain tissue. This method has been commonly used to track neurodevelopmental changes attributed to normal brain maturation, as well as assess the underlying integrity of these connections in children with neurodevelopmental disorders.

As children mature and new skills are mastered, the brain develops more efficient structural and functional neuronal connections. These changes can be characterized by different diffusion tensor imaging (DTI) indices, such as fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD), that reflect movement and direction of water molecules along fiber bundles over a period of time (see Appendix B for a description of these indices) [79]. In typically developing children, the general expectation is that across development axons become more densely packed and myelinated [82]. This is represented by increases in FA and AD along the primary axis and decreases in MD and RD along the orthogonal axes. Additionally, these indices are expected to exhibit asymmetries across the two hemispheres as different brain regions develop at different rates due to experience. However, in populations with neurodevelopmental language disorders, such as ASD, researchers have found altered patterns of white matter diffusivity in left hemisphere language tracts, which may contribute to language impairment [85,86]. In children with DLD, differences in white matter development may underlie the language impairments observed. The next section of this paper explores dMRI findings along dorsal and ventral language pathways in children with DLD.

2.3.3. Dorsal and Ventral Language Pathways

There is an abundance of evidence supporting a dual-stream (dorsal and ventral; Figure 4) model of language processing in the brain. Dorsal stream white matter pathways are thought to map sound to distinct linguistic units, and ventral stream white matter pathways are thought to map sound to meaning [87–89]. As described below, some studies have reported differences along these pathways in children with DLD when compared to age-matched, typically developing children.

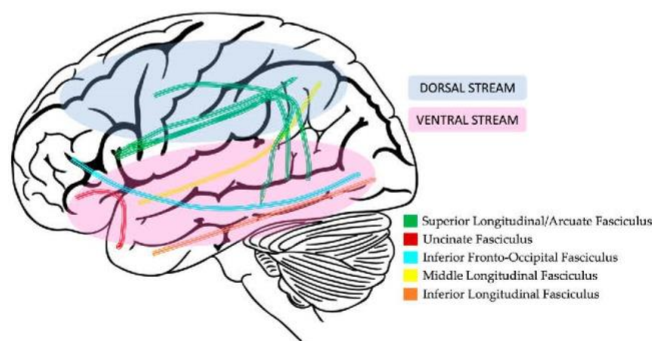


Figure 4. White matter pathways within the dorsal (blue) and ventral (pink) streams. Dorsal stream paths include the superior longitudinal fasciculus (SLF) and arcuate fasciculus (AF). Ventral stream paths include the uncinate fasciculus (UF), inferior frontal occipital fasciculus (IFOF), middle longitudinal fasciculus (MdLF), and inferior longitudinal fasciculus (ILF).

2.3.4. Dorsal Pathway Findings in DLD

From the few studies that have investigated microstructural brain differences in children with DLD, one of the common findings in the dorsal language pathway is decreased FA in the superior longitudinal fasciculus (SLF) and an increase in either MD or RD in the arcuate fasciculus (AF) [64,90,91]. This pattern is in contrast to what occurs in typically developing children in which as language skills develop, myelin content increases to create more efficient white matter pathways, which is indexed by an increase in FA and a

decrease in MD and RD [91]. This lack of change in children with DLD indicates abnormal development of dorsal stream tracts involved in language processing.

2.3.5. Ventral Pathway Findings in DLD

Longitudinal studies of ventral white matter development in typically developing children have indicated that the inferior fronto-occipital fasciculus (IFOF) and inferior longitudinal fasciculus (ILF) develop early on with increases in FA and RD and decreases in AD and MD values throughout childhood and adolescence until they peak in young adulthood. Interestingly, the uncinate fasciculus (UF) does not reach peak values until around 30–40 years of age [79,92]. Even fewer studies have investigated ventral language tracts in children with DLD, but the most consistent findings are decreased FA in the left hemisphere IFOF, UF, and ILF, with some limited evidence of decreased FA in the right hemisphere as well [64,91,93]. Vydrova et al. (2015) also found increases in MD and RD in the left hemisphere IFOF and ILF and a bilateral increase in RD for the UF [91]. This pattern of decreased FA and increased MD and RD in ventral stream language tracts of children with DLD differs from the typical pattern of white matter development. Additionally, in line with reported asymmetry and volume differences in gray matter brain regions, there also seems to be a lack of leftward asymmetry and an increase in volume in the ILF and IFOF [91,93].

In sum, there is converging evidence that suggests that children with DLD have altered micro- and macro-structures within language-related white matter pathways, but the correlation with observed language abilities remains elusive as studies have used a limited range of standardized language assessments, if at all, and as such, only a few have found correlations between language abilities and DTI indices. Importantly, differences in white matter architecture point to a possible contributor to language impairments in DLD. While there is a dearth of evidence for DLD, we can look to findings with other language-impaired populations to direct future investigations of white matter pathway anomalies and their effect on language abilities. Alterations in the development of the architecture supporting different higher-order functions such as language and learning systems could lead to alterations in function of different brain regions, which may in turn contribute to neurodevelopmental disorders. In fact, research with infants at risk for developing autism and dyslexia has revealed that early alterations in white matter pathways can impact developing language abilities among others, as the coordination and function of cortical networks is constrained by the architecture of white matter pathways [82,94,95]. Given the structural alterations reported in gray and white matter regions of the brain in children with DLD, the investigation of functional brain activity during language tasks is warranted. In the next section of this paper, we explore studies investigating functional brain activation patterns in those diagnosed with DLD.

3. Functional Neuroimaging Findings in DLD

Functional magnetic resonance imaging (fMRI) provides researchers (and clinicians) a glimpse into the window of the active brain. The examination of brain activity during specific tasks can inform theories of behavior, in this case, language.

3.1. Functional Magnetic Resonance Imaging (fMRI) Studies

Studies investigating functional brain activity in children with DLD using fMRI vary significantly across the tasks that are used and the age ranges studied. However, the general picture suggests that children with DLD differ across activation levels (hypo- and hyper-activation), locations, and laterality patterns of brain activation when compared to typically developing children during language-related tasks. Since fMRI results are largely based on task demands, it is important to understand that different tasks will produce different patterns of activation. However, the goal here is to highlight consistent patterns of regional activation differences across the broader categories of expressive and receptive tasks (though see Appendix C for a more detailed review of activation patterns across specific tasks). As

will become clear from the discussion below, more studies are needed to not only verify results (particularly across a wider range of tasks) but to also explore whether differences in the level, location, or laterality of activation patterns are due to other factors such as maturational changes (as discussed in prior sections).

3.1.1. Regional Activation Patterns for Expressive Language Tasks

Across the different expressive tasks (covert/overt naming, nonword repetition, etc.) employed in the DLD fMRI literature, one consistent finding is either a lack of activation or reduced activation in the left IFG and unexpected activation of the right IFG (see Table A3 in Appendix C for an overview) [38,96–98]. Reduced activation in the left and increased activation in the right is consistent with reports of a lack of leftward asymmetry and altered gray matter volume within this region. It is difficult to speculate on how altered gray matter and reduced activation are related given that studies differ as to the directionality of volumetric differences. On one hand, if the size of the left IFG is larger in those with DLD, then perhaps reduced activation reflects a lack of neural pruning and less efficient neural networks. On the other hand, if the size of the left IFG is smaller, then it may reflect inadequate neural architecture (including possible aberrant white matter connectivity) to support the carefully sequenced operations necessary for expressive language tasks, which may explain the recruitment of the right IFG as a compensation mechanism. In fact, individuals with post-stroke aphasia have demonstrated this pattern of right hemisphere homologue recruitment following left IFG damage in both the acute (<6 months post-stroke) and chronic (>6 months post-stroke) stages, suggesting that when there are alterations to brain structure, homologue regions may take over function in an attempt to compensate [99,100].

Other noteworthy DLD findings include altered activation in the superior temporal gyrus/sulcus (STG/STS) where the planum temporale is located and an increase in subcortical activation in both hemispheres [38,96–98]. Regional gray matter findings indicate that these regions also show patterns of asymmetry and volumetric differences which may be related to altered activation patterns, but the exact nature of this connection is unclear. Whatever the case, findings of structural and functional alterations to these distributed language regions would support accounts of aberrant language abilities in DLD, but more work is needed to understand the directionality of the neuroimaging differences. Furthermore, given the possibility of maturational effects and the variability across those diagnosed with DLD, studies employing larger sample sizes should investigate whether there are phenotypic differences in structure and function of these regions.

3.1.2. Regional Activation Patterns for Receptive Language Tasks

The results from studies that used receptive language tasks (passive listening, implicit learning, etc.) produced fewer consistencies than those from the expressive language tasks, likely due to the lack of overlap in tasks employed (see Table A4, Appendix C). However, in receptive language imaging studies, children with DLD demonstrated different patterns of activation in the left (and in one case, right) STG/STS where the planum temporale is located [101–103]. As discussed above, the planum temporale is generally larger in the left hemisphere than in the right in typically developing populations, but children with DLD do not evince this same pattern of volumetric asymmetry, nor do they show typical levels of activation in this region. Like with previous regions discussed, it is difficult to speculate on the relationship between these structural alterations and functional outcomes, but there does seem to be a connection between the aberrant structure and function of the planum temporale in DLD. These findings are consistent with theoretical accounts of auditory processing deficits (discussed below), but abnormalities in the neural architecture of those diagnosed with DLD extend beyond this early auditory processing region, so more work is needed to understand how developmental differences in the planum temporale impact language function more broadly.

To summarize, limited evidence suggests that regions that consistently show structural alterations also show functional alterations (i.e., IFG, planum temporale, and subcortical structures such as the caudate), but again, findings vary in terms of level (hyper- or hypo-activation) and location of activation patterns. While some of the variability can be attributed to differences in methodology, these results may also point to differences in the underlying properties that support brain function (e.g., neurovascular, hemodynamic, and other neurobiological processes). As described in more detail below, fMRI studies rely on capturing changes in the concentration of deoxygenated blood in the brain, which is based on underlying assumptions about the amount and rate of cerebral blood flow (CBF) to these critical brain regions. However, the underlying assumptions about CBF (and its relationship to the fMRI signal) might not be appropriate when evaluating brain activation in children with DLD [104]. If CBF deviates from typical patterns in children with DLD, particularly in language-related brain regions, it may over- or under-estimate the functional contributions of those regions. Furthermore, if blood flow to a brain region is not enough to sustain functionality (but is enough to sustain viability of the tissue), it could contribute to adverse language outcomes. Therefore, the last section of this paper looks at CBF patterns by exploring neuroimaging findings in DLD.

3.2. Cerebral Blood Flow Patterns

There is a tight coupling between neuronal activity and increased blood flow to active brain regions (e.g., neurovascular coupling). When neurons are active, they send chemical and electrical signals to blood vessels to dilate which in turn increases the flow of blood and allows an abundance of oxygen and glucose to be delivered to neurons as a fuel source. As neurons consume the influx of oxygen, the blood becomes deoxygenated. It is this change in oxygen content on which the fMRI or blood oxygen level dependent (BOLD) signal is based [105]. However, if the relationship between neural activity and the BOLD response is not accurately modeled via the hemodynamic response function (HRF), then activation patterns may be misinterpreted. Prior research has revealed that the HRF may deviate from the canonical pattern with clinical populations [106]. For example, following a stroke, the amount of time it takes for blood to perfuse neural tissue (i.e., transit delay time) may be longer than normal and the amount of blood that gets delivered to neural tissue may be reduced [99,107,108]. Thus, when conducting fMRI studies with suspected neurologically compromised populations, including neurodevelopmental groups, it is critical that the modeled HRF reflects the true nature of blood flow in the brain in order to extract accurate BOLD signal estimates.

Cerebral Blood Flow Patterns in DLD

The studies reported in this section utilized different methods to measure cerebral blood flow (CBF) including single-photon emission computed tomography (SPECT), positron emission tomography (PET), and transcranial Doppler (TCD) ultrasound. Each method relies on different mechanisms to capture blood flow patterns, and all come with inherent advantages and disadvantages, which may underlie discrepant results. Nonetheless, these methods have provided some insight into potential differences in CBF patterns between children with DLD and typically developing children.

One of the most common findings in studies utilizing SPECT is abnormal hemispheric lateralization of blood flow patterns and/or hypoperfusion (i.e., reduced CBF) in left hemisphere language regions in DLD [109–113]. Briefly, Lou et al. (1990) found that children with language impairment exhibited reduced CBF in the left perisylvian region while at rest compared to the right hemisphere, while Tzourio et al. (1994) found a lack of left hemisphere blood flow during a phonemic discrimination task [111,113]. Another common SPECT/PET finding is differences in blood flow (as indexed by glucose metabolism) in subcortical regions [112,114,115]. For example, Hwang et al. (2006) found a pattern of reduced CBF in the right basal ganglia and left globus pallidus, while Im et al. (2007) found decreased blood flow in the thalamus [114,115]. These subcortical findings are in

alignment with other studies previously discussed here that report differences in volume and activation in these regions (e.g., [35,96,98]). Subcortical regions, such as the basal ganglia, are thought to work in conjunction with regions of the brain that are known to support functions such as language learning [68,73,114]. In children with DLD, altered blood flow patterns to these linguistic and non-linguistic regions of the brain may ultimately impact language abilities.

Though there is a fair amount of agreement in findings across these early SPECT and PET studies, it should be noted that because these approaches require an injection of a radioactive isotope, the control groups were children with other clinical disorders such as ADHD, cluster headaches, or muscular dystrophy. Therefore, more studies are needed that use better validated measures that are less invasive, so as not to limit comparison groups to those diagnosed with clinical disorders.

Unlike SPECT and PET, transcranial Doppler (TCD) does not require the injection of a radioactive contrast agent and thus has been relied on in the past for CBF investigations in DLD. Using this method in conjunction with a functional task (e.g., fTCD), Whitehouse and Bishop (2008) reported abnormal patterns of CBF in young adults (mean age: 18.5) with DLD, characterized either by relatively greater right hemisphere lateralization or bilateral cerebral blood flow (indicating a lack of typical left hemisphere asymmetry) [116]. However, these results failed to be replicated in a younger sample of children with DLD (6–12 years). In typically developing populations, CBF increases across early childhood until it reaches a peak around 7–10 years of age [117,118]. Following this peak, CBF declines with age, though it remains relatively stable through early and middle adulthood [119,120]. It is possible that CBF, which is greater in childhood, may not follow the typical trajectory into adulthood in those with DLD, leading to differences in laterality. One other possibility for these reported differences is that, as a method, fTCD is highly operator dependent and it is limited to larger, basal arteries such as the middle cerebral artery (which supports a large number of language regions), and thus, it cannot be used to measure changes in blood flow to areas of the brain that are supported by smaller blood vessels [121]. Therefore, future studies investigating CBF patterns in DLD should use methods that are less user-dependent and invasive, such as MRI arterial spin labeling. Additionally, more studies across a range of ages would help elucidate differences in maturational CBF patterns that may underlie changes in the BOLD signal. By ensuring that the assumptions about the physiological properties of the BOLD signal are met, it may help to bridge disparate functional imaging findings in DLD, which in turn would help with better connecting imaging findings to theoretical accounts of DLD.

4. Interim Summary: Neuroimaging Patterns in DLD

Thus far, we have highlighted similarities as to the structural and functional differences in DLD as compared to TD across neuroimaging studies, while acknowledging that findings are based on limited evidence and often have contrasting results (likely due to methodological differences). We approached this portion of the overview by reporting converging evidence across structural (whole brain, gray matter, white matter, etc.) and functional measures (task-based activation and cerebral blood flow). The current state of the DLD neuroimaging literature suggests that *structurally*, when compared to typically developing children, children with DLD have smaller overall brain sizes, they show differences in whole brain and regional gray and white matter volume (potentially mediated by age), and they have altered white matter macro- and micro-structure of language-related tracts. *Functionally*, they demonstrate differences in the level of brain activation (i.e., hypo- and hyper-activation), the location of activation (i.e., regional differences), and laterality of activation (i.e., left vs. right hemisphere recruitment). They also show differences in the level and lateralization patterns of cerebral blood flow.

Importantly, while using a different approach, we identified similar regions of altered brain structure and function (planum temporale, inferior frontal gyrus, and caudate nucleus) to a prior systematic review of neuroimaging studies in DLD conducted by Mayes

and colleagues (2015) [16]. While it is clear from both this overview and the review conducted by Mayes et al. (2015) that altered brain structure and function are important components of DLD pathology, the connection between neuroimaging findings and observed language deficits has been less apparent, as research findings from neuroimaging studies are often reported independently of theoretical research findings. Therefore, it is our goal in this paper to begin to make those connections so that moving forward as a field we can design more theoretically informed neuroimaging studies with more sophisticated linguistic material to better tease apart how aberrant brain structure and function relates to the range of reported language impairments in DLD.

In the next section, we briefly review selected theoretical accounts of DLD, and after each section, we comment on the potential link between the proposed theoretical account and the neuroimaging findings discussed above in an attempt to elucidate brain–behavior relationships.

5. Neuroimaging Evidence Supporting Theoretical Accounts of Language Impairment Patterns in DLD

In order to illustrate how neuroimaging evidence can better inform theoretical accounts of language impairment patterns in DLD, we now discuss some common theories that have been proposed to explain language impairment patterns in DLD.

Across the published studies, there are a range of theoretical accounts that attempt to describe and explain observable language error patterns in children with DLD. While errors are part of typical language development (overgeneralizations, pronoun resolution, etc.), here we refer to error patterns that do not resolve with time [122]. Theories outlining these error patterns can generally be divided into three well represented arguments in the literature that point to deficits specific to (1) linguistic knowledge (e.g., morphosyntax), (2) domain general language processing (e.g., phonological working memory, speech perception, etc.), or (3) non-linguistic cognitive processes associated with language (e.g., working memory, processing speed, etc.) [9]. In isolation, each of these theoretical approaches have merit; however, children with DLD can exhibit both linguistic and non-linguistic impairments, making it difficult to propose a single comprehensive and encompassing theory that can account for hallmark deficits, such as difficulty with grammar, while also explaining other less consistent findings, such as deficits in attention and speed of processing. It is our hope that by making connections between theoretical accounts of DLD and the more consistent neuroimaging findings, that we can point to potential areas to focus future research endeavors. To accomplish these goals, below we present three theoretical accounts of language impairment in DLD. After each account, we integrate the imaging findings described above so as to build a bridge between two seemingly disparate areas.

5.1. Theoretical Approach: Linguistic Knowledge

Deficits in morphology and syntax (i.e., morphosyntax) are ubiquitous in children diagnosed with DLD. These observations have led to proposals suggesting that language deficits stem from limitations in linguistic knowledge (e.g., tense marking rules, phrase structure rules, movement, etc.; Table 2). One of the earliest among the **agreement, tense, and number marking** accounts is the Extended Optional Infinitive (EOI) account [123]. According to Wexler (1994), around 4–5 years of age, typically developing children undergo a stage by which they optionally mark the tense and number on finite verbs in main clauses (e.g., she drinks coffee can optionally be *she drink coffee; the asterisk represents an ungrammatical utterance) [124]. In cases where tense/number is not marked, children tend to produce the infinitive form of the verb (i.e., drink). Building off of Wexler's account, Rice et al. (1995) suggested that children with DLD remain in this optional infinitive stage for a period of time that *extends* beyond that of a typically developing child, before their grammatical usage catches up to that of an adult (if it does at all; see [125]).

The EOI account works well to characterize error patterns made by children diagnosed with DLD when speaking languages such as English and French, but it fails to account

for the grammatical errors made by children who use other languages such as Italian and Spanish due to cross-linguistic differences in syntactic structure. Thus, a number of theoretical accounts followed which expanded on the EOI premise that children with DLD struggle with aspects of tense and agreement (see Table 2) [125–127]. However, evidence has shown that children with DLD are not limited to errors in just tense and/or agreement as these accounts suggest, and thus, this theory underspecifies observed errors. To address this issue of limited scope, other accounts focused on **structural complexity**, such as the Representational Deficit for Dependent Relations (RDDR), suggesting that deficits stem from difficulty with performing these complex operations. One example would be the movement of a *wh*-question word (e.g., *who*) to the front of a sentence to form a question (Table 2) [122,128,129]. Though accounts such as the RDDR cover a wider range of deficits, especially across languages, they lack specificity, particularly concerning how and in which instances children with DLD struggle with complex operations. Further, the connection between deficits across different linguistic domains (i.e., syntax, morphology, and phonology) needs clarification since it is unclear how deficits in processing complex syntactic structures would also result in other deficits discussed in the sections below.

Other theories that focus on the **application of rules**, like the Narrow Rule Learning account [130], posit that children with DLD tend to stick to structures that have a high number of exemplars in the language, which may help bridge theoretical gaps, but no single linguistic theory can explain all of the inconsistencies in deficits across linguistic domains [122]. In addition, the majority of linguistic accounts have focused on observable production errors in individuals with DLD, which limits the ability to generalize to language deficits as a whole.

Table 2. A summary of theoretical accounts of DLD that describe deficits in linguistic knowledge. Error types are based on common groupings of described patterns but do not represent an exhaustive list of all theories proposed to date.

Error Type	Theoretical Account
Agreement/Tense/Number Marking	- Extended Optional Infinitive (EOI) Account [123] - Agreement/Tense Omission Model (ATOM) [125] - Extended Unique Checking Constraint (EUCC) [126]
Structural Complexity	- Representational Deficit for Dependent Relations (RDDR) [128] - Computational Grammatical Complexity (CGC) Account [131]
Application of Rules	Narrow Rule Learning Account [130]

Neuroimaging Evidence Supporting Linguistic Knowledge Theories

Though the source of grammatical deficits (or whether there is even a single source) is unclear in DLD, there is no doubt that children with DLD struggle with the grammatical features of language [132]. Interestingly, the type of grammatical impairments observed are often specific to the individual language spoken by the child, suggesting that both genes and the environment play a role in the abnormal development of language regions in the brain in DLD [132]. There is significant debate surrounding the neural regions that support grammatical learning, but two of the structures mentioned earlier in this overview, the inferior frontal gyrus (IFG) and the caudate, are often implicated [133]. In fact, Tagarelli et al. (2019) linked the left and right IFG regions as well as the caudate to learning the grammatical features of an artificial language in adults [133]. Common theories outside of grammatical learning have suggested that Broca's area (the pars opercularis and pars triangularis regions of the IFG) is involved in processing syntactically complex sentences, such as those with long-distance dependencies [61,134], comprehending sentences that have high working memory demands [62], and articulatory rehearsal to support comprehension [60].

In children with DLD, it may be the case that the aberrant development of the IFG impacts comprehension and production of the grammatical features of the language being

acquired. Given that the precise functional role of the left IFG is still unclear and structural findings in DLD are mixed, it is difficult to do more than speculate on the link between linguistic accounts of DLD and structural brain findings. However, overall increases or decreases in activation of the IFG as well as differences in size suggest altered function of the region and may further indicate altered microstructural architecture, such as changes in neuronal density and/or network connectivity, which impact language processes. For example, the left IFG has connections with the basal ganglia, specifically the caudate and putamen (known collectively as the striatum), through cortico-striatal circuits, a finding that has been supported via fMRI, diffusion, and functional connectivity studies [135]. These circuits may influence the learning of grammatical rules of the language spoken. Aberrant connections between the caudate and IFG may lead to an overpopulation of neurons (due to a lack of neuronal pruning), which would increase total gray matter volume and impact functionality. Alternatively, reductions in gray matter could be associated with neurotransmitter dysregulation or altered dendritic morphology, which may also impact the function of the regions. Whatever the case, there does seem to be growing evidence for alterations to the IFG and caudate that impact language abilities. However, as mentioned, grammatical deficits are a large component of DLD, but they are not the only feature of language affected. As a result, other theoretical accounts, discussed below, have suggested that the source of deficits stem from broader problems with either linguistic (but non-grammatical) or non-linguistic, cognitive systems.

5.2. Theoretical Approach: Language Processing Accounts

Linguistic-based accounts of DLD, such as those described above, benefit from being able to explain specific error patterns in language use; however, they often fail to encompass the wide range of deficits across languages. Further, they may not accurately reflect how a child with DLD processes (as opposed to produces) language. Therefore, some theories posit that language impairment stems from aberrant processing in domain general language systems that impact language use (Table 3). Among these theories are those that suggest that children with DLD have general auditory processing deficits. In a seminal series of studies in the 1970s, Tallal and Piercy [136,137], found that children with language impairment (those diagnosed with DLD and those with hearing impairments) performed worse than TD control children on a variety of tone and speech perception tasks that included categorization, discrimination, and temporal sequencing of auditory information. Children with DLD in particular seemed to struggle with auditory stimuli that were presented briefly or in rapid succession, which led the authors to suggest that the source of deficit stems from difficulties with **temporal processing** at the phoneme level.

In an attempt to expand on Tallal and colleague's supposition of an underlying temporal processing deficit, Schwartz, Scheffler, and Lopez (2013) argued that children with DLD have deficits in **perceptual processing**, specifically, categorical perception and the use of perceptual speech cues, which in turn affects storage and access to lexical representations [138]. Though these perceptual accounts can be compelling, one point of weakness is in describing how they can lead to disruptions of grammatical processing as opposed to just lexical or phonological processing. Leonard, McGregor, and Allen (1992) attempted to address this limitation by proposing the Surface Account, which posited that the complex operations required to process grammatical markers taxes the system resulting in incomplete processing of grammatical morphemes [139]. It is argued that this difficulty is then further amplified by the low perceptual saliency of grammatical morphemes, which increases the amount of exposure needed to learn them. However, evidence in support of this theory is mixed (see [122] for a review); thus, as it stands, more work needs to be carried out to understand if and how these processing differences result in the range of deficits observed.

Phonological short-term memory (also referred to as phonological working memory) is another commonly cited source of language difficulty for children with DLD. Different models of how language is stored have been proposed, but the most prominent view of

phonological short-term memory comes from Baddeley and colleagues [140–142]. Based on the model, Gathercole and Baddeley (1989) proposed that phonological short-term memory supports vocabulary development by helping to form stable phonological representations [143]. This proposal was supported by findings that demonstrated a relationship between poor nonword repetition skills and smaller vocabularies in children with DLD, indicating that they struggle to form and store stable phonological representations [144]. Thus, nonword repetition tasks have become a consistent and reliable measure for characterizing what many have suggested are phonological short-term memory impairments in children with DLD, but again, these theories are unable to account for observable impairments at the syntactic level during production and they tend to lack explanatory power for comprehension impairments [145]. Though there are processing theories that extend beyond the phoneme and word-level, the majority of studies have focused on this level. Thus, to better account for the full range of deficits observed in children with DLD, it is suggested that researchers look to other processing theories that have been proposed for other language-impaired populations as they may inform a larger range of observed deficits [146,147].

Table 3. A summary of theoretical accounts of DLD that describe deficits in language processing. Error types are based on common groupings of described patterns but do not represent an exhaustive list of all theories proposed to date.

Error Type	Theoretical Account
Temporal Processing	• Attending to rapid or brief auditory stimuli (e.g., phoneme level) [136,137]
Perceptual Processing	• Phoneme discrimination/categorization [138] • Surface Account [139]
Phonological Short-Term Memory	• Lexical selection/access (poor nonword repetition) [145] • Unstable phonological representations (smaller vocabularies) [143,144]

Neuroimaging Evidence Supporting Language Processing Theories

Prior research has shown that a white matter tract connecting regions around the auditory cortex in the temporal gyrus to the motor regions in the frontal lobe can be reconstructed in newborns using diffusion MRI, suggesting that the ability to map acoustic information to linguistic representations is already present from birth [148,149]. However, it is not until later in childhood that the pathway between the temporal lobe and inferior frontal gyrus is detectable, suggesting that dorsal pathway language tracts, involved in processing complex sentences, develop later in life [148]. Any alterations to language tracts present at birth may contribute to altered structure and function of the neural regions that support language processing as a child learns and grows.

Structural abnormalities of the planum temporale support theoretical accounts that posit that children with DLD have deficits related to temporal processing [136,137] and speech perception [138]. A reduction in left planum temporale gray matter may indicate that the microstructural architecture (densely packed cortical columns) needed to support rapid temporal processing is anomalous in individuals with DLD. This may also impact connections to other language regions such as the connection between the temporal lobe and IFG. In fact, it has been shown that both the IFG and regions in the superior temporal sulcus (STS) are highly connected hubs within the language processing network; thus, early differences within these regions may lead to language processing deficits [150].

The IFG has also been implicated in phonological short-term memory and phonological processing, which could account for the phonological deficits described in the section above [46]. Indeed, some studies with children with DLD have found differences along these tracts in terms of DTI metrics (mainly FA and MD), volume, and lateralization patterns when compared to typically developing children, but the correlation with language abilities has been more difficult to elucidate. Though there seems to be compelling neurological

evidence in support of language processing theories, some researchers have proposed that DLD is not a disorder specific to the language system, but rather affects broader cognitive domains, which in turn have an impact on language-specific processes. Similar theories have been proposed with other language-impaired populations, but additional investigations are needed to understand the precise nature of deficits in DLD.

5.3. Theoretical Approach: Non-Linguistic Cognitive Processing

The notion that children with DLD have broader processing limitations beyond language has received considerable attention in the DLD literature (Table 4). In looking at the literature from other well-studied language-impaired populations, namely individuals with aphasia, it has been proposed that linguistic knowledge remains intact in these individuals, but the ability to tap into the cognitive resources necessary to build the representations or perform complex operations with them are impaired (though see [151] for an opposing view) [152]. Studies investigating these limitations generally focus on aspects of working memory, such as resource allocation capacity and attention. Within the DLD literature, similar proposals have been investigated.

For example, Montgomery (2000) studied the ability of children with DLD to allocate resources during a word recall task [153]. Based on the assumptions of the working memory model proposed by Just and Carpenter (1992), the premise of their study was that people have a limited pool of resources by which they can process and store incoming information and children with DLD have even greater reductions in processing capacity [154]. They found that children with DLD could complete simple processing tasks, but as the task complexity increased (i.e., dual-load tasks where participants had to sort items by size and semantic category), performance worsened compared to controls, suggesting that children with DLD have reduced resources (e.g., processing capacities), which constrained the ability to successfully perform multiple, simultaneous cognitive operations. One big limitation of processing capacity theories is that it is not always clear what the “resource” being allocated is, though it is often conceived as an attentional one [141]. The problem with this is that children with DLD do not always demonstrate impairments in attention, or if they do, it tends to be situational. Further, it is challenging to design studies that can be falsified given that processing capacity is difficult to distinguish and measure.

Other non-linguistic cognitive theories have suggested that children with DLD are slower to perform a wide range of linguistic and non-linguistic tasks based on evidence from reaction time studies [122]. One early account for **reduced processing speeds** was the Generalized Slowing Hypothesis, which posits that children with DLD perform more slowly on both linguistic and non-linguistic tasks when compared to typically developing peers, and this difference is proportional to the complexity (i.e., the number of operations) required by the task [155]. Like with attentional studies, the problem with this hypothesis is that not all children with DLD show slowed reaction times on non-linguistic tasks, and those that do seem to do so selectively across different tasks [156]. Therefore, more work is needed to understand what causes some children to have slower processing speeds than others, as well as whether it affects broader, domain general neural systems or more specific ones.

One final group of domain-general cognitive theories discussed here is related to **impaired learning systems** [72]. The most comprehensive account of learning deficits in DLD is the Procedural Deficit Hypothesis (PDH) [73]. According to the PDH, children with DLD have a deficit in the procedural memory system. This system is comprised of frontal and subcortical brain regions that support the learning of linguistic, motor, and other non-linguistic sequences. The PDH posits that aberrant function of the procedural system can lead to impairments in any of the systems associated with it; thus, the PDH attempts to account for the wide range of linguistic and non-linguistic impairments reported in the DLD literature. It also makes a distinction between procedural and declarative systems. The procedural system is thought to underlie the acquisition and use of rule-governed grammatical computations, while the declarative system is thought to underlie storage

of lexical knowledge, such as semantic features and the memorization of more arbitrary, word-specific information like irregular past-tense verb forms. Research investigating sequence-based procedural learning tasks has found that children with DLD demonstrate impairments in this realm but are less likely to show deficits in non-sequenced based declarative tasks [72]. However, Ullman and Pierpoint (2005) point out in their model that the procedural and declarative systems are not entirely independent of one another due to their connections with other systems, such as those involved in working memory, so it is possible for children with DLD to show deficits in processes supported by both systems [73]. This becomes particularly relevant when trying to account for smaller vocabularies in children with DLD, since the declarative system likely supports this process.

Though the PDH provides a nice framework for capturing one of the most striking impairments in DLD (grammatical errors), more work needs to be done to refine the hypothesis, particularly in terms of the functional boundaries between the procedural and declarative systems. Further, this model provides one of the most comprehensive accounts for the varied neuroimaging findings, but in an effort to account for such a broad range of deficits, the model posits that any deficit can be explained by the procedural system or connections to it, with limited evidence to support these claims.

Table 4. A summary of theoretical accounts of DLD that describe deficits in non-linguistic cognitive processing. Error types are based on common groupings of described patterns but do not represent an exhaustive list of all theories proposed to date.

Error Type	Theoretical Account
Reduced Resource	• Reduced Processing Capacity [153]
Reduced Processing Speed	• Generalized Slowing Hypothesis [155]
Impaired Learning System	• Procedural Deficit Hypothesis (PDH) [73]

Neuroimaging Evidence Supporting Non-Linguistic Cognitive Processing Theories

Returning to the Procedural Deficit Hypothesis along with other theories of language learning and sequencing, the caudate has been identified as a locus of language learning deficits in DLD. This is the case for other language-impaired populations, such as those with aphasia as well [72,73,157]. As discussed previously, it is not clear if altered neurophysiology leads to language learning impairments or if language impairments impact the growth and development of neurons in DLD, which in turn affects learning, but subcortical circuits seem to underlie some aspects of language learning and there are reports of regional differences in these areas, so additional research is needed.

Further, theories that posit a general slowing of both linguistic and non-linguistic cognitive systems could be supported by more research investigating microstructure architecture along these pathways. For example, a number of studies have indicated that children with DLD have decreased FA along left hemisphere language tracts. FA is thought to index axonal microstructure (diameter and density), myelination concentration, and degree of fiber crossings [158]; thus, a decrease in FA may signify less efficient transmission of neural signals, which may lead to overall slower processing. However, it remains an open question whether reports of slowed processing in DLD are truly language-specific or more general, especially given the high degree of connectivity the language network has with other networks such as those involved in learning, attention, and memory. Studies investigating structural and functional connectivity patterns in DLD along with measures of tract integrity (e.g., FA, MD, RD, etc.) may help to answer these questions.

5.4. Interim Summary: Linking Theory to Brain

There are a number of different accounts that have been proposed in an attempt to explain patterns of language impairment in children with DLD. We divided these theories into three well-represented categories, namely deficits in linguistic knowledge, language

processing, and non-linguistic cognitive processing, and briefly discussed evidence supporting each. Each of these theories does well at capturing specific measured behaviors that differ in DLD compared to typically developing peers, but when zooming out more broadly to examine the range of behaviors reported (e.g., tense omission, poor phonological awareness, slower processing speed, etc.), there are a number of competing accounts that in isolation are not able to explain the broad scope of impairments in DLD. On one end of the theoretical continuum, the linguistic accounts lack explanatory power and are too narrow in scope, especially since most tend to focus on word-level, production errors; and on the other end, the more general non-linguistic processing accounts are too broad, as they cannot explain why language (and grammar) is affected above and beyond other cognitive systems in DLD if the deficit is in a domain-general system. One possibility is that DLD is a spectrum disorder (like autism) with different phenotypes [11]. If this is the case, neuroimaging evidence could help with the identification of different phenotypic groups by linking specific neural profiles to behavioral patterns. This would require much larger datasets than are typical in DLD research and would be most informative with longitudinal designs.

Alternatively, another approach could be to examine language abilities that are more commonly affected in children with DLD as a starting point to elucidate the relationship between altered brain structure/function and variable language profiles. For example, difficulty with the use of grammatical features of language and poor performance on nonword repetition tasks are common in DLD. Both of these abilities in typically developing individuals have been linked to the inferior frontal gyrus (IFG) [43,130,131]. In a recent study by Bahar and colleagues (2023) with children with DLD, the authors found that performance on a nonword repetition task was a significant predictor of surface area within the left IFG [41,46,133,134]. It may be the case that alterations within the left IFG are linked to difficulties with both of these language tasks. Further, given that the IFG is a densely connected hub within the language network, abnormal development of the region could impact other connected regions, such as the superior temporal sulcus. This would help explain empirical evidence indicating that language deficits exist across different language domains, as certain deficits could be linked back to a common neural substrate, and variations beyond those deficits could potentially be linked to alterations in structural and functional connections with other regions.

One other possibility is that the underlying neurobiological mechanisms supporting brain development are impacted in DLD. Recent work from Bahar et al. (2023) and Krishnan et al. (2022) is beginning to explore this area by investigating the underlying properties of brain tissue [41,74]. For example, as mentioned previously, Krishnan et al. (2022) measured gray matter myelin content in children and adolescence with DLD and found less myelin in the caudate nucleus and left inferior frontal gyrus. Together, these brain regions partially comprise the corticostriatal loop, which plays a role in sequential learning tasks such as learning the grammatical rules of a language. Based on their findings, the authors posited that children with DLD have difficulty learning the complex rules of language, as evinced by altered myelin content within this language learning circuitry (though they do not speculate on the causal direction of the relationship between reduced myelin and language abilities). Typical myelin development begins in utero and is subject to a number of carefully timed genetic processes that slowly give way to more environmental influences postnatally [76]. Thus, a reduction in myelin content could be related to specific genetic markers early on in DLD. Then, as a child continues to develop, experience could have a greater impact on the development of higher-order cognitive functions, like language learning. This idea is supported by the fact that myelination within the brain regions associated with these higher-order functions takes longer in comparison to sensory and motor regions to develop. This could help provide support for more domain-general theories, like the Procedural Deficit Hypothesis or the Generalized Slowing Hypothesis mentioned in Sections 5.3 and 5.4. Unlike sensory and motor cortices, the brain regions involved with language processes take longer to “mature”; thus, early alterations to the underlying properties supporting

brain function could have a detrimental impact on later-developing language network architecture, thus resulting in the range of language impairments that we observe in DLD.

6. Discussion: The Current State (and Limitations) in Linking Theory to Brain

It is clear that more work needs to be conducted to obtain a better sense of the neural organization and networks engaged in language processes in children diagnosed with DLD. Overall, the current state of the field suggests that children with DLD have atypical brain volume, laterality, and activation/connectivity patterns compared to their neurotypical peers. Behaviorally, one of the most striking impairments is in the production of grammatical morphemes, but research has demonstrated impairments in a range of other linguistic and non-linguistic tasks, such as vocabulary development, nonword repetition, and short-term memory (though it should be noted that it is difficult to create purely non-verbal short-term memory tasks). In terms of neuroimaging research, across both structural and functional brain studies, the planum temporale (located in the posterior superior temporal gyrus), the inferior frontal gyrus, and the caudate nucleus consistently show altered patterns in children with DLD when compared to typically developing children. Taken together, it is reasonable to speculate that atypical language development in DLD is not an environmental side effect but is in fact related to anomalous development of brain structures and/or function. However, few studies have attempted to link theoretical accounts of language impairment in DLD to neuroimaging findings, resulting in two disparate bodies of literature.

The goal of this overview was to synthesize the literature in a way that could help lay the groundwork for more theoretically motivated neuroimaging research. Though the connections made here are purely speculative based on the evidence presented, they do align well with the recent literature demonstrating structural and functional differences in the corticostriatal pathways that support language learning [41,72,74,159]. These recent studies utilize more consistent methodological approaches to make connections between altered brain structure and theoretical accounts of DLD, and they explore the underlying properties that support broader measures of structural brain development beyond brain volume (i.e., myelin, surface area, cortical thickness, etc.). This is important because prior neuroimaging research with children with DLD rarely overlaps in methodological approaches and often focuses on these gross brain measures, making it difficult to draw conclusions about the underlying contributors of altered brain structure or function in DLD. At this point, more research with larger sample sizes and carefully defined participant criteria is needed to replicate previous neuroimaging findings and build on our current knowledge of language impairment patterns in DLD. By laying a foundation for more theoretically motivated neuroimaging research, we may be able to better link neural differences to specific language profiles that align with current theoretical accounts of language deficits in DLD.

7. Future Directions: New Approaches in Linking Theory to Brain

There were a number of ways to craft this overview. We chose to categorize aspects of studies based on a variety of measures used to evaluate brain structure (i.e., whole brain volume, gray matter volume, white matter diffusivity, etc.) and brain function (i.e., task-based activation and cerebral blood flow). Our goal was to present converging evidence about neural regions implicated in DLD in order to link theory to brain. Importantly, using this approach, we found a similar pattern of results to a systematic review conducted by Mayes and colleagues (2015) in which they divided neuroimaging studies in DLD by the methodology employed (e.g., semi-automatic morphometry, voxel-based morphometry, etc.). Similarly to our findings, Mayes et al. (2015) reported that the posterior superior temporal gyrus, the inferior frontal gyrus, and the caudate are implicated in DLD pathology [16]. Given the consistencies across these reviews and more recent studies in DLD, future research will benefit from exploring the relationship between altered structure/function of these brain regions and performance on language tasks that are linked to activation within those regions.

A problem discussed throughout this overview, though, is the lack of consistency across studies in terms of the direction of volumetric differences (e.g., larger in the left hemisphere, smaller in the right, etc.) and the location and level of brain activation in the three brain regions frequently implicated in language impairment in DLD. One possibility is that broad measures of brain structure (i.e., volume) and brain function may overshadow important underlying properties that contribute to these gross measures. For example, as previously mentioned, Bahar et al. (2023) demonstrated that altered brain volume in DLD was largely driven by differences in surface area rather than cortical thickness, which is noteworthy as surface area and cortical thickness follow distinct developmental trajectories and are likely driven by distinct neurobiological mechanisms [41]. By exploring the underlying properties that index developmental changes, it can help to better account for inconsistent findings within the literature.

To date, one area of neuroimaging research that has received little attention is the processes underlying neuronal function and connectivity, particularly within the language network. Research from another language-impaired population, individuals with aphasia, has demonstrated that reduced cerebral blood flow to middle temporal regions correlates with auditory comprehension impairments, despite these regions appearing structurally uncompromised by the lesion [99]. It may be the case that important language regions, such as the left inferior frontal network, are hindered during development due to aberrant blood flow, underconnectivity, etc., resulting in those consistently observed morphosyntactic deficits in DLD. By examining distributed networks and the processes that underlie neuronal function (e.g., cerebral blood flow, glucose metabolism, etc.) in children with DLD (as compared to neurotypically developing children) it may help to further bridge theoretical accounts as well as aid in the identification of potential biomarkers of DLD.

Author Contributions: Conceptualization, N.A. and T.L.; writing—original draft preparation, N.A. and T.L.; writing—review and editing, N.A. and T.L.; visualization, N.A. and T.L.; funding acquisition, N.A. and T.L. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by NIH NIDCD award numbers T32 DC007361 (PI T.L., trainee N.A.), and F31 DC020374 (PI N.A.), and the SDSU College of Health and Human Services Graduate Student Research Award (awarded to N.A.).

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Acknowledgments: We thank the members of the Language and Neuroscience Group and members of N.A.'s mentoring team for their valuable feedback on the formatting and organization of this manuscript.

Conflicts of Interest: The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

Appendix A. Referenced DLD Neuroimaging Studies

Table A1. Summary of studies investigating neural differences in children with DLD using structural and functional neuroimaging methods. SLI = specific language impairment; TD = typically developing; LI = language impaired; DLD = developmental language disorder; ALI = autism + language impairment; ALN = autism + language normal; IFG = inferior frontal gyrus; LN = language normal; PT = planum temporale; ASD = autism spectrum disorder; VBM = voxel-based morphometry; CSF = cerebral spinal fluid; WM = white matter; GM = gray matter; L = left; R = right; STS = superior temporal sulcus; STG = superior temporal gyrus; ROIs = regions of interest; MTG = middle temporal gyrus; FA = fractional anisotropy; SLF = superior longitudinal fasciculus; HSL = history of speech and language; PTG = posterior temporal gyrus; DLI = developmental language impairment; ANL = autism + normal language; LH = left hemisphere; RH = right hemisphere; IFOF = inferior fronto-occipito fasciculus; ILF = inferior longitudinal fasciculus; AF = arcuate fasciculus; UF = uncinate fasciculus; ECFS = extreme capsule fiber system; BA = Brodmann area; SMG = supramarginal gyrus; NL = normal language; DSD = developmental speech disorder; SMA = supplementary motor area; TPJ = temporal parietal junction; ADHD = attention deficit hyperactive disorder.

Reference	N (M/F), Mean Age (SD or Range)	Method	Key Findings in DLD (Compared to TD)
		Structural Imaging Studies	
Plante et al., 1991 [160]	SLI: 8 (8 M), 5.2 months TD: 8 (8 M), 4.2–9.6 months	Manual Morphometry	Children with SLI had significantly larger right hemisphere perisylvian volumes and left hemisphere volumes were as expected, showing abnormal asymmetry. No significant differences were found for extra-perisylvian regions between SLI and TD due to individual differences.
Jernigan et al., 1991 [57]	LI: 20 (13 M/7 F), 8.9 (± 0.7) TD: 12 (8 M/4 F), 9.0 (± 0.7)	Semi-automatic and Manual Morphometry	Children with LI had significantly smaller volumes in the L posterior perisylvian region compared to the R region and significantly greater volume in the R prefrontal regions compared to the L region. The authors found weak statistical evidence for reversed asymmetries in the perisylvian region (right > left).
Preis et al., 1998 [58]	DLD: 21 (14 M/7 F), 8.33 (± 21 months) TD: 21 (14 M/7 F), 8.25 (± 21 months)	Manual Morphometry	There were no differences in the planum temporale or the planum parietal asymmetry between DLD and TD children. DLD children had smaller forebrain sizes, which accounted for smaller planum temporale bilaterally in DLD.
Gauger et al., 1997 [32]	SLI: 11 (8 M/3 F), 9.0 (± 2.3) TD: 19 (14 M, 5 F), 8.9 (± 1.6)	Manual Morphometry	The pars triangularis was significantly smaller in the L hemisphere of children with SLI. Children with SLI were more likely to have rightward asymmetry of language structures.
Herbert et al., 2003 [36]	DLD: 24 (16 M/8 F), 8.31 (5.7–11.3) TD: 9.1 (6.5–11)	Semi-automatic and Manual Morphometry	Total brain volume was greater in children with DLD as compared to controls. A significant main effect of sex was found, with males showing significantly larger total brain volumes as compared with females. Regional differences between DLD and control children revealed cerebral white matter volume was 13% larger in the DLD sample.

Table A1. Cont.

Reference	N (M/F), Mean Age (SD or Range)	Method	Key Findings in DLD (Compared to TD)
De Fossé et al., 2004 [59]	ALI: 16 (16 M), 9.8 (± 2.1) ALN: 6 (6 M), 8.3 (± 0.9) SLI: 9 (9 M), 9.9 (± 2.3) TD: 11 (11 M), 10.4 (± 2.7)	Semi-automatic and Manual Morphometry	Non-language-impaired individuals had larger cerebral volumes than language-impaired individuals (both SLI and ALI). The IFG was larger on the R side in LI and larger on the L side in LN participants. The PT was equal in size for language normal participants and larger in the L for language-impaired individuals.
Herbert et al., 2005 [66]	DLD: 15 (15 M) ASD: 16 (16 M) TD: 15 (15 M) Total: 46 between 5.7 and 11.3 years.	Semi-automatic and Manual Morphometry	Cerebral symmetry patterns in children with DLD and ASD were similar but differed from TD patterns. In both autistic and DLD samples, there was a substantial increase compared with controls in the aggregate amount of cortical parcellation unit (PU) asymmetry. The ASD and DLD brains showed an increase in the number (and volume) of cortical PUs with rightward asymmetry, but at the same time, they showed either no loss (ASD) or only a small loss (DLD) in the number (and volume) of cortical PUs with leftward asymmetry.
Soriano-Mas et al., 2009 [37]	SLI: 36 (24 M/12 F), 10.58 (± 2.80) TD: 36 (24 M/12 F), 10.88 (± 2.83)	VBM	Global Volume Results: Children with SLI showed larger gray and white matter volumes than controls, but no differences were observed in CSF spaces. Global gray matter and white matter was increased in children with SLI when compared to TD children, but this finding was not consistent in the older children subgroup. Regional Volume Results: Children with SLI had increased gray matter in the R perisylvian region and the occipital petalia, in the L middle occipital gyrus. Findings indicated that in younger children, several regions of gray matter increase in SLI (entorhinal area bilaterally, and the temporopolar cortex, the caudate nucleus, the motor-precentral cortex, and the precuneus of the left hemisphere). There was a specific volume increase in the left middle occipital gyrus for children with SLI. The R perisylvian region, in comparison to controls, was increased during the whole age range (i.e., no interaction between gray matter volume and age), and so was the left temporopolar cortex, with a specific volume increase in younger children with SLI (i.e., interaction between gray matter volume and age). Significant volume increases were observed in younger children with SLI in the juxtacortical WM of the right medial frontal cortex and bilaterally in the middle temporal gyrus. There were no notable findings in the older group in regard to WM.

Table A1. Cont.

Reference	N (M/F), Mean Age (SD or Range)	Method	Key Findings in DLD (Compared to TD)
Badcock et al., 2012 [38]	SLI: 10 (9 M/1 F), 13.5 (± 2.6) SLI-Sibling (SIB): 6 (4 M/2 F), 18.0 (± 3.8) TD: 16 (7 M/9 F), 12.5 (± 4.7)	VBM	Total GM volume did not differ. DLD had more GM than TD in L IFG, R insula, and L intraparietal. DLD has less GM than TD in pSTS bilaterally, R STG, R caudate, and R side of midbrain at substantia nigra, medial frontal polar cortex, R medial superior parietal, and L Occipital. DLD had more GM than SIB in L anterior intraparietal. There was less GM in the R parietal opercular and L occipital. SIB compared to TD, with more GM in ventral extent of central sulcus and retro splenial area bilaterally. SIBs had less GM in bilateral caudate, R putamen, R medial geniculate, and L fusiform than TDs.
Girbau-Massana et al., 2014 [33]	SLI: 10 (6 M/4 F), 8.5–10.9 (6 of the SLI participants had SLI + Reading Disorder or RD) TD: 14 (10 M/4 F), 8.2–11.8	VBM	Children with SLI had significantly lower overall GM volume, especially at the right postcentral parietal gyrus, and greater CSF volume. Children with SLI and RD exhibited a significant smaller volume of GM in right postcentral parietal gyrus than children with TD. The CSF volumes were significantly greater in children with SLI and RD and SLI than in children with TD. Ratios of gray to white matter were not significantly different in children with SLI and RD when compared to children with TD.
Lee et al., 2020 [64]	2 cohorts of subjects: Cohort 1: DLD: 14 (5 M/9 F), 22.42 (± 2.02) TD: 12 (4 M/8 F), 22.10 (± 0.51) Cohort 2: DLD: 19 (8 M/11 F), 16.96 (± 1.49) TD: 61 (25 M/36 F), 16.62 (± 1.40)	Semi-Automatic Morphometry and Diffusion Tensor Imaging (DTI)	Dorsal Pathway: The DLD group had significantly larger relative volumes of the L transverse temporal gyrus in the dorsal pathway than the comparison group. None of the other ROIs in the dorsal pathway showed significant age or group effects. Ventral Pathway: The ROIs comprising the ventral pathway showed significantly larger volumes for DLD in the R pars orbitalis, of the R temporal pole, and the L temporal pole for DLD subjects. Significant increases in relative volumes were seen across age for the L MTG, and for the L pars triangularis in DLD. DTI: Significantly reduced FA in the DLD group compared with the comparison group was found in the L and R SLF. There was an age-by-group interaction effect on the R SLF only for the comparison group. Significantly reduced FA values were found in the DLD group for the L IFOF and left UF. DLD group had no significantly increased FA across age in the L ILF and R UF (although the controls showed increased FA here). The DLD group also had smaller intracranial volumes.
Krishnan et al., 2022 [74]	DLD: 33 (22 M/11 F), 12.48 (± 1.80) HSL: 20 (17 M/3 F), 12.40 (± 1.67) TD: 56 (28 M/28 F), 12.41 (± 1.62)	MPM Quantitative Image (Myelin and Iron Concentration), and T1-Weighted structural	Lower myelin content in bilateral caudate nuclei and L IFG. No group differences were found for iron concentration.

Table A1. Cont.

Reference	N (M/F), Mean Age (SD or Range)	Method	Key Findings in DLD (Compared to TD)
Bahar et al., 2023 [41]	DLD: 54 (39 M/15 F), 12.4 (± 0.25) TD: 74 (41 M/33 F), 12.6 (± 0.2)	T1-Weighted Structural (Surface Area, Cortical Thickness, and Gray Matter Volume)	Surface Area: DLD showed smaller surface area bilaterally in the IFG extending to the anterior insula, in the posterior temporal and ventral occipito-temporal cortex, and in portions of the anterior cingulate and superior frontal cortex. Cortical Thickness: No differences in cortical thickness, or asymmetry of these cortical metrics. Gray Matter Volume: DLD showed smaller volumes in the R pars triangularis, L MTG, and PTG.
Lee et al., 2013 [35]	DLI: 12 (4 M/8 F), 21.99 (± 1.56) TD: 12 (4 M/8 F), 22.06 (± 0.51)	Semi-Automatic Morphometry and Diffusion Tensor Imaging	The DLI group showed smaller bilateral caudate nucleus, globus pallidus, and bilateral thalamus, as well as smaller cerebral lobes including the occipital lobe and frontal lobe. The DLI group was significantly larger than the control group in the relative volumes of the hippocampus, putamen, the R globus pallidus, and the nucleus accumbens. The DLI group showed lower FA values in the cerebral lobes including the frontal and occipital lobes (no significant findings for other ROIs).
Roberts et al., 2014 [90]	SLI: 14 (8 M/6 F), 9.73 (± 2.69) ALI: 16 (14 M/2 F), 9.80 (± 2.57) ANL: 18 (16 M/2 F), 11.47 (± 3.25) TD: 25 (16 M, 9 F), 11.42 (± 2.92)	Diffusion Tensor Imaging	Both ASD and LI were associated with elevated mean diffusivity of the LH arcuate fasciculus. There was a main effect of ASD on the axial, but not radial, component of diffusivity, and a main effect of LI on the radial, but not axial, component of diffusivity, suggesting that although ASD plus LI and SLI may share a microstructural anomaly of elevated radial diffusivity, they differ in axial diffusivity. No differences were found in L arcuate fasciculus FA for SLI or ASD. A main effect of ASD was found on axial diffusivity but not radial diffusivity; conversely, there was a main effect of LI on radial diffusivity but not axial diffusivity. There was also a significant ASD vs LI interaction on axial diffusivity. No group differences were observed in the RH arcuate fasciculus for any of the DTI measures.
Vydrova et al., 2015 [91]	SLI: 37 (25 M/12 F), 8.4 (± 1.6) TD: 34 (18 M/16 F), 8.9 (± 1.6)	Diffusion Tensor Imaging	Children with SLI had reduced FA of the investigated tracts, and corresponding increases in mean diffusivity values (AF bilaterally, L IFOF and L ILF), increases in radial diffusivity component (AF bilaterally, L IFOF, L ILF and UF bilaterally), and decreases in axial diffusivity component (R IFOF and L UF). Children with SLI showed bilaterally larger volumes of the ILF compared to controls.

Table A1. Cont.

Reference	N (M/F), Mean Age (SD or Range)	Method	Key Findings in DLD (Compared to TD)
Verly et al., 2019 [93]	DLD: 17 (11 M/6 F), 10.07 (± 2.01) TD: 22 (15 M/7 F), 11.00 (± 1.11)	Diffusion Tensor Imaging	DTI Metrics: Participants with DLD showed decreased FA values in the L ILF and middle longitudinal fascicle (MdLF). A higher tract volume of the SLF, MdLF, and the longitudinal posterior part of the superior longitudinal fascicle (SLF) was detected in children with DLD compared to TD children. Also, lower apparent diffusion coefficient (ADC) values of the ILF and a higher FA of the SLF were detected in children with DLD. There was a pattern towards increased RH FA values in patients with DLD relative to controls across the SLF, SLF_anterior, MdLF, ILF, and ECFS. A trend towards lower ADC values was observed in children with DLD relative to controls across the SLF, SLF_longitudinal, SLF_posterior, and all ventral language-related WM tracts. Finally, a trend towards a higher tract volume was observed for all dorsal and ventral WM tracts in patients with DLD. Lateralization: TD children showed LH lateralization of FA for all language-related WM tracts, except for the posterior part of the SLF and the ECFS. A significant RH lateralization was found for the anterior part of the SLF. None of the studied dorsal and ventral language-related WM tracts showed a significant L or R lateralization pattern, except for the MdLF in children with DLD.
Functional Imaging Studies			
Liegeois et al., 2003 [96]	KE Family Affected: 5 (3 M/2 F), 34.8 (± 17.0) Unaffected: 5 (3 M/2 F), 25.3 (± 3.4)	fMRI Covert and Overt Verb Generation and Word Repetition	Overall: Affected members showed significant under-activation bilaterally in Broca's area and the putamen. Covert Task: The distribution of activation was the same for the unaffected and control group in L IFG, but for affected members, there was more diffuse involvement of RH compared to LH and posterior compared with anterior bilaterally. ROIs: Under-activation for affected most notably in L BA44, but also R putamen/globus pallidus, L SMG, R IFG, and L precentral gyrus. Bilateral overactivation for affected in pSTG, L precentral, R temporal pole, and a number of parietal ROIs. Overt Task: Activation was mainly bilateral. There was activation in L IFG and bilateral putamen. No significant overactivation was detected. Repetition Task: Significant overactivation in L BA44 and L anterior insula.
Hugdahl et al., 2004 [101]	SLI: 5 (2 M/3 F), 11–70 years TD: 6 (2 M/4 F), 15–61 years	fMRI Passive Listening	Reduced activation in MTG and STS. Unlike TD, SLI also activated areas in the R inferior frontal lobe.

Table A1. Cont.

Reference	N (M/F), Mean Age (SD or Range)	Method	Key Findings in DLD (Compared to TD)
Weismer et al., 2005 [161]	DLD: 8 (5 M/3 F), 13.10 (± 6 months) TD: 8 (6 M/2 F), 14.0 (± 7 months)	fMRI Encoding and Recognition Tasks	No significant differences in activation patterns or laterality. There were two distinct activations in the IFG (BA44/45) and the insular portion of BA44. Encoding Task: Significant difference in precentral sulcus and parietal for encoding. DLDs showed hypoactivation in the insular portion of IFG during recognition. Less coactivation between IFG and STG during encoding. DLD had significant correlations between activation in parietal and frontal memory ROIs and parietal and STG during encoding. Recognition Task: DLD had a weak association between the STG and frontal ROIs and STG and parietal.
Dibbets et al., 2006 [103]	SLI: 6 (all male); 6.10 (± 8.4 months) TD: 7 (all male), 6.10 (± 6.3 months);	fMRI Switch Task	Non-Switch Task: Increased activation in L and R frontal area and superior parietal and occipital lobe. Switch Task: Increased activation in L/R frontal, temporal, and cingulate regions.
De Guibert et al., 2011 [97]	SLI: 21 (9 M/12 F), 11.4 (± 3.3) TD: 18 (9 M/9 F), 12.7 (± 3.0)	fMRI Lexico-Semantic Tasks (category fluency and responsive naming) and two Visual Phonological Tasks	Category Fluency Task: Lack of left lateralization in BA44 and reduced activation. Naming Task: More activation in RH, with no activation in some of the regions that TDs activated. Insula was bilateral for SLI, whereas it was only left-lateralized for TD. L hypoactivation in posterior STG/SMG. Minimal Pair Triplets Task: SLI showed RH activation, but TD did not. There was R hyperactivation in the insula. Segmentation Triplets Task: SLI showed no activation in the ROIs that were expected (IFG, STG, SMG, or insula). Lack of L lateralization in BA44. Overall, there was a lack of lateralization in the LH, with no differences in lateralization of the rest of the brain. The L posterior STG/SMG was hypoactivated, while the R anterior insula was hyperactivated.
Badcock et al., 2012 [38]	SLI: 10 (9 M/1 F), 13.5 (± 2.6 years) SLI-Sibling (SIB): 6 (4 M/2 F), 18.0 (± 3.8) TD: 16 (7 M/9 F), 12.5 (± 4.7)	fMRI Overt Word Generation and Passive Listening Tasks	TD and SIB showed a similar pattern of activation. DLD showed no activation in L IFG like other groups and much lower levels of activation in bilateral STG. TD and SIB showed L lateralization for speech but DLDs had less (due to a couple of individuals) in frontal and temporal areas. Structure-Function Relationship: Increased GM and decreased activation in inferior frontal region for DLDs and decreased GM and activation in posterior temporal region.
Plante et al., 2017 [102]	LI: 16 (7 M/9 F), 20.0 (± 2.2 years) NL: 16 (7 M/9 F), 20 (± 3.5 years)	fMRI Implicit Language Learning Task	There were no differences in the location of activation, but the level of activation was increased in L BA44, L SMG, L STG.

Table A1. Cont.

Reference	N (M/F), Mean Age (SD or Range)	Method	Key Findings in DLD (Compared to TD)
Pigdon et al., 2020 [98]	DLD: 18 (10 M/8 F), 124 months (± 3) DSD: 15 (5 M/10 F), 123 months (± 4) TD: 42 (22 M/20 F), 123 (± 6) TD-matched subset: 17 (8 M/9 F), 123 (± 5)	fMRI Nonword Repetition Task	DLD and DSD groups primarily activated subcortical regions (thalamus and globus pallidus), while TDs primarily activated cortical regions that are similar to adult activation patterns for nonword repetition, namely bilateral STS/STG, anterior insula, L IFG, SMA, precentral gyrus and motor cortex, L TPJ, anterior cingulate, and thalamus. However, there were no regions that survived thresholding when comparing the two groups; thus, there were no statistically significant differences.
Krishnan et al., 2021 [159]	DLD: 50 (35 M/15 F), 12.0 (10–15) TD: 67 (38 M/29 F), 12.1 (10–15)	fMRI Verb generation task	No activation differences in the L IFG or putamen and no lateralization differences. Sub-threshold activation differences in bilateral caudate and L IFG in a subset of children with poor task performance.
Cerebral Blood Flow (CBF)			
Denays et al., 1989 [110]	Dysphasia: 14 (10 M/4 F), aged 5–16 years	SPECT	Expression Deficit: Hypoperfusion in frontal convolution of LH (Broca's area). Comprehension and Expression Deficits: Hypoperfusion in the L tempo-parietal and hypoperfusion in upper and middle R frontal lobe. Three children with comprehension/expression deficits showed no abnormality. And 11 out of 14 were hypoperfused in language regions; there was hypoperfusion in areas for expressive deficits only, but for those with both, there was nothing in L IFG.
Lou et al., 1990 [111]	24 patients (median 10 yr, range 6–15) all from special school and with antenatal and perinatal events. ADHD: 9 ADHD + Phonological-syntactic dysphasia: 8 Severe phonological syntactic dysphasia: 3 Severe verbal decoding issues: 3 Severe lexical-semantic: 1	SPECT	For the language-impaired group, differences were less obvious than in other groups, but overall CBF was lower in the L perisylvian region than the R. For the phonological-syntactic only group, CBF to L prefrontal was lower than R.
Tzourio et al., 1994 [113]	Expressive–Receptive: 7 (4 M/3 F), 10 (± 1) Expressive: 7 (6 M/1 F), 8 (± 1) ADHD: 6 (6 M), 8 (± 1)	SPECT	There was an absence of LH activation during phonemic discrimination task in children with expressive–receptive deficits compared to those with only expressive difficulties and those with ADHD. Abnormal lateralization patterns were found for language in the more severely impaired group.

Table A1. Cont.

Reference	N (M/F), Mean Age (SD or Range)	Method	Key Findings in DLD (Compared to TD)
Chiron et al., 1999 [109]	Dysphasia: 8 (8 M), 10.2 Duchenne Muscular Dystrophy: 8 (8 M), 10.7	SPECT	Dichotic Task: Lack of activation in Broca's but CBF increase in R homologue compared to Duchenne Muscular Dystrophy group. Dichaptic Task: Bilateral increase in CBF as opposed to only in RH for Duchenne group.
Ors et al., 2005 [112]	SLI: 19 (11 M/8 F), 9.7 (7–15) ADHD: 12 (11 M/1 F), 9.4 (7–14)	SPECT	Children with SLI had lower CBF values in R parietal and subcortical regions and no L asymmetry as is typical in development.
Hwang et al., 2006 [114]	DLD: 21 (14 M/7 F), 4.2 (± 0.8) Tension Headaches: 17 (13 M/4 F), 11.0 (± 1.9)	SPECT	Reduced CBF patterns were found in the R putamen, R inferior parietal cortex and the L globus pallidus (though this region did not survive correction for multiple comparisons). There were no regions of increased CBF in DLD compared to controls.
Im et al., 2007 [115]	DLD: 17 (15 M/2 F), 4.7 (± 2.1) Split into 2 groups: >5 years and <5 years. ADHD: 10 (9 M/1 F), 7.0 (± 1.8)	PET	>5 Years: Abnormal findings in the thalamus, cerebellum, basal ganglia, caudate nucleus, and left temporal lobe. <5 Years: Abnormal findings in the thalamus, basal ganglia, cerebellum, caudate nucleus, and frontal lobe. Overall, the children with DLD showed decreased glucose metabolism in the frontal, temporal, and right parietal areas.
Whitehouse & Bishop, 2008 [116]	SLI: 11 (7 M/4 F), 18.15 (± 3.75) SLI-History: 9 (7 M/2 F), 18.33 (± 14.33) ASD: 11, (10 M/1 F), 19.98 (± 5.03) TD: 11 (7 M/11 F), 20.88 (± 3.29)	Functional Transcranial Doppler (fTCD) Ultrasound Covert and Overt Word Generation	The SLI-History, ASD, and TD groups all demonstrated greater activation in the LH compared to the RH during the task, indicating typical LH dominance for language. The SLI group demonstrated an altered pattern of either RH dominance or bilateral activation.

Appendix B. Diffusion Tensor Imaging (DTI) Indices

Table A2. A description of different measures of diffusivity and common findings in clinical populations compared to individuals with DLD.

Measure	What Is It Measuring?	Clinical Findings
Fractional Anisotropy (FA)	Amount of diffusion along primary axis (axon) compared to secondary and tertiary axes (perpendicular to the axon). FA increases as anisotropy increases (between 0 and 1; [102]). FA may reflect axonal microstructure (diameter and density), myelination concentration, and degree of fiber crossings [109].	Clinical Populations: Decreased FA values in patients with neurodegenerative diseases, such as Alzheimer's Disease and in normal aging [107,109]. DLD: The evidence is mixed, but findings suggest decreased FA in the superior longitudinal fasciculus and left hemisphere ventral (see Figure 4) tracts. There is limited evidence for decreased FA in the right hemisphere [62,83,110–112].
Mean Diffusivity (MD)	Average diffusion across all three axes ($\lambda_1 + \lambda_2 + \lambda_3/3$) [108]. MD may reflect structural integrity of axons [107].	Clinical Populations: Increased MD in patients with disturbed structural integrity such as those with epilepsy and chronic stroke [107,113]. DLD: Increased MD in the arcuate fasciculus [112,114].
Axial Diffusivity (AD)	Amount of diffusion along the primary axis (λ_1) [108]. AD may reflect axonal integrity/damage [115].	Clinical Populations: Decreased AD in patients with axonal degeneration and inflammation, such as individuals with multiple sclerosis (MS) [104,116]. DLD: No evidence of changes in AD. More research is needed.
Radial Diffusivity (RD)	Average diffusion perpendicular to the primary axis ($\lambda_2 + \lambda_3/2$) [108]. RD may reflect myelin integrity/damage [115].	Clinical Populations: Increased RD in patients with myelin loss, such as individuals with MS [113]. DLD: Increased RD in the arcuate fasciculus [112,114].

Appendix C. Regional Activation Patterns by Task

Table A3. Differences in network activation patterns for expressive language tasks in individuals with DLD when compared to typically developing populations. Blue boxes indicate regions where activation patterns were significantly different, and the text indicates the type/directionality of the differences found. Not significant (N.S.) indicates regions that were activated for both groups but in which no significant differences in activation patterns were found. Dashed lines indicate regions that were not investigated for either group in the study. STG/S = superior temporal gyrus/sulcus; GP = globus pallidus; PT = planum temporale; RH = right hemisphere.

Left Hemisphere Regions									Right Hemisphere Regions	
Task	Reference	Inferior Frontal Gyrus (IFG)	Non-IFG Frontal	Supramarginal/ Angular Gyrus	Precentral Gyrus/ Sulcus	Superior Temporal Gyrus/ Sulcus	Middle/ Inferior Temporal Gyrus	Sub-Cortical	IFG	Sub-Cortical
Covert Naming	Liegeois et al., 2003 [96]	Hypo-activation	N.S.	Hypo-activation	Hyper-activation	Hyper-activation	Hyper-activation	N.S.	Hypo-activation	Hypo-activation (putamen/ GP)
	De Guibert et al., 2011 [97]	Hypo-activation	N.S.	Hypo-activation	N.S.	Hypo-activation (PT)	N.S.	—	Activation found (IFG and Insula)	—
	Badcock et al., 2012 [38]	No activation found	—	—	—	Hypo-activation	—	N.S.	Activation found	Hypo-activation (putamen)

Table A3. Cont.

Task	Reference	Left Hemisphere Regions						Right Hemisphere Regions		
		Inferior Frontal Gyrus (IFG)	Non-IFG Frontal	Supramarginal/Angular Gyrus	Precentral Gyrus/Sulcus	Superior Temporal Gyrus/Sulcus	Middle/Inferior Temporal Gyrus	Sub-Cortical	IFG	Sub-Cortical
Overt Naming	Liegeois et al., 2003 [96]	Hypo-activation	N.S.	—	N.S.	N.S.	N.S.	Hypo-activation (putamen)	N.S.	Hypo-activation (putamen)
	Krishnan et al., 2021 [159]	N.S.	N.S.	Hyper-activation (at lowered voxel threshold only in RH)	—	N.S.	—	Hyper-activation (in caudate at lowered voxel threshold in low-performing subset)	N.S.	Hyper-activation (in caudate at lowered voxel threshold in low-performing subset)
Nonword Repetition	Pigdon et al., 2020 [98]	No activation found	No activation found	No activation found	No activation found	No activation found	—	Hyper-activation (thalamus/GP—uncorrected)	No activation found	Hyper-activation (thalamus/GP—uncorrected)

Table A4. Differences in network activation patterns for receptive language tasks in individuals with DLD when compared to typically developing populations. Blue boxes indicate regions where activation patterns were significantly different, and the text indicates the type/directionality of the differences found. Not significant (N.S.) indicates regions that were activated for both groups but no significant differences in activation patterns were found. Dashed lines indicate regions that were not investigated for either group in the study. STG/S = superior temporal gyrus/sulcus; PT = planum temporale; MTG = middle temporal gyrus; AG = angular gyrus.

Task	Reference	Left Hemisphere						Right Hemisphere			
		Inferior Frontal Gyrus (IFG)	Non-IFG Frontal	Supra-marginal/Angular Gyrus	Precentral Gyrus/Sulcus	Superior Temporal Gyrus/Sulcus	Middle/Inferior Temporal Gyrus	Sub-cortical	IFG	Sub-cortical	Other
Passive Listening	Hugdahl et al., 2004 [101]	—	—	—	—	Hypo-activation (PT)	Hypo-activation	—	N.S.	—	Hypo-activation (PT, MTG)
Implicit Learning	Plante et al., 2017 [102]	Hyper-activation	N.S.	Hyper-activation	N.S.	Hyper-activation	—	—	—	—	N.S. (STG/S, MTG)
Verbal Working Memory	Weismer et al., 2005 [161]	Hypo-activation (insular portion)	N.S.	—	Hypo-activation (parietal)	N.S.	—	—	N.S.	—	—
Executive Control	Dibbets et al., 2006 [103]	—	Hyper-activation (medial, orbito, superior)	—	N.S.	Hyper-activation	Hyper-activation	Hyper-activation (cingulate)	—	Hyper-activation (cingulate)	Hyper-activation (intraparietal, AG)

References

- Tomblin, J.B.; Records, N.L.; Buckwalter, P.; Zhang, X.; Smith, E.; O'Brien, M. Prevalence of Specific Language Impairment in Kindergarten Children. *J. Speech Lang. Hear. Res.* **1997**, *40*, 1245–1260. [\[CrossRef\]](#) [\[PubMed\]](#)
- Maenner, M.J.; Shaw, K.A.; Baio, J. Prevalence of autism spectrum disorder among children aged 8 years—Autism and developmental disabilities monitoring network, 11 sites, United States, 2016. *MMWR Surveill. Summ.* **2020**, *69*, 1. [\[CrossRef\]](#) [\[PubMed\]](#)
- Norbury, C.F.; Gooch, D.; Wray, C.; Baird, G.; Charman, T.; Simonoff, E.; Vamvakas, G.; Pickles, A. The impact of nonverbal ability on prevalence and clinical presentation of language disorder: Evidence from a population study. *J. Child Psychol. Psychiatry* **2016**, *57*, 1247–1257. [\[CrossRef\]](#)
- Zablotsky, B.; Black, L.I.; Maenner, M.J.; Schieve, L.A.; Danielson, M.L.; Bitsko, R.H.; Blumberg, S.J.; Kogan, M.D.; Boyle, C.A. Prevalence and trends of developmental disabilities among children in the United States: 2009–2017. *Pediatrics* **2019**, *144*, e20190811. [\[CrossRef\]](#) [\[PubMed\]](#)

5. Clegg, J.; Hollis, C.; Mawhood, L.; Rutter, M. Developmental language disorders—A follow-up in later adult life. Cognitive, language and psychosocial outcomes. *J. Child Psychol. Psychiatry* **2005**, *46*, 128–149. [\[CrossRef\]](#)
6. Maggio, V.; Grañana, N.E.; Richaudeau, A.; Torres, S.; Giannotti, A.; Suburo, A.M. Behavior problems in children with specific language impairment. *J. Child Neurol.* **2014**, *29*, 194–202. [\[CrossRef\]](#) [\[PubMed\]](#)
7. Sansavini, A.; Favilla, M.E.; Guasti, M.T.; Marini, A.; Millepiedi, S.; Di Martino, M.V.; Vecchi, S.; Battajon, N.; Bertolo, L.; Capirci, O.; et al. Developmental Language Disorder: Early Predictors, Age for the Diagnosis, and Diagnostic Tools. A Scoping Review. *Brain Sci.* **2021**, *11*, 654. [\[CrossRef\]](#)
8. Bishop, D.V. Cerebral asymmetry and language development: Cause, correlate, or consequence? *Science* **2013**, *340*, 1230531. [\[CrossRef\]](#)
9. Schwartz, R.G. *Handbook of Child Language Disorders*, 2nd ed.; Psychology Press: London, UK, 2017. [\[CrossRef\]](#)
10. Bishop, D.V.; Norbury, C.F. Exploring the borderlands of autistic disorder and specific language impairment: A study using standardised diagnostic instruments. *J. Child Psychol. Psychiatry* **2002**, *43*, 917–929. [\[CrossRef\]](#) [\[PubMed\]](#)
11. Lancaster, H.S.; Camarata, S. Reconceptualizing developmental language disorder as a spectrum disorder: Issues and evidence. *Int. J. Lang. Commun. Disord.* **2019**, *54*, 79–94. [\[CrossRef\]](#)
12. Tager-Flusberg, H. Do autism and specific language impairment represent overlapping language disorders? In *Developmental Language Disorders*; Psychology Press: London, UK, 2004; pp. 42–63.
13. Pena, E.D.; Spaulding, T.J.; Plante, E. The composition of normative groups and diagnostic decision making: Shooting ourselves in the foot. *Am. J. Speech Lang. Pathol.* **2006**, *15*, 247–254. [\[CrossRef\]](#)
14. Spaulding, T.J.; Plante, E.; Farinella, K.A. Eligibility criteria for language impairment. *Lang. Speech Hear. Serv. Sch.* **2006**, *37*, 61–72. [\[CrossRef\]](#) [\[PubMed\]](#)
15. Bishop, D.V.; Snowling, M.J.; Thompson, P.A.; Greenhalgh, T.; Consortium, C.; Adams, C.; Archibald, L.; Baird, G.; Bauer, A.; Bellair, J. Phase 2 of CATALISE: A multinational and multidisciplinary Delphi consensus study of problems with language development: Terminology. *J. Child Psychol. Psychiatry* **2017**, *58*, 1068–1080. [\[CrossRef\]](#) [\[PubMed\]](#)
16. Mayes, A.K.; Reilly, S.; Morgan, A.T. Neural correlates of childhood language disorder: A systematic review. *Dev. Med. Child Neurol.* **2015**, *57*, 706–717. [\[CrossRef\]](#) [\[PubMed\]](#)
17. Evans, J.L.; Brown, T.T. Specific language impairment. In *Neurobiology of Language*; Elsevier: Amsterdam, The Netherlands, 2016; pp. 899–912.
18. Webster, R.I.; Shevell, M.I. Topical review: Neurobiology of specific language impairment. *J. Child Neurol.* **2004**, *19*, 471–481. [\[CrossRef\]](#) [\[PubMed\]](#)
19. Lebel, C.; Deoni, S. The development of brain white matter microstructure. *Neuroimage* **2018**, *182*, 207–218. [\[CrossRef\]](#)
20. Stiles, J.; Jernigan, T.L. The Basics of Brain Development. *Neuropsychol. Rev.* **2010**, *20*, 327–348. [\[CrossRef\]](#)
21. Yap, Q.J.; Teh, I.; Fusar-Poli, P.; Sum, M.Y.; Kuswanto, C.; Sim, K. Tracking cerebral white matter changes across the lifespan: Insights from diffusion tensor imaging studies. *J. Neural Transm.* **2013**, *120*, 1369–1395. [\[CrossRef\]](#)
22. Jernigan, T.L.; Gamst, A.C. Changes in volume with age—Consistency and interpretation of observed effects. *Neurobiol. Aging* **2005**, *26*, 1271–1274. [\[CrossRef\]](#)
23. Pirozzi, F.; Nelson, B.; Mirzaa, G. From microcephaly to megalencephaly: Determinants of brain size. *Dialogues Clin. Neurosci.* **2018**, *20*, 267–282. [\[CrossRef\]](#)
24. Bayard, F.; Nymberg Thunell, C.; Abé, C.; Almeida, R.; Banaschewski, T.; Barker, G.; Bokde, A.L.W.; Bromberg, U.; Büchel, C.; Quinlan, E.B.; et al. Distinct brain structure and behavior related to ADHD and conduct disorder traits. *Mol. Psychiatry* **2020**, *25*, 3020–3033. [\[CrossRef\]](#) [\[PubMed\]](#)
25. Brieber, S.; Neufang, S.; Bruning, N.; Kamp-Becker, I.; Remschmidt, H.; Herpertz-Dahlmann, B.; Fink, G.R.; Konrad, K. Structural brain abnormalities in adolescents with autism spectrum disorder and patients with attention deficit/hyperactivity disorder. *J. Child Psychol. Psychiatry* **2007**, *48*, 1251–1258. [\[CrossRef\]](#)
26. Hasan, K.M.; Molfese, D.L.; Walimuni, I.S.; Stuebing, K.K.; Papanicolaou, A.C.; Narayana, P.A.; Fletcher, J.M. Diffusion tensor quantification and cognitive correlates of the macrostructure and microstructure of the corpus callosum in typically developing and dyslexic children. *NMR Biomed.* **2012**, *25*, 1263–1270. [\[CrossRef\]](#)
27. Krain, A.L.; Castellanos, F.X. Brain development and ADHD. *Clin. Psychol. Rev.* **2006**, *26*, 433–444. [\[CrossRef\]](#) [\[PubMed\]](#)
28. Nickl-Jockschat, T.; Habel, U.; Maria Michel, T.; Manning, J.; Laird, A.R.; Fox, P.T.; Schneider, F.; Eickhoff, S.B. Brain structure anomalies in autism spectrum disorder—a meta-analysis of VBM studies using anatomic likelihood estimation. *Hum. Brain Mapp.* **2012**, *33*, 1470–1489. [\[CrossRef\]](#)
29. Xia, Z.; Hoeft, F.; Zhang, L.; Shu, H. Neuroanatomical anomalies of dyslexia: Disambiguating the effects of disorder, performance, and maturation. *Neuropsychologia* **2016**, *81*, 68–78. [\[CrossRef\]](#)
30. Lange, N.; Travers, B.G.; Bigler, E.D.; Prigge, M.B.D.; Froehlich, A.L.; Nielsen, J.A.; Cariello, A.N.; Zielinski, B.A.; Anderson, J.S.; Fletcher, P.T.; et al. Longitudinal Volumetric Brain Changes in Autism Spectrum Disorder Ages 6–35 Years. *Autism Res.* **2015**, *8*, 82–93. [\[CrossRef\]](#)
31. Bethlehem, R.A.I.; Seidlitz, J.; White, S.R.; Vogel, J.W.; Anderson, K.M.; Adamson, C.; Adler, S.; Alexopoulos, G.S.; Anagnostou, E.; Arces-Gonzalez, A.; et al. Brain charts for the human lifespan. *Nature* **2022**, *604*, 525–533. [\[CrossRef\]](#) [\[PubMed\]](#)
32. Gauger, L.M.; Lombardino, L.J.; Leonard, C.M. Brain morphology in children with specific language impairment. *J. Speech Lang. Hear. Res.* **1997**, *40*, 1272–1284. [\[CrossRef\]](#)

33. Girbau-Massana, D.; Garcia-Marti, G.; Marti-Bonmati, L.; Schwartz, R.G. Gray–white matter and cerebrospinal fluid volume differences in children with specific language impairment and/or reading disability. *Neuropsychologia* **2014**, *56*, 90–100. [\[CrossRef\]](#) [\[PubMed\]](#)
34. Herbert, M.R.; Ziegler, D.A.; Makris, N.; Filipek, P.A.; Kemper, T.L.; Normandin, J.J.; Sanders, H.A.; Kennedy, D.N.; Caviness, V.S., Jr. Localization of white matter volume increase in autism and developmental language disorder. *Ann. Neurol.* **2004**, *55*, 530–540. [\[CrossRef\]](#) [\[PubMed\]](#)
35. Lee, J.C.; Nopoulos, P.C.; Tomblin, J.B. Abnormal subcortical components of the corticostriatal system in young adults with DLI: A combined structural MRI and DTI study. *Neuropsychologia* **2013**, *51*, 2154–2161. [\[CrossRef\]](#)
36. Herbert, M.R.; Ziegler, D.A.; Makris, N.; Bakardjiev, A.; Hodgson, J.; Adrien, K.T.; Kennedy, D.N.; Filipek, P.A.; Caviness, V.S., Jr. Larger brain and white matter volumes in children with developmental language disorder. *Dev. Sci.* **2003**, *6*, F11–F22. [\[CrossRef\]](#)
37. Soriano-Mas, C.; Pujol, J.; Ortiz, H.; Deus, J.; López-Sala, A.; Sans, A. Age-related brain structural alterations in children with specific language impairment. *Hum. Brain Mapp.* **2009**, *30*, 1626–1636. [\[CrossRef\]](#)
38. Badcock, N.A.; Bishop, D.V.; Hardiman, M.J.; Barry, J.G.; Watkins, K.E. Co-localisation of abnormal brain structure and function in specific language impairment. *Brain Lang.* **2012**, *120*, 310–320. [\[CrossRef\]](#) [\[PubMed\]](#)
39. Carper, R.A.; Moses, P.; Tighe, Z.D.; Courchesne, E. Cerebral Lobes in Autism: Early Hyperplasia and Abnormal Age Effects. *NeuroImage* **2002**, *16*, 1038–1051. [\[CrossRef\]](#)
40. Wierenga, L.M.; Langen, M.; Oranje, B.; Durston, S. Unique developmental trajectories of cortical thickness and surface area. *Neuroimage* **2014**, *87*, 120–126. [\[CrossRef\]](#) [\[PubMed\]](#)
41. Bahar, N.; Cler, G.J.; Krishnan, S.; Asaridou, S.S.; Smith, H.J.; Willis, H.E.; Healy, M.P.; Watkins, K.E. Differences in cortical surface area in developmental language disorder. *bioRxiv* **2023**. [\[CrossRef\]](#)
42. White, T.; Su, S.; Schmidt, M.; Kao, C.-Y.; Sapiro, G. The development of gyrification in childhood and adolescence. *Brain Cogn.* **2010**, *72*, 36–45. [\[CrossRef\]](#)
43. Fedorenko, E.; Thompson-Schill, S.L. Reworking the language network. *Trends Cogn. Sci.* **2014**, *18*, 120–126. [\[CrossRef\]](#)
44. Friederici, A.D.; Chomsky, N.; Berwick, R.C.; Moro, A.; Bolhuis, J.J. Language, mind and brain. *Nat. Hum. Behav.* **2017**, *1*, 713–722. [\[CrossRef\]](#) [\[PubMed\]](#)
45. Hertrich, I.; Dietrich, S.; Ackermann, H. The margins of the language network in the brain. *Front. Commun.* **2020**, *5*, 519955. [\[CrossRef\]](#)
46. Price, C.J. The anatomy of language: A review of 100 fMRI studies published in 2009. *Ann. N. Y. Acad. Sci.* **2010**, *1191*, 62–88. [\[CrossRef\]](#) [\[PubMed\]](#)
47. Ocklenburg, S.; Friedrich, P.; Fraenz, C.; Schlüter, C.; Beste, C.; Güntürkün, O.; Genç, E. Neurite architecture of the planum temporale predicts neurophysiological processing of auditory speech. *Sci. Adv.* **2018**, *4*, eaar6830. [\[CrossRef\]](#) [\[PubMed\]](#)
48. Galuske, R.A.; Schlote, W.; Bratzke, H.; Singer, W. Interhemispheric asymmetries of the modular structure in human temporal cortex. *Science* **2000**, *289*, 1946–1949. [\[CrossRef\]](#)
49. Dorsaint-Pierre, R.; Penhune, V.B.; Watkins, K.E.; Neelin, P.; Lerch, J.P.; Bouffard, M.; Zatorre, R.J. Asymmetries of the planum temporale and Heschl's gyrus: Relationship to language lateralization. *Brain* **2006**, *129*, 1164–1176. [\[CrossRef\]](#)
50. Foundas, A.L.; Leonard, C.M.; Gilmore, R.; Fennell, E.; Heilman, K.M. Planum temporale asymmetry and language dominance. *Neuropsychologia* **1994**, *32*, 1225–1231. [\[CrossRef\]](#) [\[PubMed\]](#)
51. Geschwind, N.; Levitsky, W. Human brain: Left-right asymmetries in temporal speech region. *Science* **1968**, *161*, 186–187. [\[CrossRef\]](#) [\[PubMed\]](#)
52. Rojas, D.C.; Camou, S.L.; Reite, M.L.; Rogers, S.J. Planum temporale volume in children and adolescents with autism. *J. Autism Dev. Disord.* **2005**, *35*, 479–486. [\[CrossRef\]](#)
53. Eckert, M.A.; Leonard, C.M. Structural imaging in dyslexia: The planum temporale. *Ment. Retard. Dev. Disabil. Res. Rev.* **2000**, *6*, 198–206. [\[CrossRef\]](#) [\[PubMed\]](#)
54. Plante, E.; Swisher, L.; Vance, R.; Rapcsak, S. MRI findings in boys with specific language impairment. *Brain Lang.* **1991**, *41*, 52–66. [\[CrossRef\]](#)
55. Cohen, M.; Campbell, R.; Yaghai, F. Neuropathological abnormalities in developmental dysphasia. *Ann. Neurol. Off. J. Am. Neurol. Assoc. Child Neurol. Soc.* **1989**, *25*, 567–570. [\[CrossRef\]](#) [\[PubMed\]](#)
56. Galaburda, A.M.; Sherman, G.F.; Rosen, G.D.; Aboitiz, F.; Geschwind, N. Developmental dyslexia: Four consecutive patients with cortical anomalies. *Ann. Neurol. Off. J. Am. Neurol. Assoc. Child Neurol. Soc.* **1985**, *18*, 222–233. [\[CrossRef\]](#) [\[PubMed\]](#)
57. Jernigan, T.L.; Hesselink, J.R.; Sowell, E.; Tallal, P.A. Cerebral structure on magnetic resonance imaging in language- and learning-impaired children. *Arch. Neurol.* **1991**, *48*, 539–545. [\[CrossRef\]](#)
58. Preis, S.; Jäncke, L.; Schittler, P.; Huang, Y.; Steinmetz, H. Normal intrasylvian anatomical asymmetry in children with developmental language disorder. *Neuropsychologia* **1998**, *36*, 849–855. [\[CrossRef\]](#)
59. De Fossé, L.; Hodge, S.M.; Makris, N.; Kennedy, D.N.; Caviness, V.S.; McGrath, L.; Steele, S.; Ziegler, D.A.; Herbert, M.R.; Frazier, J.A.; et al. Language-association cortex asymmetry in autism and specific language impairment. *Ann. Neurol.* **2004**, *56*, 757–766. [\[CrossRef\]](#) [\[PubMed\]](#)
60. Rogalsky, C.; Matchin, W.; Hickok, G. Broca's area, sentence comprehension, and working memory: An fMRI study. *Front. Hum. Neurosci.* **2008**, *2*, 237. [\[CrossRef\]](#)
61. Grodzinsky, Y. The neurology of syntax: Language use without Broca's area. *Behav. Brain Sci.* **2000**, *23*, 1–21. [\[CrossRef\]](#)

62. Martin, R.C. Language processing: Functional organization and neuroanatomical basis. *Annu. Rev. Psychol.* **2003**, *54*, 55–89. [\[CrossRef\]](#) [\[PubMed\]](#)
63. Hope, T.M.; Prejawa, S.; Parker Jones, Ö.; Oberhuber, M.; Seghier, M.L.; Green, D.W.; Price, C.J. Dissecting the functional anatomy of auditory word repetition. *Front. Hum. Neurosci.* **2014**, *8*, 246. [\[CrossRef\]](#)
64. Lee, J.C.; Dick, A.S.; Tomblin, J.B. Altered brain structures in the dorsal and ventral language pathways in individuals with and without developmental language disorder (DLD). *Brain Imaging Behav.* **2020**, *14*, 2569–2586. [\[CrossRef\]](#)
65. Watkins, K.E.; Vargha-Khadem, F.; Ashburner, J.; Passingham, R.E.; Connelly, A.; Friston, K.J.; Frackowiak, R.S.; Mishkin, M.; Gadian, D.G. MRI analysis of an inherited speech and language disorder: Structural brain abnormalities. *Brain* **2002**, *125*, 465–478. [\[CrossRef\]](#)
66. Herbert, M.R.; Ziegler, D.A.; Deutsch, C.; O'Brien, L.M.; Kennedy, D.N.; Filipek, P.; Bakardjiev, A.; Hodgson, J.; Takeoka, M.; Makris, N. Brain asymmetries in autism and developmental language disorder: A nested whole-brain analysis. *Brain* **2005**, *128*, 213–226. [\[CrossRef\]](#) [\[PubMed\]](#)
67. Booth, J.R.; Wood, L.; Lu, D.; Houk, J.C.; Bitan, T. The role of the basal ganglia and cerebellum in language processing. *Brain Res.* **2007**, *1133*, 136–144. [\[CrossRef\]](#)
68. Crosson, B.; Benefield, H.; Cato, M.A.; Sadek, J.R.; Moore, A.B.; Wierenga, C.E.; Gopinath, K.; Soltysik, D.; Bauer, R.M.; Auerbach, E.J.; et al. Left and right basal ganglia and frontal activity during language generation: Contributions to lexical, semantic, and phonological processes. *J. Int. Neuropsychol. Soc.* **2003**, *9*, 1061–1077. [\[CrossRef\]](#)
69. Tan, A.P.; Ngoh, Z.M.; Yeo, S.S.P.; Koh, D.X.P.; Gluckman, P.; Chong, Y.S.; Daniel, L.M.; Rifkin-Graboi, A.; Fortier, M.V.; Qiu, A.; et al. Left lateralization of neonatal caudate microstructure affects emerging language development at 24 months. *Eur. J. Neurosci.* **2021**, *54*, 4621–4637. [\[CrossRef\]](#)
70. Thibault, S.; Py, R.; Gervasi, A.M.; Salemm, R.; Koun, E.; Lövdén, M.; Boulenger, V.; Roy, A.C.; Brozzoli, C. Tool use and language share syntactic processes and neural patterns in the basal ganglia. *Science* **2021**, *374*, eabe0874. [\[CrossRef\]](#) [\[PubMed\]](#)
71. Wahl, M.; Marzinzik, F.; Friederici, A.D.; Hahne, A.; Kupsch, A.; Schneider, G.-H.; Saddy, D.; Curio, G.; Klostermann, F. The Human Thalamus Processes Syntactic and Semantic Language Violations. *Neuron* **2008**, *59*, 695–707. [\[CrossRef\]](#) [\[PubMed\]](#)
72. Krishnan, S.; Watkins, K.E.; Bishop, D.V.M. Neurobiological Basis of Language Learning Difficulties. *Trends Cogn. Sci.* **2016**, *20*, 701–714. [\[CrossRef\]](#) [\[PubMed\]](#)
73. Ullman, M.T.; Pierpont, E.I. Specific language impairment is not specific to language: The procedural deficit hypothesis. *Cortex* **2005**, *41*, 399–433. [\[CrossRef\]](#)
74. Krishnan, S.; Cler, G.J.; Smith, H.J.; Willis, H.E.; Asaridou, S.S.; Healy, M.P.; Papp, D.; Watkins, K.E. Quantitative MRI reveals differences in striatal myelin in children with DLD. *eLife* **2022**, *11*, e74242. [\[CrossRef\]](#)
75. Corrigan, N.M.; Yamykh, V.L.; Hippe, D.S.; Owen, J.P.; Huber, E.; Zhao, T.C.; Kuhl, P.K. Myelin development in cerebral gray and white matter during adolescence and late childhood. *NeuroImage* **2021**, *227*, 117678. [\[CrossRef\]](#)
76. Timmler, S.; Simons, M. Grey matter myelination. *Glia* **2019**, *67*, 2063–2070. [\[CrossRef\]](#)
77. Zhao, T.; Xu, Y.; He, Y. Graph theoretical modeling of baby brain networks. *NeuroImage* **2019**, *185*, 711–727. [\[CrossRef\]](#) [\[PubMed\]](#)
78. Dubois, J.; Dehaene-Lambertz, G.; Kulikova, S.; Poupon, C.; Hüppi, P.S.; Hertz-Pannier, L. The early development of brain white matter: A review of imaging studies in fetuses, newborns and infants. *Neuroscience* **2014**, *276*, 48–71. [\[CrossRef\]](#)
79. Lebel, C.; Gee, M.; Camicioli, R.; Wieler, M.; Martin, W.; Beaulieu, C. Diffusion tensor imaging of white matter tract evolution over the lifespan. *NeuroImage* **2012**, *60*, 340. [\[CrossRef\]](#)
80. Lebel, C.; Treit, S.; Beaulieu, C. A review of diffusion MRI of typical white matter development from early childhood to young adulthood. *NMR Biomed.* **2019**, *32*, e3778. [\[CrossRef\]](#)
81. Kaestner, E.; Balachandra, A.R.; Bahrami, N.; Reyes, A.; Lalani, S.J.; Macari, A.C.; Voets, N.L.; Drane, D.L.; Paul, B.M.; Bonilha, L. The white matter connectome as an individualized biomarker of language impairment in temporal lobe epilepsy. *NeuroImage Clin.* **2020**, *25*, 102125. [\[CrossRef\]](#)
82. Langer, N.; Peysakhovich, B.; Zuk, J.; Drott, M.; Sliva, D.D.; Smith, S.; Becker, B.L.; Grant, P.E.; Gaab, N. White matter alterations in infants at risk for developmental dyslexia. *Cereb. Cortex* **2017**, *27*, 1027–1036. [\[CrossRef\]](#)
83. Olivé, G.; Slušná, D.; Vaquero, L.; Muchart-López, J.; Rodríguez-Fornells, A.; Hinzen, W. Structural connectivity in ventral language pathways characterizes non-verbal autism. *Brain Struct. Funct.* **2022**, *227*, 1817–1829. [\[CrossRef\]](#) [\[PubMed\]](#)
84. Vanderauwera, J.; Wouters, J.; Vandermosten, M.; Ghesquière, P. Early dynamics of white matter deficits in children developing dyslexia. *Dev. Cogn. Neurosci.* **2017**, *27*, 69–77. [\[CrossRef\]](#)
85. Fletcher, P.T.; Whitaker, R.T.; Tao, R.; Dubray, M.B.; Froehlich, A.; Ravichandran, C.; Alexander, A.L.; Bigler, E.D.; Lange, N.; Lainhart, J.E. Microstructural connectivity of the arcuate fasciculus in adolescents with high-functioning autism. *NeuroImage* **2010**, *51*, 1117–1125. [\[CrossRef\]](#) [\[PubMed\]](#)
86. Li, M.; Wang, Y.; Tachibana, M.; Rahman, S.; Kagitani-Shimono, K. Atypical structural connectivity of language networks in autism spectrum disorder: A meta-analysis of diffusion tensor imaging studies. *Autism Res.* **2022**, *15*, 1585–1602. [\[CrossRef\]](#)
87. Dick, A.S.; Bernal, B.; Tremblay, P. The language connectome: New pathways, new concepts. *Neuroscientist* **2014**, *20*, 453–467. [\[CrossRef\]](#)
88. Hickok, G.; Poeppel, D. Dorsal and ventral streams: A framework for understanding aspects of the functional anatomy of language. *Cognition* **2004**, *92*, 67–99. [\[CrossRef\]](#)

89. Saur, D.; Kreher, B.W.; Schnell, S.; Kümmerer, D.; Kellmeyer, P.; Vry, M.-S.; Umarova, R.; Musso, M.; Glauche, V.; Abel, S.; et al. Ventral and dorsal pathways for language. *Proc. Natl. Acad. Sci. USA* **2008**, *105*, 18035–18040. [\[CrossRef\]](#)
90. Roberts, T.; Heiken, K.; Zarnow, D.; Dell, J.; Nagae, L.; Blaskey, L.; Solot, C.; Levy, S.; Berman, J.; Edgar, J. Left hemisphere diffusivity of the arcuate fasciculus: Influences of autism spectrum disorder and language impairment. *Am. J. Neuroradiol.* **2014**, *35*, 587–592. [\[CrossRef\]](#) [\[PubMed\]](#)
91. Vydrova, R.; Komarek, V.; Sanda, J.; Sterbova, K.; Jahodova, A.; Maulisova, A.; Zackova, J.; Reissigova, J.; Krsek, P.; Kyncl, M. Structural alterations of the language connectome in children with specific language impairment. *Brain Lang.* **2015**, *151*, 35–41. [\[CrossRef\]](#)
92. Simmonds, D.J.; Hallquist, M.N.; Asato, M.; Luna, B. Developmental stages and sex differences of white matter and behavioral development through adolescence: A longitudinal diffusion tensor imaging (DTI) study. *NeuroImage* **2014**, *92*, 356–368. [\[CrossRef\]](#)
93. Verly, M.; Gerrits, R.; Sleurs, C.; Lagae, L.; Sunaert, S.; Zink, I.; Rommel, N. The mis-wired language network in children with developmental language disorder: Insights from DTI tractography. *Brain Imaging Behav.* **2019**, *13*, 973–984. [\[CrossRef\]](#)
94. Liu, J.; Tsang, T.; Jackson, L.; Ponting, C.; Jeste, S.S.; Bookheimer, S.Y.; Dapretto, M. Altered lateralization of dorsal language tracts in 6-week-old infants at risk for autism. *Dev. Sci.* **2019**, *22*, e12768. [\[CrossRef\]](#)
95. Baum, G.L.; Cui, Z.; Roalf, D.R.; Ciric, R.; Betzel, R.F.; Larsen, B.; Cieslak, M.; Cook, P.A.; Xia, C.H.; Moore, T.M.; et al. Development of structure–function coupling in human brain networks during youth. *Proc. Natl. Acad. Sci. USA* **2020**, *117*, 771–778. [\[CrossRef\]](#)
96. Liégeois, F.; Baldeweg, T.; Connelly, A.; Gadian, D.G.; Mishkin, M.; Vargha-Khadem, F. Language fMRI abnormalities associated with FOXP2 gene mutation. *Nat. Neurosci.* **2003**, *6*, 1230–1237. [\[CrossRef\]](#)
97. De Guibert, C.; Maumet, C.; Jannin, P.; Ferré, J.-C.; Tréguier, C.; Barillot, C.; Le Rumeur, E.; Allaire, C.; Biraben, A. Abnormal functional lateralization and activity of language brain areas in typical specific language impairment (developmental dysphasia). *Brain* **2011**, *134*, 3044–3058. [\[CrossRef\]](#)
98. Pigdon, L.; Willmott, C.; Reilly, S.; Conti-Ramsden, G.; Liegeois, F.; Connelly, A.; Morgan, A.T. The neural basis of nonword repetition in children with developmental speech or language disorder: An fMRI study. *Neuropsychologia* **2020**, *138*, 107312. [\[CrossRef\]](#)
99. Abbott, N.T.; Baker, C.J.; Chen, C.; Liu, T.T.; Love, T.E. Defining Hypoperfusion in Chronic Aphasia: An Individualized Thresholding Approach. *Brain Sci.* **2021**, *11*, 491. [\[CrossRef\]](#) [\[PubMed\]](#)
100. Kiran, S.; Thompson, C.K. Neuroplasticity of Language Networks in Aphasia: Advances, Updates, and Future Challenges. *Front. Neurol.* **2019**, *10*, 295. [\[CrossRef\]](#)
101. Hugdahl, K.; Gundersen, H.; Brekke, C.; Thomsen, T.; Rimol, L.M.; Ersland, L.; Niemi, J. fMRI brain activation in a Finnish family with specific language impairment compared with a normal control group. *J. Speech Lang. Hear. Res.* **2004**, *47*, 162–172. [\[CrossRef\]](#) [\[PubMed\]](#)
102. Plante, E.; Patterson, D.; Sandoval, M.; Vance, C.J.; Asbjørnsen, A.E. An fMRI study of implicit language learning in developmental language impairment. *NeuroImage Clin.* **2017**, *14*, 277–285. [\[CrossRef\]](#)
103. Dibbets, P.; Bakker, K.; Jolles, J. Functional MRI of task switching in children with specific language impairment (SLI). *Neurocase* **2006**, *12*, 71–79. [\[CrossRef\]](#) [\[PubMed\]](#)
104. Schmithorst, V.J.; Vannest, J.; Lee, G.; Hernandez-Garcia, L.; Plante, E.; Rajagopal, A.; Holland, S.K.; Consortium, C.A. Evidence that neurovascular coupling underlying the BOLD effect increases with age during childhood. *Hum. Brain Mapp.* **2015**, *36*, 1–15. [\[CrossRef\]](#)
105. Shaw, K.; Bell, L.; Boyd, K.; Grijseels, D.M.; Clarke, D.; Bonnar, O.; Crombag, H.S.; Hall, C.N. Neurovascular coupling and oxygenation are decreased in hippocampus compared to neocortex because of microvascular differences. *Nat. Commun.* **2021**, *12*, 3190. [\[CrossRef\]](#) [\[PubMed\]](#)
106. Bonakdarpour, B.; Parrish, T.B.; Thompson, C.K. Hemodynamic response function in patients with stroke-induced aphasia: Implications for fMRI data analysis. *NeuroImage* **2007**, *36*, 322–331. [\[CrossRef\]](#)
107. Brumm, K.P.; Perthen, J.E.; Liu, T.T.; Haist, F.; Ayalon, L.; Love, T. An arterial spin labeling investigation of cerebral blood flow deficits in chronic stroke survivors. *Neuroimage* **2010**, *51*, 995–1005. [\[CrossRef\]](#)
108. Love, T.; Swinney, D.; Wong, E.; Buxton, R. Perfusion imaging and stroke: A more sensitive measure of the brain bases of cognitive deficits. *Aphasiology* **2002**, *16*, 873–883. [\[CrossRef\]](#) [\[PubMed\]](#)
109. Chiron, C.; Pinton, F.; Masure, M.; Duvelloy-Hommet, C.; Leon, F.; Billard, C. Hemispheric specialization using SPECT and stimulation tasks in children with dysphasia and dystrophia. *Dev. Med. Child Neurol.* **1999**, *41*, 512–520. [\[CrossRef\]](#)
110. Denays, R.; Tondeur, M.; Foulon, M.; Verstraeten, F.; Ham, H.; Piepsz, A.; Noël, P. Regional brain blood flow in congenital dysphasia: Studies with technetium-99m HM-PAO SPECT. *J. Nucl. Med.* **1989**, *30*, 1825–1829.
111. Lou, H.; Henriksen, L.; Bruhn, P. Focal cerebral dysfunction in developmental learning disabilities. *Lancet* **1990**, *335*, 8–11. [\[CrossRef\]](#) [\[PubMed\]](#)
112. Ors, M.; Ryding, E.; Lindgren, M.; Gustafsson, P.; Blennow, G.; Rosén, I. SPECT findings in children with specific language impairment. *Cortex* **2005**, *41*, 316–326. [\[CrossRef\]](#)
113. Tzourio, N.; Heim, A.; Zilbovicius, M.; Gerard, C.; Mazoyer, B.M. Abnormal regional CBF response in left hemisphere of dysphasic children during a language task. *Pediatr. Neurol.* **1994**, *10*, 20–26. [\[CrossRef\]](#)
114. Hwang, J.W.; Lee, J.-B.; Kim, B.-N.; Lee, H.-Y.; Lee, D.-S.; Shin, M.-S.; Cho, S.-C. Regional cerebral perfusion abnormalities in developmental language disorder. *Eur. Arch. Psychiatry Clin. Neurosci.* **2006**, *256*, 131–137. [\[CrossRef\]](#) [\[PubMed\]](#)

115. Im, S.-H.; Park, E.S.; Kim, D.Y.; Song, D.H.; Lee, J.D. The neuroradiological findings of children with developmental language disorder. *Yonsei Med. J.* **2007**, *48*, 405–411. [\[CrossRef\]](#) [\[PubMed\]](#)
116. Whitehouse, A.J.O.; Bishop, D.V.M. Cerebral dominance for language function in adults with specific language impairment or autism. *Brain* **2008**, *131*, 3193–3200. [\[CrossRef\]](#)
117. Paniukov, D.; Lebel, R.; Giesbrecht, G.; Lebel, C. Cerebral Blood Flow Increases Across Early Childhood. *Neuroimage* **2020**, *204*, 116224. [\[CrossRef\]](#)
118. Avants, B.B.; Duda, J.T.; Kilroy, E.; Krasileva, K.; Jann, K.; Kandel, B.T.; Tustison, N.J.; Yan, L.; Jog, M.; Smith, R. The pediatric template of brain perfusion. *Sci. Data* **2015**, *2*, 150003. [\[CrossRef\]](#)
119. Moses, P.; Hernandez, L.M.; Orient, E. Age-related differences in cerebral blood flow underlie the BOLD fMRI signal in childhood. *Front. Psychol.* **2014**, *5*, 300. [\[CrossRef\]](#)
120. Wu, C.; Honarmand, A.R.; Schnell, S.; Kuhn, R.; Schoeneman, S.E.; Ansari, S.A.; Carr, J.; Markl, M.; Shaibani, A. Age-related changes of normal cerebral and cardiac blood flow in children and adults aged 7 months to 61 years. *J. Am. Heart Assoc.* **2016**, *5*, e002657. [\[CrossRef\]](#) [\[PubMed\]](#)
121. Purkayastha, S.; Sorond, F. Transcranial Doppler ultrasound: Technique and application. *Semin. Neurol.* **2012**, *32*, 411–420. [\[CrossRef\]](#)
122. Leonard, L.B. Children with specific language impairment and their contribution to the study of language development. *J. Child Lang.* **2014**, *41*, 38–47. [\[CrossRef\]](#) [\[PubMed\]](#)
123. Rice, M.L.; Wexler, K.; Cleave, P.L. Specific language impairment as a period of extended optional infinitive. *J. Speech Lang. Hear. Res.* **1995**, *38*, 850–863. [\[CrossRef\]](#)
124. Wexler, K.; Lightfoot, D.; Homstein, N. *Verb Movement*; Cambridge University Press: Cambridge, UK, 1994.
125. Rice, M.L.; Wexler, K.; Hershberger, S. Tense over time: The longitudinal course of tense acquisition in children with specific language impairment. *J. Speech Lang. Hear. Res.* **1998**, *41*, 1412–1431. [\[CrossRef\]](#)
126. Wexler, K.; Schütze, C.T.; Rice, M. Subject case in children with SLI and unaffected controls: Evidence for the Agr/Tns omission model. *Lang. Acquis.* **1998**, *7*, 317–344. [\[CrossRef\]](#)
127. Wexler, K. Very early parameter setting and the unique checking constraint: A new explanation of the optional infinitive stage. *Lingua* **1998**, *106*, 23–79. [\[CrossRef\]](#)
128. Van der Lely, H.K. SLI in children: Movement, economy, and deficits in the computational-syntactic system. *Lang. Acquis.* **1998**, *7*, 161–192. [\[CrossRef\]](#)
129. Marshall, C.R.; Van Der Lely, H.K. The impact of phonological complexity on past tense inflection in children with Grammatical-SLI. *Adv. Speech Lang. Pathol.* **2007**, *9*, 191–203. [\[CrossRef\]](#)
130. Ingram, D.; Carr, L. When morphology ability exceeds syntactic ability: A case study. In Proceedings of the Convention of the American Speech-Language-Hearing Association, New Orleans, LA, USA, 17–21 November 1994.
131. Marshall, C.R.; van der Lely, H.K. A challenge to current models of past tense inflection: The impact of phonotactics. *Cognition* **2006**, *100*, 302–320. [\[CrossRef\]](#)
132. Leonard, L.B.; Kueser, J.B. Five overarching factors central to grammatical learning and treatment in children with developmental language disorder. *Int. J. Lang. Commun. Disord.* **2019**, *54*, 347–361. [\[CrossRef\]](#)
133. Tagarelli, K.M.; Shattuck, K.F.; Turkeltaub, P.E.; Ullman, M.T. Language learning in the adult brain: A neuroanatomical meta-analysis of lexical and grammatical learning. *NeuroImage* **2019**, *193*, 178–200. [\[CrossRef\]](#)
134. Kuhnke, P.; Meyer, L.; Friederici, A.D.; Hartwigsen, G. Left posterior inferior frontal gyrus is causally involved in reordering during sentence processing. *Neuroimage* **2017**, *148*, 254–263. [\[CrossRef\]](#)
135. Copland, D.A.; Brownsett, S.; Iyer, K.; Angwin, A.J. Corticostriatal regulation of language functions. *Neuropsychol. Rev.* **2021**, *31*, 472–494. [\[CrossRef\]](#)
136. Tallal, P.; Piercy, M. Defects of Non-Verbal Auditory Perception in Children with Developmental Aphasia. *Nature* **1973**, *241*, 468–469. [\[CrossRef\]](#)
137. Tallal, P.; Piercy, M. Developmental aphasia: Rate of auditory processing and selective impairment of consonant perception. *Neuropsychologia* **1974**, *12*, 83–93. [\[CrossRef\]](#)
138. Schwartz, R.G.; Scheffler, F.L.V.; Lopez, K. Speech perception and lexical effects in specific language impairment. *Clin. Linguist. Phon.* **2013**, *27*, 339–354. [\[CrossRef\]](#) [\[PubMed\]](#)
139. Leonard, L.B.; McGregor, K.K.; Allen, G.D. Grammatical morphology and speech perception in children with specific language impairment. *J. Speech Lang. Hear. Res.* **1992**, *35*, 1076–1085. [\[CrossRef\]](#) [\[PubMed\]](#)
140. Baddeley, A. The episodic buffer: A new component of working memory? *Trends Cogn. Sci.* **2000**, *4*, 417–423. [\[CrossRef\]](#)
141. Baddeley, A. Working memory and language: An overview. *J. Commun. Disord.* **2003**, *36*, 189–208. [\[CrossRef\]](#)
142. Baddeley, A.D.; Hitch, G. Working memory. In *Psychology of Learning and Motivation*; Elsevier: Amsterdam, The Netherlands, 1974; Volume 8, pp. 47–89.
143. Gathercole, S.E.; Baddeley, A.D. Evaluation of the role of phonological STM in the development of vocabulary in children: A longitudinal study. *J. Mem. Lang.* **1989**, *28*, 200–213. [\[CrossRef\]](#)
144. Gathercole, S.E.; Baddeley, A.D. Phonological memory deficits in language disordered children: Is there a causal connection? *J. Mem. Lang.* **1990**, *29*, 336–360. [\[CrossRef\]](#)

145. Estes, K.G.; Evans, J.L.; Else-Quest, N.M. Differences in the nonword repetition performance of children with and without specific language impairment: A meta-analysis. *J. Speech Lang. Hear. Res.* **2007**, *50*, 177–195. [\[CrossRef\]](#)
146. Ferrill, M.; Love, T.; Walenski, M.; Shapiro, L.P. The time-course of lexical activation during sentence comprehension in people with aphasia. *Am. J. Speech-Lang. Pathol.* **2012**, *21*, S179–S189. [\[CrossRef\]](#) [\[PubMed\]](#)
147. Robertson, E.K.; Gallant, J.E. Eye tracking reveals subtle spoken sentence comprehension problems in children with dyslexia. *Lingua* **2019**, *228*, 102708. [\[CrossRef\]](#)
148. Brauer, J.; Anwander, A.; Perani, D.; Friederici, A.D. Dorsal and ventral pathways in language development. *Brain Lang.* **2013**, *127*, 289–295. [\[CrossRef\]](#)
149. Perani, D.; Saccuman, M.C.; Scifo, P.; Anwander, A.; Spada, D.; Baldoli, C.; Poloniato, A.; Lohmann, G.; Friederici, A.D. Neural language networks at birth. *Proc. Natl. Acad. Sci. USA* **2011**, *108*, 16056–16061. [\[CrossRef\]](#)
150. Labache, L.; Joliot, M.; Saracco, J.; Jobard, G.; Hesling, I.; Zago, L.; Mellet, E.; Petit, L.; Crivello, F.; Mazoyer, B.; et al. A SENtence Supramodal Areas Atlas (SENSAAS) based on multiple task-induced activation mapping and graph analysis of intrinsic connectivity in 144 healthy right-handers. *Brain Struct. Funct.* **2019**, *224*, 859–882. [\[CrossRef\]](#) [\[PubMed\]](#)
151. Love, T.; Swinney, D.; Walenski, M.; Zurif, E. How left inferior frontal cortex participates in syntactic processing: Evidence from aphasia. *Brain Lang.* **2008**, *107*, 203–219. [\[CrossRef\]](#) [\[PubMed\]](#)
152. Hula, W.D.; McNeil, M.R. Models of attention and dual-task performance as explanatory constructs in aphasia. *Semin. Speech Lang.* **2008**, *29*, 169–187. [\[CrossRef\]](#) [\[PubMed\]](#)
153. Montgomery, J.W. Relation of working memory to off-line and real-time sentence processing in children with specific language impairment. *Appl. Psycholinguist.* **2000**, *21*, 117–148. [\[CrossRef\]](#)
154. Just, M.A.; Carpenter, P.A. A capacity theory of comprehension: Individual differences in working memory. *Psychol. Rev.* **1992**, *99*, 122. [\[CrossRef\]](#)
155. Kail, R. A method for studying the generalized slowing hypothesis in children with specific language impairment. *J. Speech Lang. Hear. Res.* **1994**, *37*, 418–421. [\[CrossRef\]](#)
156. Windsor, J.; Kohnert, K. The Search for Common Ground. *J. SpeechLang. Hear. Res.* **2004**, *47*, 877–890. [\[CrossRef\]](#)
157. Jednoróg, K.; Marchewka, A.; Altarelli, I.; Monzalvo Lopez, A.K.; Van Ermingen-Marbach, M.; Grande, M.; Grabowska, A.; Heim, S.; Ramus, F. How reliable are gray matter disruptions in specific reading disability across multiple countries and languages? insights from a large-scale voxel-based morphometry study. *Hum. Brain Mapp.* **2015**, *36*, 1741–1754. [\[CrossRef\]](#)
158. Friedrich, P.; Fraenz, C.; Schlüter, C.; Ocklenburg, S.; Mädler, B.; Güntürkün, O.; Genç, E. The relationship between axon density, myelination, and fractional anisotropy in the human corpus callosum. *Cereb. Cortex* **2020**, *30*, 2042–2056. [\[CrossRef\]](#)
159. Krishnan, S.; Asaridou, S.S.; Cler, G.J.; Smith, H.J.; Willis, H.E.; Healy, M.P.; Thompson, P.A.; Bishop, D.V.M.; Watkins, K.E. Functional organisation for verb generation in children with developmental language disorder. *NeuroImage* **2021**, *226*, 117599. [\[CrossRef\]](#)
160. Plante, E. MRI findings in the parents and siblings of specifically language-impaired boys. *Brain Lang.* **1991**, *41*, 67–80. [\[CrossRef\]](#) [\[PubMed\]](#)
161. Weismer, S.E.; Plante, E.; Jones, M.; Tomblin, J.B. A functional magnetic resonance imaging investigation of verbal working memory in adolescents with specific language impairment. *J. Speech Lang. Hear. Res.* **2005**, *48*, 405–425. [\[CrossRef\]](#)

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Acknowledgements

Chapter 2, in full, is a reprint of the material as it appears in Abbott, N., & Love, T. (2023). Bridging the Divide: Brain and Behavior in Developmental Language Disorder. *Brain Sciences*, 13(11), 1606. The dissertation author was the primary investigator and author of this paper.

Chapter 3
BRAIN FUNCTION IN DEVELOPMENTAL LANGUAGE DISORDER

1. Introduction

Developmental Language Disorder (DLD) is a heterogeneous neurodevelopmental disorder that impacts a child's ability to comprehend and produce spoken or written language. DLD affects around 7-8% of kindergarten-age children in the United States making it more prevalent in childhood than other more widely recognized neurodevelopmental disorders such as ADHD (~5%) and ASD (~2.8%) of the population (Conti-Ramsden, 2001; Maenner et al., 2020; McGregor, 2020). Importantly, the language deficits observed in DLD cannot be attributed to hearing loss, intellectual disability, or neurological damage. Children with DLD experience higher levels of social anxiety and depression than typically developing (TD) children and these challenges often persist into adulthood (Botting, 2020). Despite the disorder's prevalence and significant impact on overall well-being, the underlying neurobiological mechanisms remain poorly understood, largely due to inconsistent findings across neuroimaging studies. Nonetheless, there is growing evidence that both structural and functional brain differences exist. This chapter aims to elucidate functional brain abnormalities in children with DLD, focusing on cerebral blood flow and functional connectivity patterns.

Functional magnetic resonance imaging (fMRI) is a widely used tool for exploring brain activity in children with and without neurodevelopmental disorders. Using fMRI, researchers can observe how specific brain regions are activated during language tasks, offering insights into the neural substrates that support or disrupt language processing. However, the few functional magnetic resonance imaging (fMRI) studies of children with DLD have found varying results for between- and within- group comparisons, which has made it difficult to draw conclusions about differences in functional brain activation patterns between TD children and children with DLD. Despite the difficulty of aggregating findings across studies, some notable brain regions have been consistently implicated in DLD, including the inferior frontal gyri, the superior temporal

gyri, and the basal ganglia (Abbott & Love, 2023; Ullman et al., 2024), but the precise nature of these differences in DLD is still unclear. As previously discussed in Abbott et al. (2023) (chapter 2), one reason for the discrepant results across studies has to do with differences in methodology, including but not limited to the tasks employed in the scanner, the age ranges of the children included, and the processing pipelines and analyses used. However, discrepant results may also be related to differences in the underlying properties that support brain function. In this chapter, I argue for the importance of better characterizing cerebral blood flow and functional connectivity patterns in children with DLD to better inform future investigations of functional brain differences in DLD.

1.1. Cerebral Blood Flow in Child Populations

Cerebral blood flow (CBF) is intricately linked to neuronal activity, with active neurons demanding increased blood flow to supply necessary oxygen and glucose. The fMRI blood oxygen level-dependent (BOLD) signal hinges on this relationship, capturing changes in blood oxygenation as a proxy for neural activity (Li et al., 2012; Ogawa et al., 1990). However, the BOLD signal is also sensitive to changes in cerebral blood volume (CBV) and cerebral metabolic rate of oxygen (CMRO₂), which together with CBF, influence the observed signal (Simon & Buxton, 2015). Thus, accurate interpretation of the BOLD signal requires assumptions about neurovascular coupling, which may not hold true in clinical populations like children with DLD. Early studies measuring CBF using single-photon emission computed tomography (SPECT) and positron emission tomography (PET) indicated abnormal hemispheric lateralization and hypoperfusion (reduced CBF) in left hemisphere language regions in children with DLD (Lou et al., 1990; Tzourio et al., 1994). More recent methods, such as transcranial Doppler (TCD), also suggest atypical CBF patterns, including reduced perfusion in language-related brain areas

(Whitehouse & Bishop, 2008). To date, no studies have investigated CBF patterns using arterial spin labeling (ASL) MRI in children with DLD. ASL is a non-invasive method (unlike SPECT/PET which require the injection of a radioactive tracer), that quickly captures whole brain CBF patterns and provides quantified values that can be compared between populations (Alsop et al., 2015).

A number of studies have sought to determine average CBF values in gray and white matter by age in TD children as a benchmark for typical development. For example, in a longitudinal study by Paniukov et al. (2020), the authors investigated changes in CBF values in children between the ages of 2-7 years (Paniukov et al., 2019). In support of previous findings, they found that CBF steadily increased across age at a rate of about 3.20 mL/100g/min per year in gray matter (Avants et al., 2015; Paniukov et al., 2019). Studies have varied in terms of peak mean CBF values in gray matter, but most suggest a peak around 8-10 years of age of about ~75-100 mL/100g tissue/min (Avants et al., 2015; Jain et al., 2012; Liu et al., 2018; Taki et al., 2011), with a decline into adolescence around ~60-75 mL/100g tissue/min (Paniukov et al., 2019; Satterthwaite et al., 2014; Soni et al., 2016). Findings of the relationship between CBF changes and biological sex have also been varied. For example, one study reported no differences between CBF values based on biological sex (Paniukov et al., 2019), while another reported that females have higher regional CBF values in the precuneus and posterior cingulate cortex bilaterally, as well as the left thalamus (Taki et al., 2011). Others have found that this relationship changes across development. In these studies, younger children demonstrated more pronounced differences, with males peaking earlier than females (Lenroot et al., 2007) and females experiencing increases in CBF levels into adolescence rather than decreases (Satterthwaite et al., 2014)

In clinical pediatric populations, these CBF values can differ. For example, Yerys et al. (2018) found a relationship between decreased CBF in areas of the brain related to social perception and cognition in children with ASD (Yerys et al., 2018). Similarly, Ye et al. (2022) found a relationship between poorer language abilities and decreased CBF in the left frontal lobe of children with ASD (Ye et al., 2022). Findings such as these have important implications for modeling the hemodynamic response function (HRF) during fMRI BOLD studies (Lindquist et al., 2009). The HRF is a model of the coupling between neuronal activity and the resulting changes in blood oxygen levels (Rangaprakash et al., 2021). The canonical shape of the HRF typically includes an initial dip, reflecting a brief increase in deoxyhemoglobin due to neural activity, followed by a sharp rise to a peak as blood flow increases, delivering oxygenated blood to the active area. This peak is then followed by a gradual return to baseline as the neural activity subsides and blood flow normalizes (Kim & Ress, 2016). Any alterations to CBF, CBV, and CMRO₂ can impact this model (Bonakdarpour et al., 2007; Duarte et al., 2015; Kim & Ress, 2016; Rangaprakash et al., 2021; Yan et al., 2018). For example, reduced CBF could lead to decreases in amplitude (response height) of the HRF or delays in the time-to-peak (Rangaprakash et al., 2021). These impacts necessitate careful consideration in fMRI studies, particularly when comparing populations that may have differing baseline CBF levels, such as may be the case in children with DLD. Inaccurate modeling and interpretation of the HRF could contribute to misinterpretations of functional imaging results, underscoring the need for precise modeling of hemodynamic responses in this population.

1.2. Functional Connectivity in Clinical Pediatric Populations

Functional connectivity refers to the temporal correlation of neural activity between distinct brain regions, reflecting the coordinated functioning of neural networks (Bijsterbosch et

al., 2017). The correlation of neural activity is measured through the BOLD signal, in that regions that have similar BOLD signal timeseries at-rest are considered functionally connected. As children grow, the cortical networks supporting language function reorganize, leading to more efficient connections that reflect enhanced language proficiency. Primary sensory networks, which resemble adult-like structures soon after birth, exhibit minimal changes during the first year of life (Gao et al., 2015). In contrast, the connectivity in higher-order networks, such as those governing language, undergo extended maturation and strengthen with age over the first decade of life (Dosenbach et al., 2010). This prolonged development is characterized by increasing specialization, which parallels the acquisition of various cognitive and behavioral skills across human development (Chen et al., 2021; Dosenbach et al., 2010). Specifically, the intrahemispheric connectivity (leftward asymmetry) of language regions becomes more pronounced with age and maturing language abilities (Berl et al., 2014; Emerson et al., 2016). This process highlights the dynamic nature of neural network development, which supports the refinement of language and other complex cognitive functions as children mature.

Prior research with children with neurodevelopmental disorders has revealed a relationship between altered language networks and language abilities. For example, in children with ASD who have concomitant language impairment, studies have found atypical lateralization patterns for language networks in younger kids (Eyler et al., 2012) and patterns of overconnectivity in older kids (Gao et al., 2019). This pattern suggests that aberrant development and organization of brain regions within the language network likely begins early in life and continues to contribute to adverse language outcomes later in life. To date, no studies have investigated resting-state functional connectivity patterns in children with DLD. Given that DLD strongly impacts language abilities, and these impacts often persist into adulthood, research

investigating network connectivity patterns is needed, as it may help explain the different patterns of neural activity that have been observed in fMRI studies and it could potentially help account for differences in language production and processing.

1.3. Current Study

In the current study, we argue that variable fMRI findings in children with DLD may have to do with differences in the underlying properties that support brain function (e.g., hemodynamic, network connectivity, etc.). Accurately characterizing the underlying properties of functional brain signals is essential for advancing our understanding of DLD.

Misinterpretations stemming from unaccounted variations in CBF, or an incomplete understanding of network connectivity can obscure neural activation patterns in DLD. While functional neuroimaging has provided valuable insights into the brain abnormalities associated with DLD, continued advancements in imaging methodologies and a deeper understanding of neurovascular dynamics and neural architecture are crucial. This will ensure that future studies can more accurately capture the complex neural underpinnings of DLD, paving the way for improved diagnostic and therapeutic approaches.

As an initial investigation into brain function in DLD, we employ metrics of brain health and functionality that include measures of CBF and resting state (intrinsic) functional connectivity (iFC) patterns to investigate potential biomarkers of DLD and their relationship to language abilities. In isolation, each of these brain measures has the potential to reveal insights into aberrant brain function in DLD, but when combined, they may reveal even greater insight into the efficiency of the neural system (Jann et al., 2015). In typically developing humans, there is a strong relationship between functional connectivity strength and CBF at rest in functional network hubs, such as those within the medial prefrontal cortex, posterior cingulate cortex, and

lateral temporal and parietal cortices (which are associated with the default mode network) (Liang et al., 2013). When neurons fire, blood vessels dilate and CBF increases in response to changing metabolic demands. As glucose and oxygen are consumed, the oxygenated content of the blood changes giving rise to the BOLD signal fluctuations that indicate functionally connected networks. In that way, CBF and FC strength are inextricably linked through brain metabolism. In particular, regions of the brain with long-range connections involved in higher order functions (such as the medial and lateral prefrontal cortex and temporo-parietal cortices) show higher correlations between CBF and FC strength than short range connections (Liang et al., 2013). Further, network hubs and long-range connections have high degrees of connectivity making them more metabolically demanding and susceptible to alterations between CBF and neural activity. In fact, a number of studies with individuals who have either developmental (e.g., ASD and Wilson's disease) or acquired (e.g., schizophrenia and traumatic brain injury) neurological disorders have demonstrated altered coupling between CBF and FC within networks implicated in the disorder (Hu et al., 2019; Jann et al., 2015; Sours et al., 2015; Zhu et al., 2017). Therefore, characterizing CBF and FC patterns as well as their relationship is an important step forward in better understanding how brain function contributes to language behavior in DLD.

The aims of the current study are as follows: (1) characterize patterns of CBF in children with DLD as compared to age-matched TD children; (2) examine network connectivity patterns in children with DLD as compared to age-matched TD children; and (3) determine if there is a relationship between CBF, iFC, and language behavior. Only a limited number of studies have investigated CBF patterns in DLD (using invasive methods) and no studies have investigated iFC patterns. Thus, we consider this an initial exploration into the underlying properties supporting

brain function in DLD. Our hypotheses are limited for aims 1 and 2 to expecting to see altered patterns in our DLD sample compared to our TD sample. For aim 3, we anticipate seeing a correlation between CBF and FC in our TD population. In addition, we expect that alterations in CBF and FC will be related to poorer language abilities.

2. Methods

2.1. Participants

Two male participants with DLD (mean age $\pm$ SD: 10.3 years $\pm$ 0.46) and 22 TD children (9.45 years $\pm$ 1.95, 13F/9M) participated in the study. Inclusion criteria for all participants were as follows: (i) heard/spoke only English from birth to 6 years of age; (ii) right-handed; (iii) between 6-12 years of age; (iv) scored at least 85 (within 1 SD of the normative mean) on the Test of Nonverbal Intelligence, Version 3 (TONI-3) deviation quotient (Brown et al., 1997); (v) had hearing within normal limits based on the ASHA Pure-Tone Screening Procedure (i.e., 50, 500, 1000, 2000, 3000, 4000, 6000, and 8000 Hz at 25dB or less (American Speech-Language-Hearing Association, 2005)); (vi) had no diagnosis of ASD or genetic disorders (e.g., Down syndrome, Williams Disorder, etc.); (vii) had no history of neurological impairments (e.g., epilepsy, head trauma, etc.); and (viii) had no contraindications to MRI (e.g., braces, claustrophobia). A summary of demographic information is provided in Table 3.1.

Participants with DLD were actively receiving services for speech and language difficulties at the time of testing. A diagnosis of DLD was further confirmed using the Clinical Evaluation of Language Fundamentals, Version 5 (CELF-5; (Wiig et al., 2013). Participants were categorized as having DLD if their scaled score was at least one standard deviation below the normative mean (≤ 7) on two or more of the four core language score (CLS) subtests of the CELF-5. Participants were categorized as TD children if they had no history of speech and

language problems, and they scored within one standard deviation of the normative mean on at least three of the CLS subtests.

All participants were recruited through flyers posted throughout the greater San Diego region, San Diego State University's (SDSU) Speech-Language Clinic, and previous child participant pools. Parents brought the children to SDSU for two behavioral testing sessions and one MRI session, each lasting approximately one hour. After each session, children were compensated for their time and got to choose a prize from the treasure chest. The study was approved under both the University of California San Diego (UCSD) and San Diego State University's Internal Review Board (IRB).

2.2 Language and Cognitive Assessment Battery

In addition to parents completing an extensive language and background questionnaire, participants completed a battery of standardized and non-standardized assessments to evaluate their language and cognitive skills. Since a diagnosis is based on exclusionary criteria, the expectation is that all participants will perform within normal limits on non-verbal measures with the DLD participants showing varying degrees of impairment in language and phonological working memory domains. All assessments were administered by the first author (N.A.) or trained research assistants in the Speech, Language, and Hearing Sciences Department at SDSU.

Participants' overall **language ability** was assessed using the four CLS subtests of the CELF-5 based on age group. For children 9-12 years of age, these subtests included Word Classes, Formulated Sentence, Recalling Sentences, and Semantic Relationships. For children 6-8 years of age, these subtests included, Sentence Comprehension, Word Structure, Formulated Sentences, and Recalling Sentences. Grammatical comprehension was assessed using the Test for Reception of Grammar, Version 2 (Bishop & Garsell, 2003). With the TROG-2, participants

are orally presented with 80 sentences with a range of complexity (e.g., active, clefts, object relatives, pronouns, etc.). Participants saw an array of four pictures while listening to each sentence and were instructed to select the picture that best matched the sentence they heard.

Phonological working memory was assessed using the Nonword Repetition (NWR) Task (Dollaghan & Campbell, 1998). During this task, participants heard nonsense words that increased in syllable length from one to four syllables and were asked to repeat the words exactly as they heard them. The TONI-3 was used as a measure of **non-verbal intelligence**. The TONI-3 assesses abstract/figural problem solving and reasoning while reducing the motoric, linguistic, and cultural loads of more traditional intelligence quotient (IQ) measures, thus making it useful for child and clinical populations. For this assessment, children were presented with a series of abstract or geometric images and were asked to select the correct image to complete a sequence or pattern.

Twenty-one out of the 22 participants completed all behavioral testing sessions, as one participant did not complete the TONI or TROG. For the CELF, TROG, and TONI, raw scores were converted to standard scores and percentiles based on age. For the NWR task, the total and percentage of correctly articulated phonemes was calculated. For all planned analyses, standard scores were used. Participant scores are reported in Table 3.1.

Table 3.1. Participant demographics for the TD children (averaged across group) and the two participants with DLD. Significant mean differences between each of the DLD participants and the TD group are denoted as follows: * $p < 0.05$, ** $p < 0.01$. Clinical Evaluation of Language Fundamentals, Core Language Score (CELF-CLS); Test of Nonverbal Intelligence (TONI); Test for Reception of Grammar (TROG); Non-Word Repetition (NWR). ¹All standardized scores have a mean of 100 (50th percentile -%ile) and standard deviation (SD) of ± 15 . ²For the TONI and TROG, $n = 21$ for the TD group as one participant did not complete the last testing session.

	DLD002	TD Group	DLD003	Mean Differences
N	-	22	-	-
Age mean (SD) / range (years)	10.75	9.45 (± 1.95) 6-12 years	10.42	DLD002 = TD Group DLD003 = TD Group
Sex	M	13 F / 9 M	M	-
CELF-CLS ¹ mean ($\pm$ SD) / %ile	77 6th	115.5 (± 11.2) 79th	84 14th	DLD002 < TD Group** DLD003 < TD Group**
TONI Standard Score ^{1, 2} mean ($\pm$ SD) / %ile	120 91st	109.1 (± 14.3) 66th	108 70th	DLD002 = TD Group DLD003 = TD Group
TROG Standard Score ^{1, 2} mean ($\pm$ SD) / %ile	106 66th	107.6 (± 8.5) 68th	88 21st	DLD002 = TD Group DLD003 < TD Group*
NWR Total Correct (out of 96) mean ($\pm$ SD) / % corr	84 87.5%	88.1 (± 6.1) 92%	88 92%	DLD002 = TD Group DLD003 = TD Group

2.2 MRI Acquisition

MRI data were acquired at SDSU's Imaging Center on a Siemens Prisma 3T scanner using a 32-channel head coil. Foam padding was used to reduce participant head motion during scanning. Participants were equipped with Optoacoustics OptoActive II Active Noise Cancelling Headphones and a microphone. A mirror was placed on the head coil for viewing videos on the scanner screen.

High resolution structural T1 images were acquired using a Magnetization Prepared Rapid Gradient Echo sequence with prospective motion correction (MPRAGE PROMO). In an effort to reduce head movement during the structural scan, participants could choose a movie or TV show to watch. Scan parameters were as follows: TR = 2.3 s; TE = 2.98 ms; slice thickness =

1.0 mm; voxel size = $1.0 \times 1.0 \times 1.0$ mm; matrix = 256×256 mm; flip angle = 9° ; FOV = 256×256 mm; scan time = 5:21 mins.

Resting-state cerebral blood flow (CBF) data were obtained using a pseudo-continuous arterial spin labeling (PCASL) sequence. With this technique, radiofrequency (RF) pulses invert the magnetization of protons in the blood. This inverted magnetization acts as an endogenous tracer, allowing blood flow to be tracked throughout the brain (Dai et al., 2008). During the scan, participants were asked to lie still in the scanner while watching a silent version of Inscapes (Vanderwal et al., 2015). Inscapes is a well-validated way to reduced head-motion and drowsiness during resting state scans, while also minimizing the cognitive aspects associated with watching a movie or performing a task. The video uses abstract shapes and movements reminiscent of nature (e.g., floating manta rays) and lacks typical features of movies like perspective changes, scene cuts, and drastic changes in luminance. Scan parameters were as follows: Labeling duration = 1.8 s; post labeling delay = 1.8 s; label offset = 90.00 mm; TE = 36.76 ms; TR = 4100 ms; M0 TR = 5000 ms; slices = 16; voxel size = 2.5 mm isotropic; flip angle = 120° ; FOV = 225mm x 225 mm x 150 mm; matrix size = 90 x 90 x 50; tag gap = 20 mm; scan time = 5:32 mins.

Finally, resting-state functional connectivity MRI (rs-fMRI) scans were obtained using a Multiband Echo Planar Imaging (EPI) sequence. During this scan participants watched Inscapes again but with the sound on to reduce boredom. The soundtrack was a piano score designed to complement the frequency of the Siemens scanner during the EPI sequence. It featured a slow tempo with limited pitch changes and used repetitive patterns. Scan parameters included: 2mm isotropic voxel size; TR = 800 ms; TE = 35 ms; flip angle = 52° ; slices = 72; multiband acceleration factor = 8; 104 x 104 matrix; FOV = 20.8 cm; scan time = 6:08 mins.

2.3.1. Arterial Spin-Labeled MRI Preprocessing and Cerebral Blood Flow Computation

Arterial spin-labeled MRI images were preprocessed using ASLPrep 0.2.8, which is based on Nipype 1.7.0 (Gorgolewski et al., 2011). The processing steps are reported based on the boilerplate methods provided through ASLPrep.

2.3.1.1. Anatomical data preprocessing. sMRIPrep 0.6.1 was used to process the anatomical data. A total of 1 T1-weighted (T1w) image was found within the input BIDS dataset. The T1-weighted (T1w) image was corrected for intensity non-uniformity (INU) with N4BiasFieldCorrection (Tustison et al., 2010), which is distributed with ANTs 2.3.1 (Avants et al., 2008). sMRIPrep uses this T1w reference throughout the workflow. The T1w-reference was then skull-stripped with a Nipype implementation of the antsBrainExtraction.sh workflow using OASIS30ANTs as the target template. Brain tissue segmentation of cerebrospinal fluid (CSF), white-matter (WM) and gray-matter (GM) was performed on the brain-extracted T1w reference image using FSL's FAST (Zhang et al., 2001). Nonlinear registration of the brain-extracted T1w reference image to the brain-extracted template was accomplished using antsRegistration. The following template was selected for spatial normalization: ICBM 152 Nonlinear Asymmetrical template version 2009c (Fonov et al., 2011).

2.3.1.2. ASL data preprocessing. For the 1 ASL run found per subject (across all tasks and sessions), the following preprocessing was performed. First, the middle volume of the ASL timeseries was selected as the reference volume and brain extracted using Nipype's custom brain extraction workflow. Head-motion parameters were estimated using FSL's mcflirt (Jenkinson et al., 2002). Next, ASLPrep wrote head-motion parameters to the ASL run's confound file. Susceptibility distortion correction (SDC) was omitted. ASLPrep co-registered the ASL reference to the T1w reference using FSL's flirt (Jenkinson & Smith, 2001), which implemented

the boundary-based registration cost-function (Greve & Fischl, 2009). Co-registration used 6 degrees of freedom. The quality of co-registration and normalization to template was quantified using the Dice and Jaccard indices, the cross-correlation with the reference image, and the overlap between the ASL and reference images (e.g., image coverage). Several confounding timeseries were calculated, including both framewise displacement (FD) and DVARS. FD and DVARS are calculated using the implementations in Nipype (following the definition by (Power et al., 2014)) for each ASL run. ASLPrep summarizes in-scanner motion as the mean framewise displacement and relative root-mean square displacement.

2.3.1.3. Cerebral blood flow computation and denoising. ASLPrep was configured to calculate cerebral blood flow (CBF) using the following methods. The cerebral blood flow (CBF) was quantified from preprocessed ASL data using a general kinetic model (Buxton et al., 1998). Structural Correlation based Outlier Rejection (SCORE) algorithm was applied to the CBF timeseries to discard CBF volumes with outlying values (Dolui, Wang, et al., 2017) before computing the mean CBF. Following SCORE, the Structural Correlation with RobUst Bayesian (SCRUB) algorithm was applied to the CBF maps using structural tissue probability maps to reweight the mean CBF (Dolui, Wolf, et al., 2017; Dolui et al., 2016). CBF was also computed with Bayesian Inference for Arterial Spin Labeling (BASIL) (Chappell et al., 2009), as implemented in FSL 6.0.3. BASIL computes CBF using a spatial regularization of the estimated perfusion image and additionally calculates a partial-volume corrected CBF image (Chappell et al., 2011). For each CBF map, the ROIs for the following atlases were extracted: the Harvard-Oxford and the Schaefer 200 and 400-parcel resolution atlases. The Quality evaluation index (QEI) was computed for each CBF map (Dolui et al., 2016). QEI is based on the similarity between the CBF and the structural images, the spatial variability of the CBF image, and the

percentage of grey matter voxels containing negative CBF values. All resampling in ASLPrep uses a single interpolation step that concatenates all transformations. Gridded (volumetric) resampling was performed using `antsApplyTransforms`, configured with Lanczos interpolation to minimize the smoothing effects of other kernels (Lanczos, 1964). Many internal operations of ASLPrep use Nilearn 0.8.1 (Abraham et al., 2014), NumPy (Harris et al., 2020), and SciPy (Virtanen et al., 2020). For more details of the pipeline, see [the ASLPrep documentation](#).

2.3.2. Resting State Functional Connectivity Preprocessing

Results included in this manuscript come from analyses performed using CONN (Whitfield-Gabrieli & Nieto-Castanon, 2012) (RRID:SCR_009550) release 21.a (Nieto-Castanon & Whitfield-Gabrieli, 2021) and SPM (Penny et al., 2011) (RRID:SCR_007037) release 12.7487. The processing steps are reported based on the boilerplate methods provided through CONN.

2.3.2.1. Preprocessing. Functional and anatomical data were preprocessed using a flexible preprocessing pipeline (Nieto-Castanon, 2020b) including realignment with correction of susceptibility distortion interactions, outlier detection, direct segmentation and MNI-space normalization, and smoothing. Functional data were realigned using SPM realign & unwarp procedure (Andersson et al., 2001), where all scans were co-registered to a reference image (first scan of the first session) using a least squares approach and a 6 parameter (rigid body) transformation (Friston et al., 1995), and resampled using b-spline interpolation to correct for motion and magnetic susceptibility interactions. Potential outlier scans were identified using ART (Whitfield-Gabrieli et al., 2011) as acquisitions with framewise displacement above 0.9 mm or global BOLD signal changes above 5 standard deviations (Nieto-Castanon, 2022; Power et al., 2014), and a reference BOLD image was computed for each subject by averaging all scans

excluding outliers. Functional and anatomical data were normalized into standard MNI space, segmented into grey matter, white matter, and CSF tissue classes, and resampled to 2 mm isotropic voxels following a direct normalization procedure (Calhoun et al., 2017; Nieto-Castanon, 2022) using SPM unified segmentation and normalization algorithm (Ashburner, 2007; Ashburner & Friston, 2005) with the default IXI-549 tissue probability map template. Last, functional data were smoothed using spatial convolution with a Gaussian kernel of 6 mm full width half maximum (FWHM).

2.3.2.2. Denoising. In addition, functional data were denoised using a standard denoising pipeline (Nieto-Castanon, 2020a) including the regression of potential confounding effects characterized by white matter timeseries (5 CompCor noise components), CSF timeseries (5 CompCor noise components), motion parameters and their first order derivatives (12 factors) (Friston et al., 1996), outlier scans (below 155 factors) (Power et al., 2014), session effects and their first order derivatives (2 factors), and linear trends (2 factors) within each functional run, followed by bandpass frequency filtering of the BOLD timeseries (Hallquist et al., 2013) between 0.008 Hz and 0.08 Hz. CompCor (Behzadi et al., 2007; Chai et al., 2012) noise components within white matter and CSF were estimated by computing the average BOLD signal as well as the largest principal components orthogonal to the BOLD average, motion parameters, and outlier scans within each subject's eroded segmentation masks. From the number of noise terms included in this denoising strategy, the effective degrees of freedom of the BOLD signal after denoising were estimated to range from 22.5 to 47.6 (average 43.2) across all subjects (Nieto-Castanon, 2022)

2.2. Analyses

Below we detail the approach to analyzing the neuroimaging and behavioral data within the framework of each of the stated aims of the paper.

2.4.1. Aim 1: Characterize Cerebral Blood Flow (CBF)

2.4.1.1. Between group comparisons. Recall, Aim 1 of this study was to characterize CBF patterns in children with DLD compared to TD children. To that end, we calculated CBF in the whole brain (WB), the left hemisphere (LH) and the right hemisphere (RH) for the TD group. In addition, we calculated CBF in language regions of interest (ROIs) that have shown structural and functional differences in children with DLD when compared to controls, using the Harvard-Oxford atlas. These regions include bilaterally the inferior frontal gyri (IFG), posterior superior temporal gyri (pSTG), posterior middle temporal gyri (pMTG), planum temporale (PT), insula, and angular gyri (AG) (Abbott & Love, 2023; Liégeois et al., 2014; Ullman et al., 2024). For the purposes of analysis, we refer to this group of ROIs as the “language network” or language-specific ROIs. In addition to these regions, we also created a separate group of ROIs that have been strongly implicated in DLD, which include the caudate and putamen bilaterally (known collectively as the striatum) and the frontal (frontal medial cortex, frontal operculum, frontal pole, IFG, and middle frontal gyrus) and parietal (supramarginal and angular gyri) regions, bilaterally (Ullman et al., 2024). We refer to this group of ROIs as the “language-related network” or just language-related ROIs in our analyses. We then compared the group averages for the WB, LH, RH, and network ROIs to each participant with DLD using the Crawford & Howell’s modified t-test (Crawford et al., 2009; Crawford & Howell, 1998). The Crawford & Howell’s t-test was designed to compare a single case subject to a larger group. The statistical method enables researchers to ascertain whether the participant’s score deviates significantly from the control group. Significant p-values indicate that the single case subject does not belong

to the control population. To correct for multiple comparisons, we applied FDR correction separately for each DLD participant for the global brain measures (three comparisons: WB, LH, RH) and ROIs (two comparisons: language ROIs and language-related ROIs).

2.4.1.2. Within group comparisons. Our sample of TD children included both males and females between 6-12 years of age. Given that CBF values change across development and some studies have shown variations between sex, we performed a simple linear regression with the TD group to explore the effect of these biological variables on CBF patterns. Next, to investigate laterality differences between the above measures by hemisphere (left vs right: WB, language-specific ROIs, and language-related ROIs), we then performed a series of paired samples t-tests, FDR corrected for multiple comparisons within each group.

2.4.2. Aim 2: Characterize intrinsic (resting state) functional connectivity patterns (iFC)

The goal of Aim 2 was to characterize iFC patterns in children with DLD compared to TD children. Thus, ROI-to-ROI connectivity (RRC) matrices were estimated indicating the functional connectivity between each ROI, yielding functional connectivity similarity matrices for each participant individually as well as the TD group as a whole (Desikan et al., 2006). Functional connectivity strength was represented by Fisher-transformed bivariate correlation coefficients (z-scores) from a general linear model (weighted-GLM (Nieto-Castanon, 2020b)), estimated separately for each pair of ROIs, characterizing the association between their BOLD signal timeseries. In order to compensate for possible transient magnetization effects at the beginning of each run, individual scans were weighted by a step function convolved with an SPM canonical hemodynamic response function and rectified. Using the generated similarity matrices, we selected a subset of ROIs to match those from aim 1. As a reminder, these consisted of language-specific ROIs within the left and right IFG, insula, pMTG, pSTG, PT, and AG; and

the language-related ROIs consisted of the caudate, putamen, frontal medial cortex, frontal operculum, frontal pole, IFG, middle frontal gyrus (mFG), supramarginal gyrus (SMG), and AG bilaterally.

It is well known that both child and clinical populations are more prone to movement during scans which can create spurious connections within the BOLD time series (Van Dijk et al., 2012). Thus, to first rule out head motion as a confounding factor in our follow-up analyses, we compared mean head displacement of the TD group to each of our DLD participants. Using Crawford & Howell's modified t-tests we found no significant differences between the DLD and TD participants (DLD002: $t(20) = 1.86, p = 0.08$; DLD003: $t(20) = 1.33, p = 0.20$).

Next, we triangulated each TD participant's similarity matrix within our two pre-defined networks of interest (language-specific and language-related) and compared it to the average of all the other TD similarity matrices ($n-1$) using Pearson correlation to determine how similar each child was to the group average. The resulting value is a single correlation coefficient for each participant. All but two participants showed strong correlations ($r > 0.6$) with the group. To ensure that the reason for the low correlations in the two TD participants wasn't due to motion, we again used Crawford & Howell's modified t-test to compare their mean head displacement to the groups and found no significant differences (TD001: $t(20) = -1.14, p = 0.23$; TD005: $t(20) = -0.02, p = 0.98$), thus they were retained for the analyses. Next, the correlation coefficient for each DLD participant was compared to the correlation coefficients from the TD participants using the Crawford & Howell's modified t-test. This was done within each pre-defined network of interest.

As previously discussed, regions of the brain that are highly connected with other regions may be more susceptible to alterations (Liang et al., 2013). Therefore, we also looked at connectivity patterns within specific hubs in our pre-defined networks. For the language-specific

network, based on findings from Qi et al. (2021), we examined the connections between the pars opercularis portion of the left IFG (L IFG-PO) and the following regions: the right IFG-PO (R IFG-PO), and the L/R IFG pars triangularis (L/R IFG-PT). We also looked at the connections between the L IFG-PT and the following: L insula (L IN), L posterior superior temporal gyrus (L pSTG), and L posterior middle temporal gyrus (L pMTG). For the language-related ROIs, we focused on the connections between the L caudate and the following: L putamen, L IFG-PT, and L frontal operculum (L FO). All Crawford & Howell t-tests were corrected for multiple comparisons.

2.4.3. Aim 3: The Relationship between CBF, iFC, and Language Abilities

The purpose of Aim 3 was to determine whether there was a relationship between our functional brain measures, CBF and iFC, and our language measures.

2.4.3.1. Functional Brain Measures and CELF-CLS. A simple linear regression model was conducted to examine the relationship between WB CBF and scores on the core language subtests of the CELF. Additional simple regression models were calculated for the language-specific and language-related networks. Both sex and age were included in the models as covariates due to their potential influence on brain development. Next, we investigated the relationship between these variables and functional connectivity patterns. Given the large number of ROI-to-ROI pairs that would be generated from a WB analysis, we focused these analyses on our pre-determined language networks. For each TD participant, we calculated their mean connectivity within each network and used those values in calculating our models. Given the sample size of our DLD participants, we only included TD children in our models, but discuss the implications of the findings for children with DLD in the Results and Discussion sections of the manuscript.

2.4.3.2. The Relationship between FC and CBF. As previously discussed, CBF and the BOLD signal are tightly linked. Therefore, altered coupling between the two could signal dysfunction. Here, our aim is to characterize the relationship between CBF and FC within the language-specific and language-related networks in TD children to inform our understanding of abnormal patterns. To do so, we performed correlation analyses between mean FC and CBF within our language-specific and language-related networks.

2.4.3.3. CBF, FC and the CELF. Our final goal for this research is to understand how both measures of brain function contribute to language abilities as well as impaired language processes. To that end, we conducted two separate (language-specific and language-related) linear regression analyses with CBF, FC z-scores, and the interaction between age and sex to determine if average CBF and FC values in our network ROIs predicted CELF-CLS scores.

3. Results

All statistical analyses were performed using R (R Core Team, 2023).

3.1. Behavioral Measures

Scores from the behavioral measures are reported in Table 3.1. The results of an independent samples t-test indicated that there were no differences in age between biological males and females in our sample ($t(13) = -0.79, p > 0.05$). There were also no significant differences in assessment scores based on sex ($p > 0.05$ for all comparisons).

3.2. Neuroimaging Measures

3.2.1. Aim 1: Cerebral Blood Flow (CBF)

Of the 22 TD children included in this study, 2 TD children were unable to complete the ASL-MRI sequence due to issues with MRI hardware ($n=1$) and software ($n=1$). Thus, 20 TD children ($9.43 \text{ years} \pm 2.02$, 11F/9M) and the 2 children with DLD, were included in the analysis (Figure 3.1).

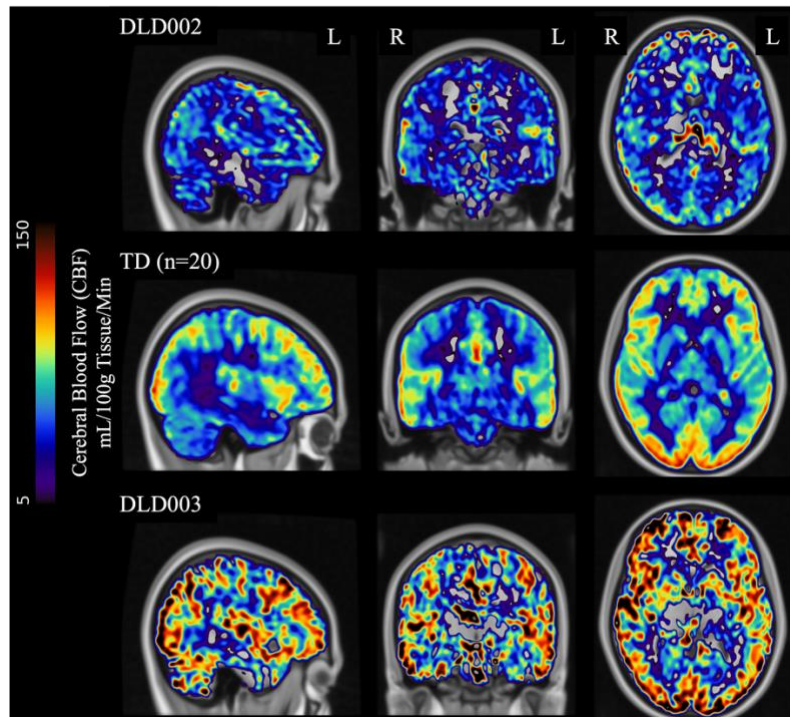


Figure 3.1 Whole brain (WB) cerebral blood flow (CBF) maps in each participant with DLD and the TD group (averaged across TD participants), registered to the MNI-152 template. Heat maps indicate the amount of CBF in tissue per minute. Images are presented in radiological view (i.e., left hemisphere is on the right side).

3.2.2. Between group comparisons

3.2.2.1. Global measures. To determine if the participants with DLD showed equivalent CBF patterns to our TD group, we first performed two separate comparisons between each of our participants with DLD and the TD group ($n = 20$). Here we explored the CBF gray matter patterns in the whole brain (WB), left hemisphere (LH), right hemisphere (RH), and selected ROIs. First, we present in Table 3.2 the mean and standard deviation for the TD participants and the mean for each of the DLD participants for the three global brain region comparisons (WB, LH, and RH). The results from the Crawford-Howell's modified t-test are also reported. Significant results are adjusted for multiple comparisons using FDR correction (i.e., *p-adjusted*).

Table 3.2. Comparisons between cerebral blood flow (CBF) in whole brain (WB), left hemisphere (LH), and right hemisphere (RH) gray matter. Means and standard deviations (SD) are reported. Significant differences between TD and DLD participants are in bold.

CBF in GM (mL/100g Tissue/min)	DLD002 Male; 10.75	TD n = 20; 11F/9M; mean _{age} = 9.43 ± 2.02	DLD003 Male; 10.42
WB mean ± SD	51.50 ± 11.94 <i>t</i>(19) = -2.95, <i>p</i> = 0.008, <i>p-adjusted</i> = 0.02	73.69 ± 7.34	79.98 ± 14.64 <i>t</i> (19) = 0.84, <i>p</i> = 0.41
LH mean ± SD	54.67 ± 12.45 <i>t</i> (19) = -1.9, <i>p</i> = 0.06	70.46 ± 7.84	77.06 ± 16.19 <i>t</i> (19) = 0.82, <i>p</i> = 0.42
RH mean ± SD	51.02 ± 11.23 <i>t</i>(19) = -2.44, <i>p</i> = 0.02, <i>p-adjusted</i> = 0.03	69.20 ± 7.28	75.48 ± 13.01 <i>t</i> (19) = 0.84, <i>p</i> = 0.41

For **DLD002** (when compared to the TD group) results indicated a significant difference in gray matter CBF values in WB ($t(19) = -2.95, p = 0.008, p\text{-adjusted} = 0.024$) and RH ($t(19) = -2.44, p = 0.02, p\text{-adjusted} = 0.03$), but not for LH CBF in gray matter ($t(19) = -1.9, p = 0.06$). Overall, CBF in gray matter for DLD002 was significantly lower than the TD group mean. By contrast there were no significant differences between **DLD003** and the TD group ($p > 0.05$ for all comparisons). DLD002 performed worse on the CELF-CLS, scoring in the 6th percentile, whereas DLD003 scored in the 14th percentile. Although both participants have behavioral scores that fell well below the 50th percentile (average score) indicating a language impairment, the global CBF measures alone cannot account for the behavioral deficits since they do not show a similar pattern. Given these results, it is reasonable to investigate the impact of regional differences in CBF patterns on language behavior. What follows is an investigation of CBF within the language-specific ROIs and language-related ROIs have been implicated in DLD.

3.2.2.2. ROI comparisons. Table 3.3 shows the CBF values in the language-specific ROIs for the two participants with DLD and the TD group. When comparing each DLD

participant to the TD group CBF patterns, no statistical differences were found (**DLD002 vs TD group** ($t(19) = -1.82, p = 0.08$); **DLD003 vs TD group** ($t(19) = 0.91, p = 0.37$).

Table 3.3. Cerebral blood flow (CBF) within language regions of interest (ROIs) in the left (L) and right (R) hemispheres. Mean values are reported for each DLD participant and the mean and standard deviation (SD) are reported for TD participants as a group. The last row of the table indicates the mean and SD for all of the language-specific ROIs. Angular gyrus (AG); inferior frontal gyrus, pars opercularis (IFG-PO); inferior frontal gyrus, pars triangularis (IFG-PT); insula (IN); posterior middle temporal gyrus (pMTG); planum temporale (PT); posterior superior temporal gyrus (pSTG).

CBF in Language ROIs (mL/100g Tissue/min)	DLD002 Male; 10.75	TD n = 20; 11F/9M; mean _{age} = 9.43 ± 2.02	DLD003 Male; 10.42
L/R AG mean (±SD)	60.53 / 59.68	82.16 (±9.07) / 82.17 (±8.33)	97.78 / 95.76
L/R IFG-PO mean (±SD)	73.04 / 68.08	90.49 (±12.78) / 83.86 (±7.56)	99.31 / 90.29
L/R IFG-PT mean (±SD)	77.37 / 66.02	89.14 (±10.95) / 85.01 (±7.09)	90.00 / 83.54
L/R IN mean (±SD)	52.35 / 50.95	68.54 (±8.30) / 65.19 (±9.15)	63.21 / 73.30
L/R pMTG mean (±SD)	64.74 / 48.47	80.76 (±8.38) / 79.36 (±9.91)	92.77 / 83.51
L/R PT mean (±SD)	61.30 / 63.66	74.02 (±10.40) / 75.95 (±9.47)	72.91 / 79.51
L/R pSTG mean (±SD)	72.22 / 54.20	78.53 (±8.66) / 74.94 (±9.46)	97.04 / 80.86
L/R Language Network Average mean (±SD)	65.94 (±8.73) / 58.72 (±7.66)	80.52 (±12.11) / 78.07 (±10.67)	87.57 (±13.98) / 83.82 (±7.33)

Interestingly, in the other language-related ROIs that have been implicated in DLD, a significant difference in CBF was observed for **DLD002** compared to the TD group ($t(19) = -2.31, p = 0.03$), though this result approached, but did not reach, significance after FDR correction ($p\text{-adjusted} = 0.06$). This suggests that while there is a notable difference in CBF in language-related ROIs for DLD002, further analysis is required to pinpoint the areas that are impacted. Conversely, no significant difference was found for **DLD003** ($t(19) = 0.87, p = 0.39$), indicating CBF levels in these other language related areas for DLD003 were similar to those of the TD group. CBF values for these regions can be found in Table 3.4.

Table 3.4. Cerebral blood flow (CBF) within language-related regions of interest (ROIs) in the left (L) and right (R) hemispheres. Mean values are reported for each DLD participant and the mean and standard deviation (SD) are reported for TD participants as a group. The last row of the table indicates the mean and SD for the language-related network. Frontal medial cortex (FMC); frontal operculum (FO); frontal pole (FP); inferior frontal gyrus, pars opercularis (IFG-PO); inferior frontal gyrus, pars triangularis (IFG-PT); posterior middle frontal gyrus (MFG); angular gyrus (AG); posterior supramarginal gyrus (SMG).

CBF in Language Related ROIs (mL/100g Tissue/min)	DLD002 Male; 10.75	TD n = 20; 11F/9M; mean _{age} = 9.43 ± 2.02	DLD003 Male; 10.42
L/R Caudate mean (±SD)	46.14 / 59.04	47.44 (±12.99) / 45.08 (±12.97)	39.57 / 57.24
L/R Putamen mean (±SD)	49.45 / 40.77	55.51 (±7.62) / 53.86 (±9.16)	64.26 / 65.52
L/R FMC mean (±SD)	58.89 / 60.42	74.13 (±26.45) / 72.82 (±24.33)	94.45 / 73.29
L/R FO mean (±SD)	62.37 / 59.56	77.07 (±11.64) / 74.44 (±15.78)	92.52 / 79.64
L/R FP mean (±SD)	49.67 / 50.60	75.28 (±8.32) / 74.45 (±8.21)	87.30 / 81.00
L/R IFG-PO mean (±SD)	73.04 / 68.08	90.49 (±12.78) / 83.86 (±7.56)	99.31 / 90.29
L/R IFG-PT mean (±SD)	77.38 / 66.02	89.14 (±10.95) / 85.01 (±7.09)	90.00 / 83.54
L/R MFG mean (±SD)	55.76 / 54.12	83.65 (±11.11) / 83.53 (±7.86)	91.65 / 89.32
L/R AG mean (±SD)	60.53 / 59.68	82.16 (±9.07) / 82.17 (8.33)	97.78 / 95.76
L/R SMG mean (±SD)	58.65 / 56.65	83.70 (±9.74) / 81.46 (±9.10)	94.34 / 93.00
L/R Language Network Average mean (±SD)	59.19 (±10.01) / 57.49 (±7.78)	75.86 (±18.51) / 73.67 (±17.60)	85.12 (±18.76) / 80.86 (±12.42)

In sum, significant differences in CBF levels (compared to the TD group) were only found for one of the two participants with DLD (DLD002). Surprisingly, the significant differences for DLD002 were not in the traditional language ROIs or the LH, but rather were found in the WB, RH, and language-related ROIs (though this latter comparison did not survive FDR correction). Results indicated that overall, DLD002 had reduced CBF compared to TD children. In contrast, when looking at average CBF values for DLD003, they were much higher

overall than DLD002's and just above the mean values for the TD group (though this difference was not significant). Keeping in mind that only two participants met the behavioral impairment criteria for DLD in this study, it is intriguing to see the neural differences between the DLD participants that emerged. As described earlier, the literature points to many factors that can affect CBF levels, including age and biological sex. Previous research demonstrated that CBF values peak around 9-10 years of age and that there are potential biological sex differences (Satterthwaite et al., 2014). Maturational and biological sex effects as general characteristics cannot explain the overall (global) difference in CBF levels found between DLD002 and DLD003, since both are 10-year-old males. Thus, a secondary analysis of WB CBF values was conducted with age and biological sex as covariates for the TD group to better understand how they influence typical developmental changes in CBF patterns.

3.2.3. TD within Group Comparisons

3.2.3.1. Effect of age and biological sex on whole brain CBF. As previously discussed, our TD group was comprised of both biological male and female children between the ages of 6-12 years. Given the span of this age range and potential biological sex differences, we conducted a simple linear regression model to examine the relationship between CBF and the predictors Age and Sex, including their interaction. Overall, the model explained approximately 3.03% of the variance in CBF (Adjusted $R^2 = 0.029$, $F(3,2236) = 23.32$, $p < 0.001$). Results indicated a significant main effect of Sex, with males showing higher CBF values compared to females (Estimate = 16.650, $p < 0.001$ 95% CI [9.62, 23.68]). The interaction between Age and Sex was also significant (Estimate = -1.636, $p < 0.001$, 95% CI [-2.37, -0.91]), indicating that the decline in CBF with age is steeper for males than for females (Figure 3.2). However, the main effect of Age was not significant (Estimate = -0.429, $p = 0.118$, 95% CI [-0.97, 0.11]). These results

suggest that sex significantly influences CBF, and the relationship between age and CBF varies by sex, with males experiencing a more pronounced age-related decline in CBF.

Given the limited sample size of DLD participants, we did not include them in the regression analysis, however, the results do suggest that the increased CBF in DLD003 warrants further investigation, as he has higher mean CBF values despite being one of the older males in our sample.

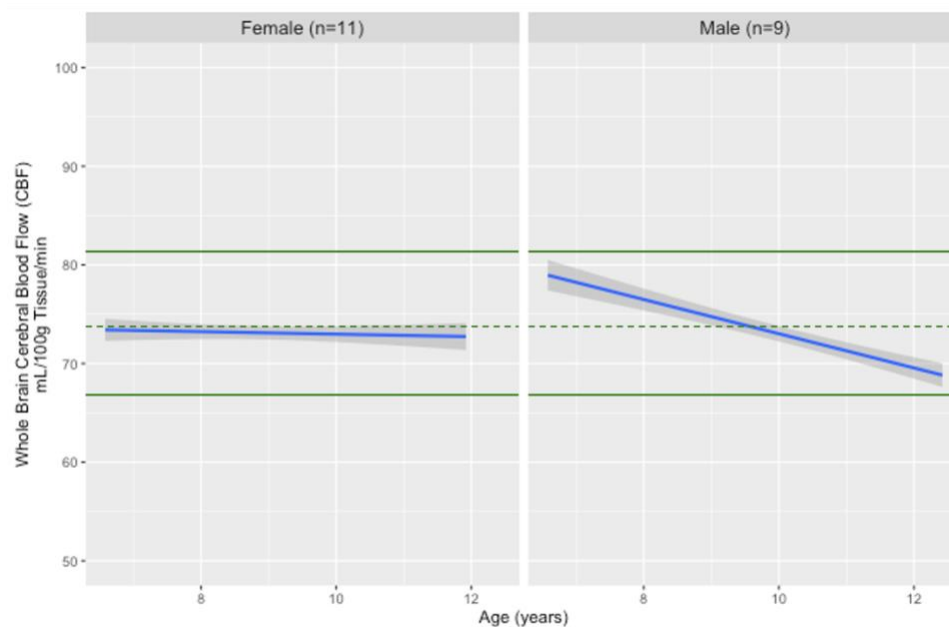


Figure 3.2. Differences in whole brain (WB) cerebral blood flow (CBF) across age for typically developing (TD) females and males. The dashed line indicates mean CBF for the group with the solid lines depicting 1 standard deviation above and below the mean.

3.2.3.2. CBF lateralization patterns. The WB and RH CBF comparisons between DLD002 and the TD group were significant, but we did not see any significant differences for DLD003 when compared to the TD group despite having impaired language abilities. The differences observed between the two children with DLD suggests that language impairments may manifest differently across individuals. Detailed within-group comparisons may reveal distinct or common patterns of CBF that could help account for language impairment in both

children. In this section, we start by first characterizing CBF lateralization patterns in TD children and then turn to the children with DLD in our study.

To examine whether TD children demonstrated differences in CBF values between the left and right hemispheres as well as in language-specific and language-related ROIs, we performed paired samples t-tests, FDR corrected for multiple comparisons. The differences between each hemisphere ($t(1119) = 5.20, p < 0.0001, p\text{-adjusted} < 0.0001$), the left and right language-specific ROIs ($t(139) = 3.07, p = 0.003, p\text{-adjusted} = 0.009$), and the left and right language-related ROIs ($t(199) = 3.96, p = 0.0001, p\text{-adjusted} = 0.0002$) were all significant. In each case, the mean CBF was higher in the left hemisphere than in the right hemisphere by a small amount (see Table 3.3 and Table 3.4). The results found here are in alignment with reports of typical left hemisphere asymmetries and provide confirmation of typical patterns by which to compare the results of the children with DLD to in the next section (Abbott & Love, 2023).

3.2.4. DLD within Group Comparisons

Like with the TD group, we examined differences in CBF in the left and right hemispheres as well as the left and right ROI pairs in both children with DLD separately (Figure 3.3). We found a similar pattern to TD children, in that both children had slightly higher CBF values in the left hemisphere than in the right, but an interesting pattern of significance emerged. For **DLD002**, differences in CBF between the left and right hemispheres were significant ($t(54) = 3.55, p = 0.0008, p\text{-adjusted} < 0.001$), while differences between left and right language ROIs approached but did not reach significance after FDR correction ($t(6) = 2.38, p = 0.05, p\text{-adjusted} = 0.07$). In contrast, for **DLD003**, neither comparison between the hemispheres ($t(54) = 1.18, p = 0.24$) or language ROIs ($t(6) = 1.06, p = 0.33$) were significant, indicating that DLD003 did not show the typical left lateralization pattern. The comparison between the language-related ROIs in

the left and right hemispheres also did not reach significance for either participant (DLD002: $t(9) = 0.82, p = 0.43$; DLD003: $t(9) = 1.33, p = 0.22$).

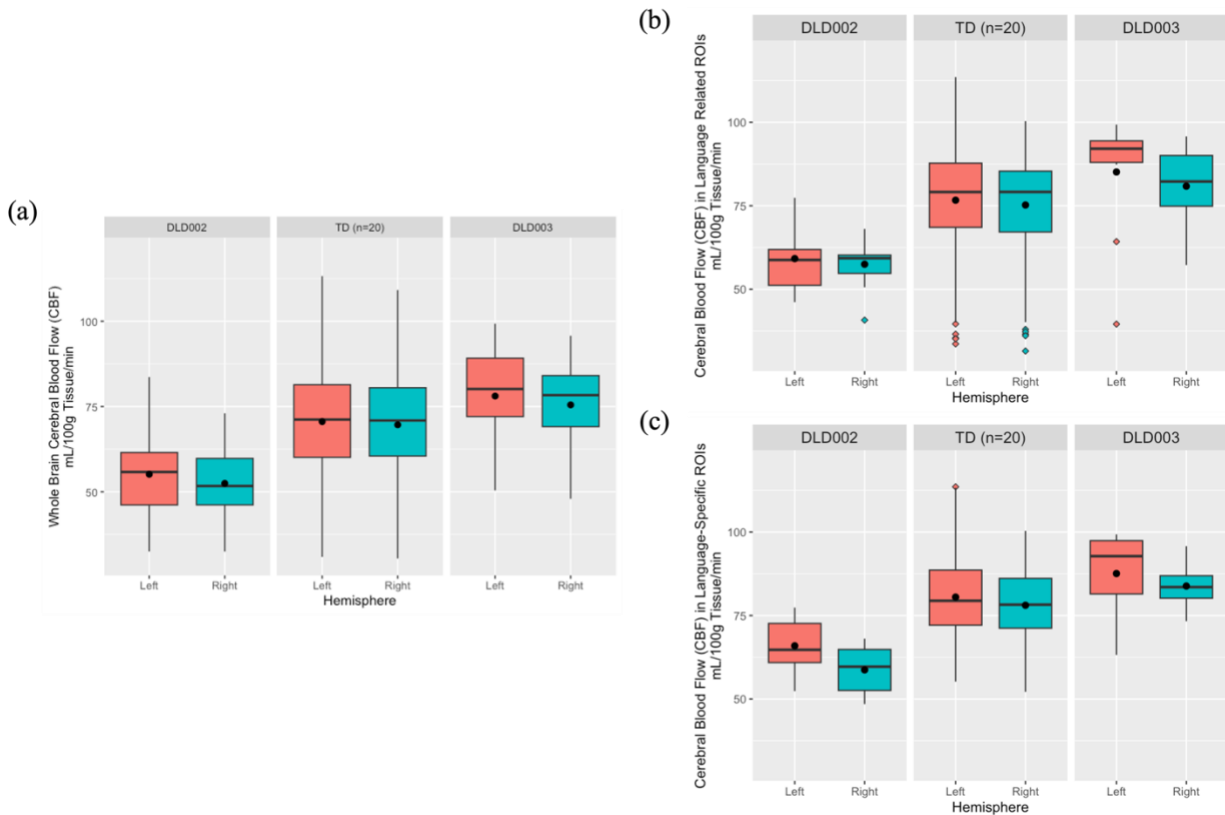


Figure 3.3. Within group (DLD002, DLD003, and TD average) comparisons in CBF between left and right a) hemispheres; b) language-specific ROIs; and c) language-related ROIs.

To summarize, our results revealed no between (WB, LH, and RH CBF) or within (left/right WB, language ROIs, and language-related ROIs) differences for **DLD003**. This pattern suggests that overall, the global CBF patterns for DLD003 are similar to the group pattern. However, when exploring lateralization patterns, DLD003 shows a different pattern than the TD group. According to the literature, CBF reaches a peak around 9-10 years of age, which aligns with DLD003's age. It may be the case, that the increased CBF values are related to maturation, or they could be masking other important lateralization or regional differences. Both DLD003 and DLD002 performed poorly on the CELF (and well on the TONI), but still demonstrated very

different patterns of results. DLD002 had overall reduced CBF and showed both global, regional, and hemispheric lateralization differences compared to the TD children. In particular, the right hemisphere showed significant decreases in CBF which aligns well with previous SPECT/PET studies that found altered lateralization patterns in DLD (Abbott & Love, 2023). The CBF results from this study are compelling, though, given the small degrees of freedom and case study comparisons, they should be interpreted with caution and further explored with larger sample sizes.

3.2.2. Aim 2: Intrinsic Functional Connectivity (iFC)

As a reminder, the goal of Aim 2 was to characterize iFC patterns in children with DLD compared to TD children. For this aim, we explored connectivity patterns within pre-defined language-specific and language-related networks, to determine whether the children with DLD showed aberrant connectivity patterns. Of the 22 TD children included in this study, 1 TD child did not complete the ASL-MRI sequence due to issues with MRI software. Thus, 21 TD children ($9.31 \text{ years} \pm 1.87$, 13F/8M) and the 2 children with DLD, were included in the analysis

The overall intrinsic functional connectivity patterns across the language network were not significantly different for either participant with DLD compared to the group average (DLD002: $t(20) = 1.75$, $p = 0.10$; DLD003: $t(20) = -0.27$, $p = 0.79$). Connectivity matrices within the language-specific ROIs can be seen for each participant with DLD compared to the TD group average in Figure 3.4. It is possible that the age range of TD children masks important differences in the children with DLD, thus future analyses should compare a subset of older TD children's iFC patterns to each of the DLD participants.

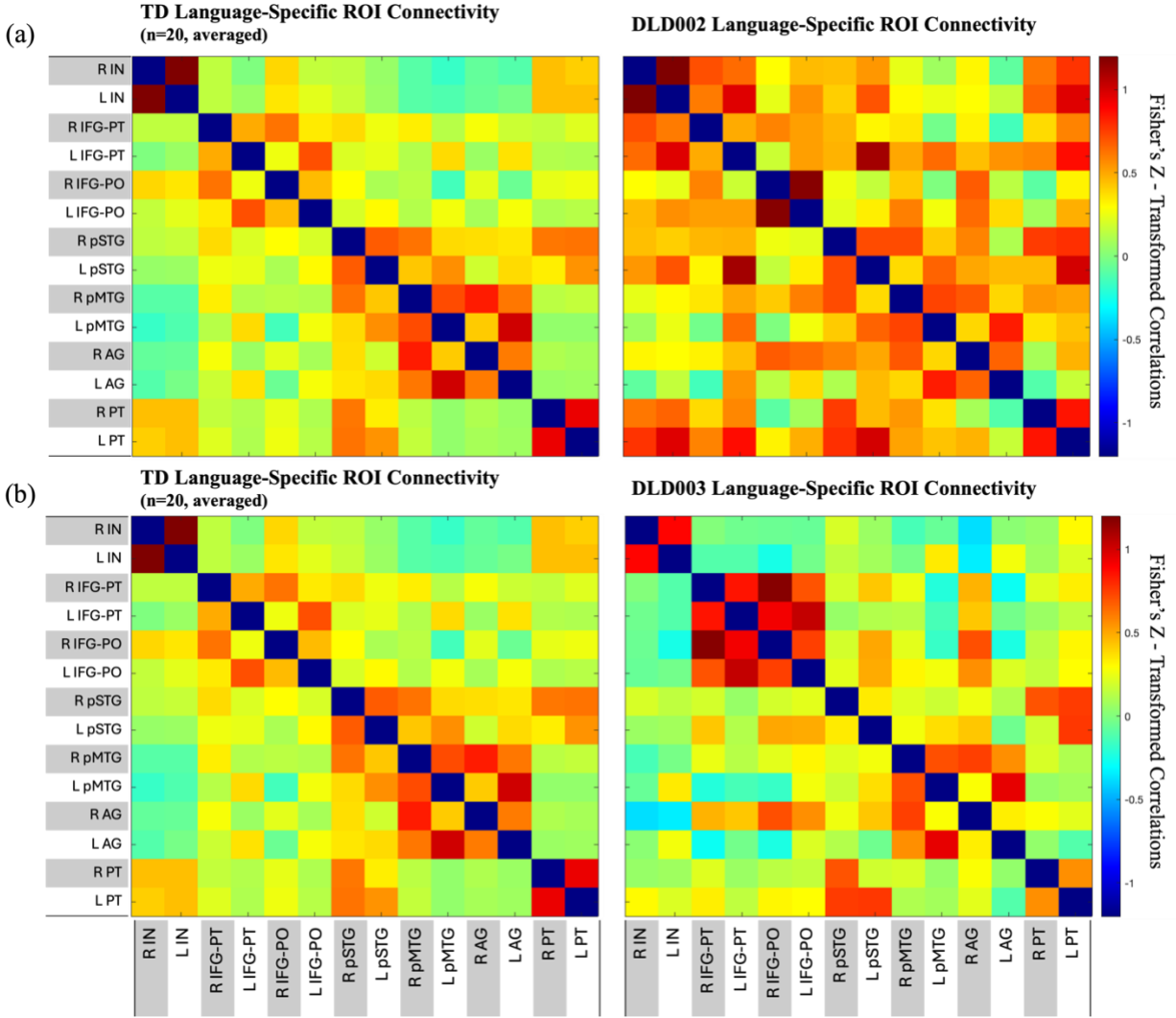


Figure 3.4. Intrinsic functional connectivity across the language-specific ROIs in a) DLD002 compared to the TD group average; and b) DLD003 compared to the TD group average. Results are displayed as Fisher z-transformed correlations in right (R) and left (L) hemisphere regions. Insula (IN); inferior frontal gyrus, pars triangularis (IFG-PT); inferior frontal gyrus, pars opercularis (IFG-PO); posterior superior temporal gyrus (pSTG); posterior middle temporal gyrus (pMTG); angular gyrus (AG); planum temporale (PT).

For the language-related network, both participants with DLD had different patterns of overall network connectivity compared to TD children (DLD002: $t(20) = 2.85, p = 0.01$; DLD003: $t(20) = 3.22, p = 0.004$). DLD002 demonstrated overconnectivity within the language-related ROIs, whereas DLD003 demonstrated and overall pattern of underconnectivity with more ant-correlated regions (Figure 3.5).

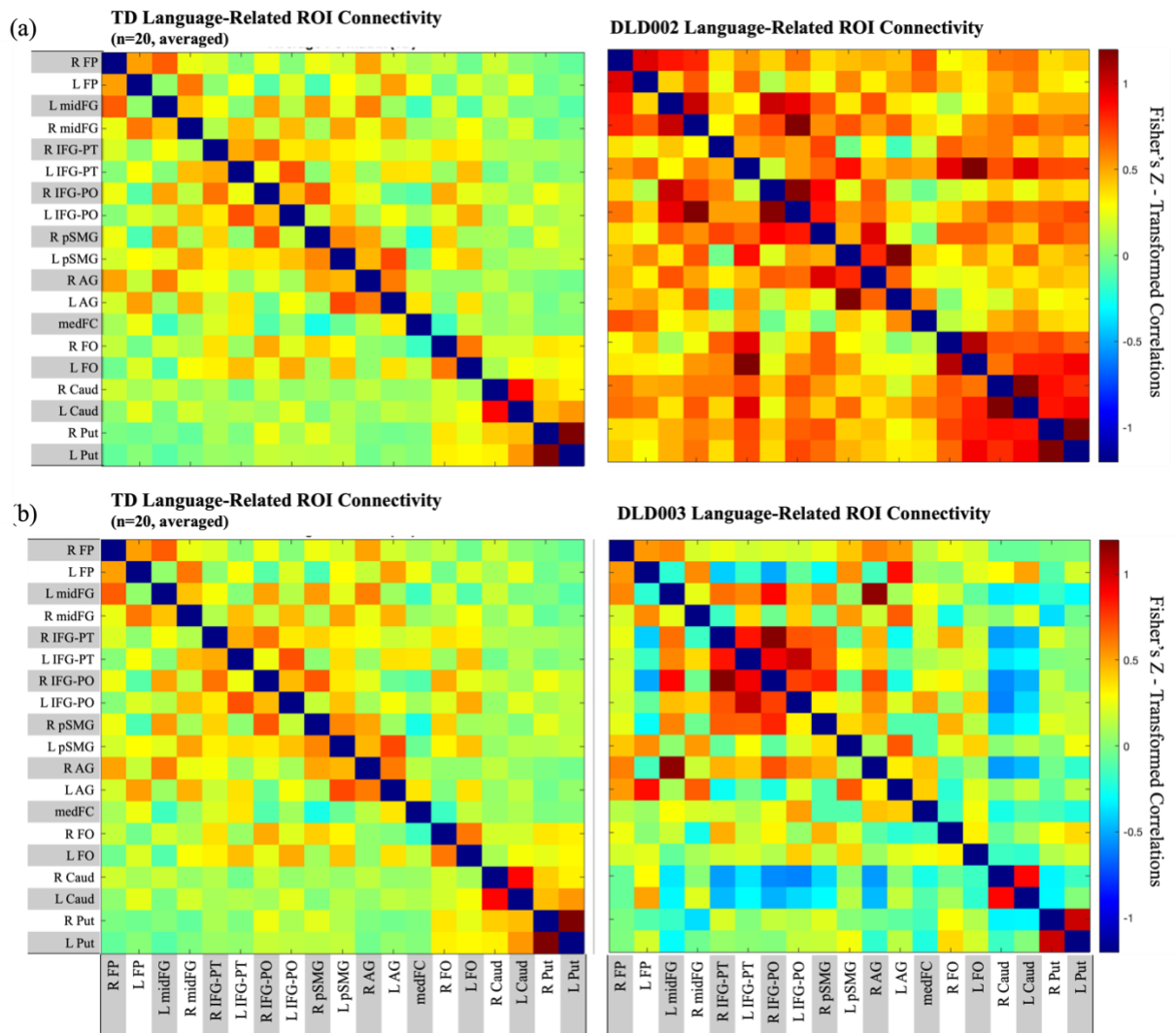


Figure 3.5. Intrinsic functional connectivity across the language-related ROIs in a) DLD002 compared to the TD group average; and b) DLD003 compared to the TD group average. Results are displayed as Fisher z-transformed correlations in right (R) and left (L) hemisphere regions. Frontal pole (FP); middle frontal gyrus (midFG); inferior frontal gyrus, pars triangularis (IFG-PT); inferior frontal gyrus, pars opercularis (IFG-PO); posterior supramarginal gyrus (pSMG); angular gyrus (AG); medial frontal cortex (medFC); frontal operculum (FO); caudate (Caud); putamen (Put).

Next to examine the connectivity patterns of specific hub regions within the language network, we first looked at the connectivity strength between the L IFG-PO and the following regions: the R IFG-PO, and the L/R IFG-PT. As can be seen in Figure 3.6, DLD003's pattern of connectivity was very similar to the TD group with higher within hemisphere connectivity, that

decreased for the right hemisphere homologue and PT regions. Though the connectivity pattern is higher overall for DLD003 none of the comparisons were significant ($p > 0.05$). In contrast DLD002 exhibited increased connectivity between the L and R IFG-PO, though after correcting for multiple comparisons, this effect was marginal ($t(20) = 2.56$, $p = 0.02$, p -adjusted = 0.056).

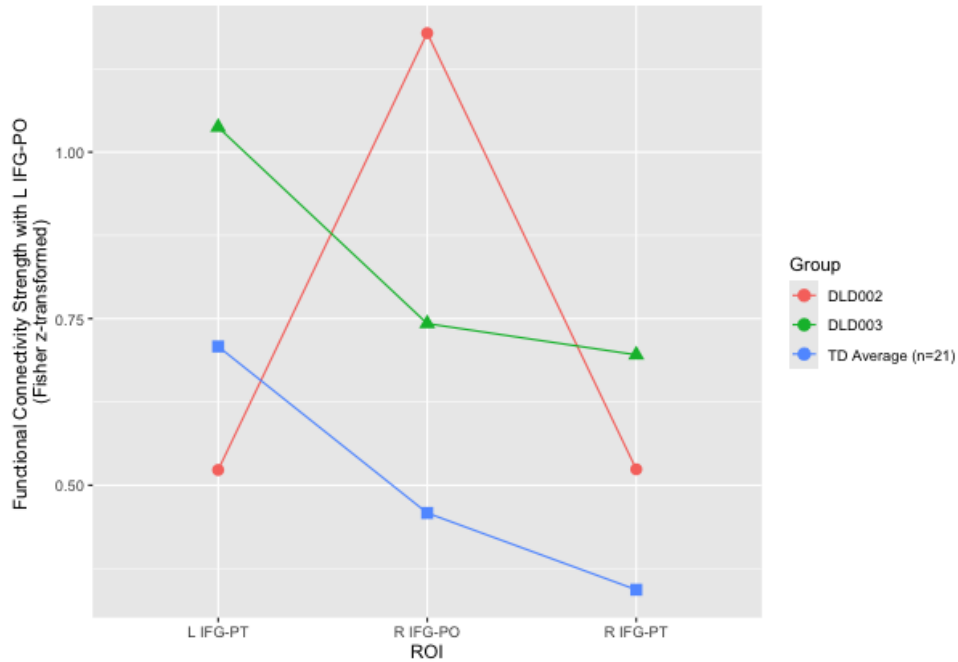


Figure 3.6. Functional connectivity between the left inferior frontal gyrus, pars opercularis (L IFG-PO) and the following three regions of interest (ROI): left inferior frontal gyrus, pars triangularis (L IFG-PT), right inferior frontal gyrus, pars opercularis (R IFG-PO), and right inferior frontal gyrus, pars triangularis (R IFG-PT). For the TD group, the functional connectivity average is shown in blue.

We then looked at connectivity between L IFG-PT and the L IN, L pSTG, and L pMTG and found that DLD002 demonstrated greater connectivity between the L IFG-PT and the L IN ($t(20) = 3.52$, $p = 0.002$, p -adjusted = 0.03) and the L pMTG ($t(20) = 4.12$, $p = 0.0005$, p -adjusted = 0.002; Figure 3.7). Interestingly, the TD group had very low correspondence between spontaneous BOLD fluctuations in these regions, which may indicate that DLD002 is recruiting altered, less efficient language networks. The difference in L STG connectivity strength between

groups, did not reach significance ($t(20) = 1.34$, $p = 0.19$). No differences in connectivity patterns were found for DLD003 in these regions ($p > 0.05$).

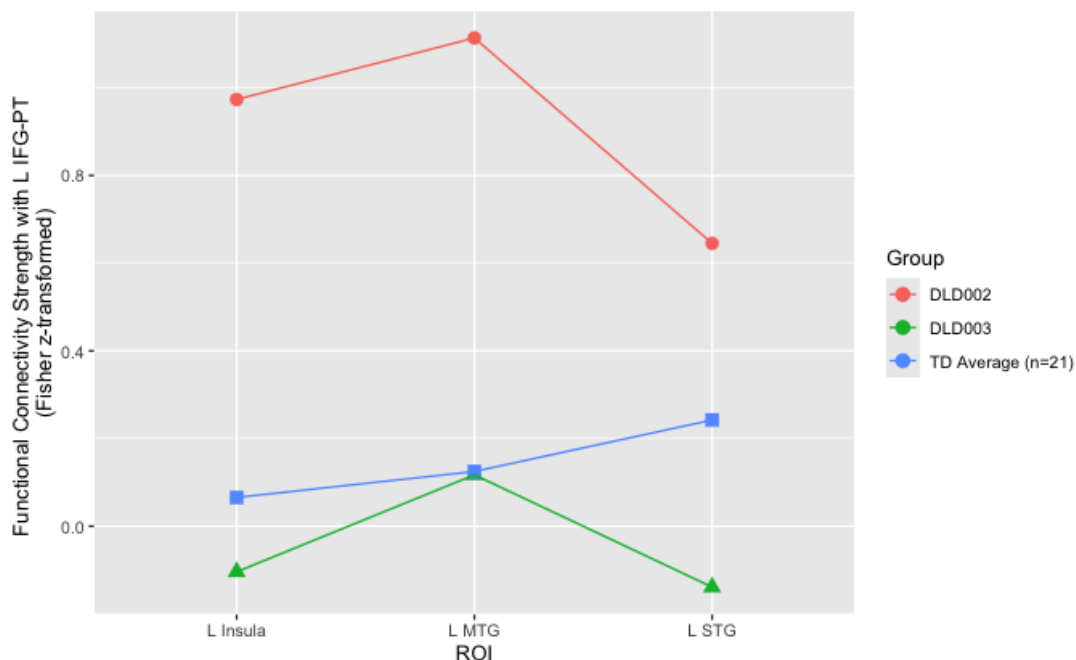


Figure 3.7. Functional connectivity between the left inferior frontal gyrus, pars triangularis (L IFG-PT) and the following three regions of interest (ROI): left (L) insula), left middle temporal gyrus (L MTG) and the left superior temporal gyrus (L STG). For the TD group, the functional connectivity average is shown in blue.

Finally, for the language-related network, we compared connectivity between the L caudate and the following: the L putamen, L IFG-PT, and L FO (Figure 3.8). Results again revealed differences between DLD002 and the TD group, with increased connectivity between the L caudate and the L IFG-PT ($t(20) = 5.47$, $p < 0.0001$, $p\text{-adjusted} < 0.0001$) and the L putamen ($t(20) = 2.31$, $p = 0.03$, $p\text{-adjusted} = 0.048$). DLD003 also demonstrated differences in connectivity within the L caudate and the L IFG-PT ($t(20) = -2.76$, $p = 0.01$, $p\text{-adjusted} = 0.04$) and the L putamen ($t(20) = -2.04$, $p = 0.05$, $p\text{-adjusted} = 0.05$) as well as the L FO ($t(20) = -2.08$, $p = 0.05$, $p\text{-adjusted} = 0.05$). However, unlike DLD002, results showed greater negative correlations between regions, which could indicate aberrant pathway signaling (e.g., when one

region is activated, the other disengages). Though these preliminary results are compelling, more work is needed with larger sample sizes to understand the direction of these differences and their implications for language impairment.

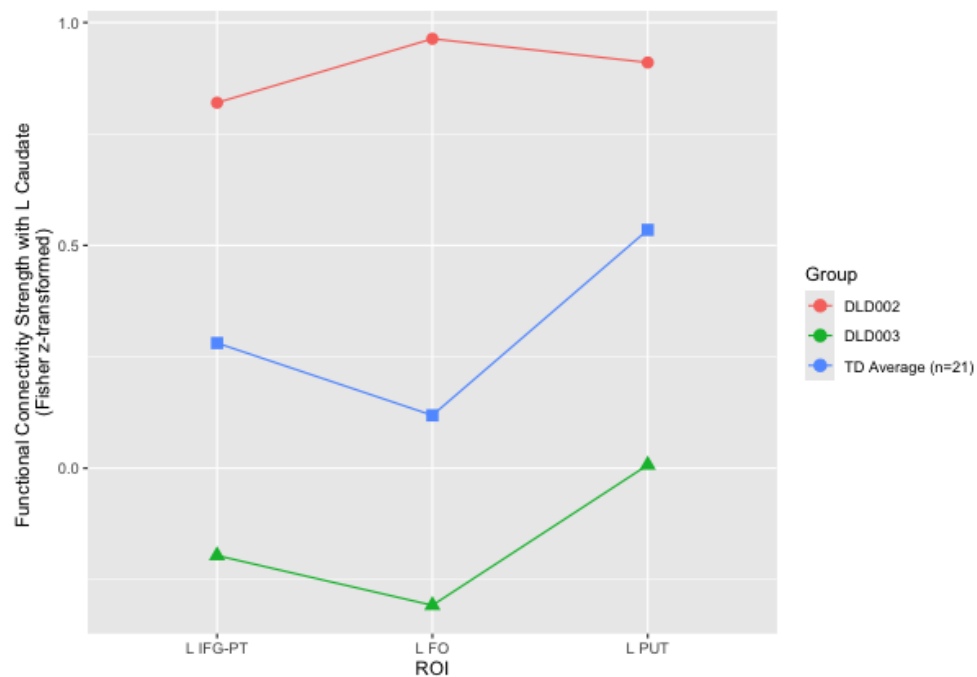


Figure 3.8. Functional connectivity between the left (L) caudate and the following three regions of interest (ROI): inferior frontal gyrus, pars triangularis (L IFG-PT), left frontal operculum (L FO), and left putamen (L PUT). For the TD group, the functional connectivity average is shown in blue.

3.2.3. Aim 3: The Relationship between CBF, FC and Language

3.2.3.1. WB CBF and Language Scores from the CELF. For Aim 3 of this study, we sought to examine the relationship between each of our functional brain measures and performance on the core language score subtests of the CELF-5 (CELF-CLS). However, as previously mentioned, CBF and FC patterns show differences between biological males and females and change throughout development (Taki et al., 2011). Therefore, we conducted a linear regression analysis with the TD group only to examine the effects of language (measured

with the CELF-CLS), Sex, and Age on WB CBF, including the interaction between CELF-CLS and Sex. Age was included as a continuous variable in the model, but for the purpose of visualization (Figure 3.9), we split male and female participants into young and old groups based on the median split (median = 9.25 years).

The overall model was statistically significant ($F(4, 2235) = 13.93, p < 0.001$). The residual standard error was 16.67, and the model explained approximately 2.43% of the variance in CBF (Adjusted $R^2 = 0.0226$). The results indicated significant main effects for Sex (Estimate = 19.894, $p = 0.02$, 95% CI [3.74, 36.05]) and Age (Estimate = -1.426, $p < 0.001$, 95% CI [-1.84, -1.01]). The CELF-CLS variable showed a marginally significant effect (Estimate = 0.106, $p = 0.054$, 95% CI [-0.002, 0.21]). There was also a significant interaction between CELF-CLS and Sex (Estimate = -0.163, $p = 0.02$, 95% CI [-0.30, -0.02]), suggesting that for older TD females, higher CELF-Scores are related to increased CBF and for younger females, higher language scores are related to Lower CBF values. This pattern is reversed for males; higher CBF for older males is associated with worse performance on the CELF, and lower CBF is associated with better scores for younger males (Figure 3.9). Both our participants with DLD are older males. In line with these findings, DLD003 demonstrated increased WB CBF and performed poorly on the CELF. DLD002 on the other hand, had significantly lower WB CBF values, suggesting 1) that there may be a threshold by which decreased (or increased) CBF in older male children becomes maladaptive, and 2) that the underlying physiological properties of the brain may not follow the typical developmental trajectory, particularly in language-associated regions of the brain. Thus, in the next sections we investigate the relationship between CBF and language in our pre-define language and language-related networks.

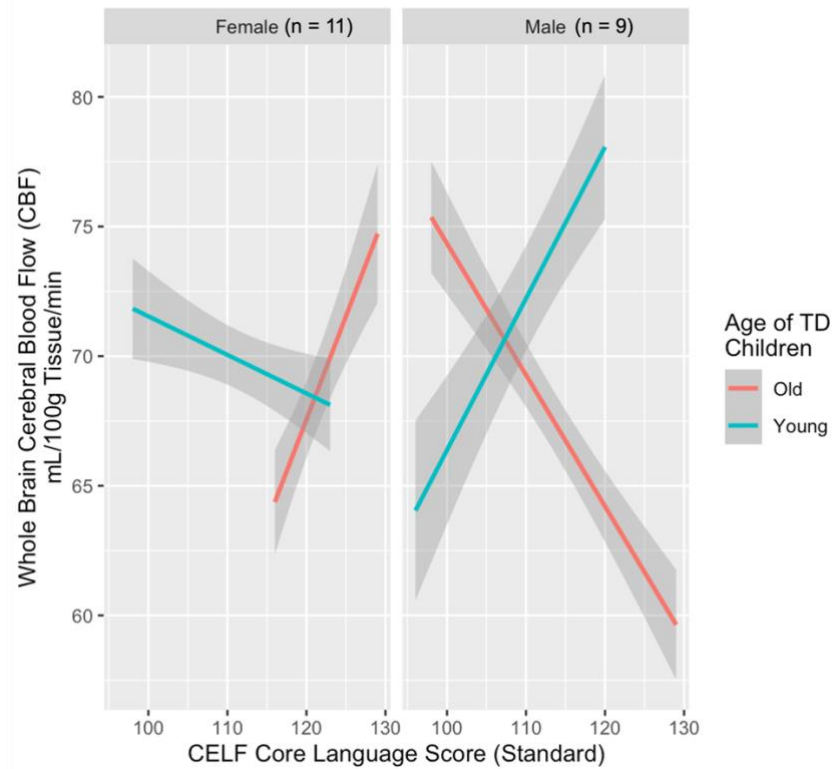


Figure 3.9. Whole brain cerebral blood flow (CBF) values and CELF core language scores (CELF-CLS) for female and male TD participants. Age was included as a continuous variable in the regression model, however, for the purpose of visualizing the interaction, participants were divided into young and old based on the median value of 9.25 years.

3.2.3.2. CBF in Language ROIs and Language Scores from the CELF. A linear regression analysis was conducted to investigate the impact of CELF-CLS, Sex, and Age on CBF in the language network ROIs, including the interaction between CELF-CLS and Sex. The overall model was statistically significant ($F(4, 275) = 8.359, p < 0.001$) explaining approximately 10.84% of the variance in CBF (Adjusted $R^2 = 0.095$) with a residual standard error of 10.9. The results indicated significant main effects for CELF-CLS (Estimate = 0.299, $p = 0.004$, 95% CI [0.10, 0.50]), Sex (Estimate = 44.468, $p = 0.004$, 95% CI [14.48, 74.46]), and Age (Estimate = -2.050, $p < 0.001$, 95% CI [-2.83, -1.28]). Additionally, there was a significant interaction between CELF-CLS and Sex (Estimate = -0.358, $p = 0.008$, 95% CI [-0.62, -0.10]), suggesting that the relationship between CELF-CLS and CBF within language ROIs differed by

sex (Figure 3.10). Like with the WB analysis, these findings suggest that higher CBF values within the language network are related to better scores on the CELF for older females and worse scores for older males and vice versa.

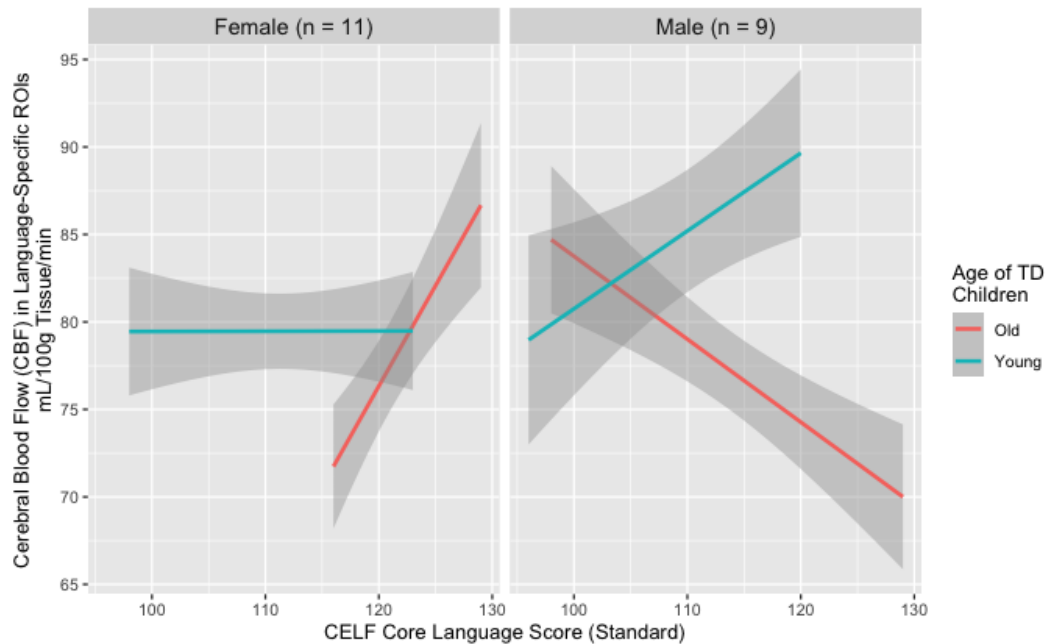


Figure 3.10. Cerebral blood flow (CBF) values and CELF core language scores (CELF-CLS) within language-specific ROIs for female and male TD participants. Age was included as a continuous variable in the regression model, however, for the purpose of visualizing the interaction, participants were divided into young and old based on the median value of 9.25 years.

3.2.3.3. Language Related ROIs. Lastly, we looked at the relationship between CBF in language related ROIs and performance on the CELF. Again, we used a simple regression analysis to explore the influence of CELF-CLS, Sex, and Age on cerebral blood flow (CBF), incorporating the interaction between CELF-CLS and Sex. The overall model accounted for approximately 4.21% of the variance in CBF (Adjusted $R^2 = 0.0324$; $F(4,395) = 4.345$, $p = 0.002$). The results revealed significant main effects for Age (Estimate = -1.788, $p = 0.001$; 95% CI [-2.84 -0.73]) and Sex (Estimate = 44.225, $p = 0.034$; 95% CI [3.36 85.09]), indicating that older age is associated with decreased CBF, and males tend to have higher CBF compared to

females. However, the relationship between CELF-CLS and CBF was not statistically significant (Estimate = 0.1785, $p = 0.199$; 95% CI [-0.09 0.45]), suggesting that CELF-CLS may not directly influence CBF in non-language-related regions. Moreover, a significant interaction was observed between CELF-CLS and Sex (Estimate = -0.3612, $p = 0.047$; 95% CI [-0.72 -0.004]), indicating that, like for the other comparisons, the relationship between CELF-CLS and CBF differs between males and females in non-language-related regions (Figure 3.11). Overall, these findings suggest that while age and sex play significant roles in predicting CBF in language-related regions, the relationship between these variables might be more nuanced.

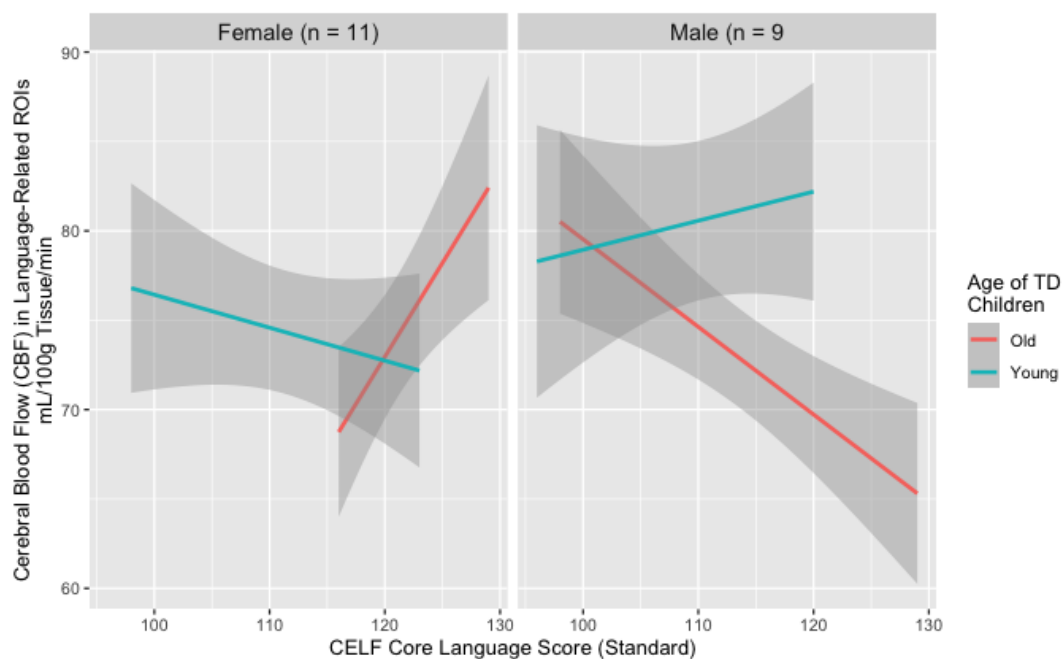


Figure 3.11. Cerebral blood flow (CBF) values and CELF core language scores (CELF-CLS) within language-related ROIs for female and male TD participants. Age was included as a continuous variable in the regression model, however, for the purpose of visualizing the interaction, participants were divided into young and old based on the median value of 9.25 years.

Turning to how these patterns apply to children with DLD, the experiment revealed a clear distinction in brain and behavior for DLD002. Overall, DLD002 had decreased CBF within whole brain regions as well as the language networks of interest. Based on the results from the

TD participants, better language scores are associated with decreased CBF as males get older. However, there clearly is a point at which declines in CBF lead to dysfunction or are at least somehow related to it. For DLD003, the picture is less clear as they showed higher CBF (though not statistically different from the TD group) but still performed poorly on the CELF. Despite these differences, both DLD children fall somewhere outside of the range of what is considered typical (Figure 3.12). In the last sections of this paper, we explore how functional connectivity patterns relate to language in our TD group and how CBF, functional connectivity, and language abilities are connected, with a goal of providing a foundation for which to continue exploring these factors in children with DLD.

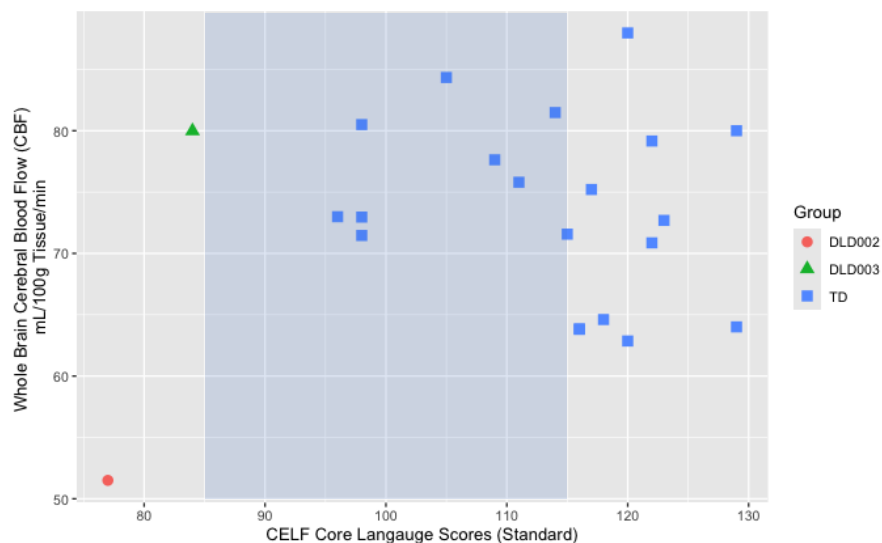


Figure 3.12. Scatterplot representing the whole brain cerebral blood flow (CBF) values by standard CELF core language scores for each participant. The shaded area represents 1 standard deviation above and below the average (100).

3.2.3.4. Functional Connectivity and Performance on the CELF in Language ROIs.

A linear regression analysis on the TD group's performance was conducted to examine the relationship between the CELF-CLS and mean functional connectivity within language-related ROIs, considering Sex, Age, and the interaction between mean FC and Sex as predictors.

The overall model was not statistically significant ($F(4, 16) = 1.340, p = 0.28$), indicating that the predictors collectively did not significantly predict CELF scores. The model's multiple R-squared value was 0.26, with an adjusted R-squared value of 0.07284, suggesting that approximately 26% of the variance in CELF scores was explained by the predictors, although the adjusted R-squared indicated only a modest fit. The main effects of mean FC in the language ROIs, Age, Sex, and the interaction between mean FC and Sex were all non-significant.

3.2.3.5. Functional Connectivity and Performance on the CELF in Language-Related ROIs. To investigate the relationship between functional connectivity in language-specific ROIs and the CELF-CLS in TD children, we conducted a linear regression analysis. The model included mean functional connectivity (FC), sex, and age as predictors, as well as the interaction between FC and sex. Contrary to our hypotheses, the overall model was not significant (Adjusted $R^2 = 0.07, F(1,16) = 1.396, p = 0.28$) though 25.87% of the variance in CELF scores was explained by the model. The main effects of mean FC, Sex, and Age were not significant ($p > 0.1$) indicating no significant association between mean functional connectivity in language-related ROIs and CELF scores. Given the previous results from this study of altered functional connectivity within specific hubs of the language network (rather than the whole language network), as well as regions within the language-related network (e.g., the caudate and frontal lobe regions), it is possible that a pattern would emerge with more narrowly defined comparisons. Future work should explore the relationship between iFC patterns and language scores within specific regions of the brain that show altered function in DLD, as these regions may be key to understanding both typical and aberrant functional architecture of the brain. In addition, functional connectivity patterns should be explored in conjunction with other functional

measures to provide more insight into the dynamic nature of brain function. In the next section, we turn to investigating the relationship between our functional connectivity and CBF.

3.2.3.6. The Relationship between CBF and FC patterns. A Pearson's product-moment correlation was conducted to examine the relationship between mean FC and mean CBF values in the language-specific ROIs. Results indicated a moderately positive ($r = 0.47$) correlation between FC and CBF values ($t(17) = 2.19$, $p = 0.04$; 95% CI [0.0186 to 0.7610]). These results suggest that in TD children higher levels of functional connectivity are associated with higher levels of cerebral blood flow in language-specific ROIs. Conversely, for the language-related ROIs, we conducted another Pearson correlation analysis to examine the relationship between mean FC and mean CBF values and did not find a significant relationship ($r = 0.34$; $t(17) = 1.48$, $p = 0.16$). The significant positive correlation between CBF and FC in the language-specific ROIs supports our hypothesis of a positive relationship between the two in our TD participants and is in alignment with previous research with TD pediatric populations (Baller et al., 2022). DLD002 and DLD003 demonstrated patterns between the two measures that suggested an inverse rather than positive relationship between the two, though we did not statistically test these patterns. DLD002 had decreased CBF and increased functional connectivity, whereas DLD003 had what appeared to be elevated CBF values and reduced connectivity. These results are intriguing as they indicate an inverse relationship between CBF and FC but in different directions, which may suggest that deviations from the typical positive association between the two can signal dysfunction.

3.2.3.7. CBF, FC, and the CELF. While the relationship between CBF and FC in language-specific ROIs suggests a positive association in TD children, we also explored how these measures relate to language performance as assessed by the CELF.

A linear regression analysis was conducted to examine the relationship between the CELF and mean FC and CBF values in language-specific ROIs, while considering sex and age as potential moderators. The model had a multiple R-squared value of 0.3495 and an adjusted R-squared value of 0.09928, indicating that the predictors collectively accounted for 34.95% of the variance in CELF scores. However, the F-test for the overall model was not statistically significant ($F(5, 13) = 1.40, p = 0.229$), suggesting that the model did not significantly predict CELF scores. The analysis revealed that mean FC (Estimate = 22.48, $SE = 24.10, t = 0.93, p = 0.37$) and mean CBF (Estimate = 0.13, $SE = 0.40, t = 0.32, p = 0.75$), were not significantly associated with CELF scores. However, sex emerged as a significant predictor (Estimate = 4.21, $SE = 1.80, t = 2.40, p = 0.03$), indicating that females scored higher on the CELF compared to males. Age and the interaction between sex and age were not significant predictors of CELF scores.

These results suggest that neither mean functional connectivity nor mean cerebral blood flow in the language ROIs significantly predict language abilities as measured by the CELF. However, the significant effect of sex on CELF scores warrants further exploration in larger samples to understand its implications for language development.

Lastly, a linear regression analysis was conducted to investigate the relationship between the measures discussed above and the language-related ROIs. Overall, the model had low explanatory power, with a multiple R-squared value of 0.28 and an adjusted R-squared value of -0.0008. Furthermore, the F-test for the overall model was not statistically significant ($F(5, 13) = 0.1, p = 0.46$), indicating that the model did not significantly predict CELF scores. The analysis further revealed that none of the predictors, were significantly associated with CELF scores.

For Aim 3, we predicted that there would be a relationship between CBF, FC, and CELF scores. However, across the 21 TD participants who completed the resting-state functional connectivity scan, 19 showed no significant differences in connectivity patterns when compared individually to the group and almost all performed above average on the CELF. Therefore, it is not surprising given the stable patterns within the group that FC and CBF were not significant predictors of CELF scores. It is somewhat surprising, however, that there was not a stronger relationship between the functional measures and age and sex on the CELF, given our earlier findings from this study. There was evidence of females performing better on the CELF, but this was not associated with CBF or FC. It is possible that comparisons between TD children and children with DLD will yield clearer differences in the relationship between these variables. Nonetheless, the lack of a positive association between CBF and FC and poor performance on the CELF implicate these functional brain measures in DLD and warrant future investigations of the relationship among them.

4. Discussion

In this study, we explored measures of brain function in children with DLD compared to TD children through three aims: 1) characterize CBF patterns in children with DLD (compared to TD children); 2) characterize functional connectivity patterns at rest (iFC) in children with DLD (compared to TD children); and 3) explore the relationship between CBF, iFC, and CELF core language scores (CELF-CLS), a standardized measure of language abilities. We discuss our findings in light of each aim and due to our small sample size for the children with DLD, we offer suggestions for future research in each of these areas.

4.1. Aim 1: CBF Patterns

Prior research investigating CBF patterns in DLD has used invasive methods (e.g., the injection of a radioactive tracer with PET/SPECT) to measure blood flow and thus, has been

limited in this population. Here, we used a non-invasive and relatively quick method to measure CBF, known as arterial spin labeling (ASL) MRI. To our knowledge, this was the first study to explore CBF patterns using this method. We first examined differences in global measures of CBF between each of the DLD participants compared to the TD group (averaged) across whole brain (WB), left hemisphere (LH), and right hemisphere (RH) gray matter regions. Interestingly, DLD002 exhibited significantly lower CBF values in the WB and RH compared to the TD group, while DLD003 showed slightly elevated CBF values compared to the TD group (though this pattern was not significant).

To better understand whether certain brain regions were driving these patterns, we then looked at CBF within pre-defined networks that included traditional language regions (language-specific network) and other regions that have been implicated in DLD (language-related network). While no significant differences in CBF were found in the *language-specific* ROIs, DLD002 displayed significant differences in *language-related* ROIs compared to the TD group (though the comparison did not survive FDR correction), indicating potential neural differences beyond traditional language areas. In contrast, DLD003 showed similar CBF levels to the TD group in these regions. The findings revealed intriguing distinctions between the two DLD participants, with DLD002 exhibiting reduced CBF compared to TD children and DLD003 exhibiting CBF that was greater than the TD mean. Notably, the differences for DLD002 were not confined to traditional language regions suggesting that network dysfunction may be more widespread, or perhaps more parsimoniously (when considering differences between DLD002 and DLD003) specific regions of the brain, not explored in this paper, are implicated. These possibilities extend beyond the scope of this initial exploration but are important aspects to

consider for future research. Another important component of this research are the ages and biological sex of the participants included.

The brain undergoes a number of maturational changes between childhood and adolescence, which could influence CBF values. The TD group in our study was comprised of males and females between the ages of 6-12, while both children with DLD were 10-year-old males, which means that any differences found between each DLD participant and the TD group were likely not due to differences in age or sex. However, to better understand how CBF patterns differ across age and sex in the TD participants (as a means for comparison), we conducted a secondary analysis of this relationship and found that overall, TD males had greater CBF values, but experienced more pronounced age-related declines in CBF. For DLD003, the elevated CBF values are unexpected given that he is one of the older males in our sample. Thus, more work is needed to understand the effect of sex and age in light of the patterns observed for our DLD participants.

When examining CBF lateralization patterns in TD children, significant differences were observed between the left and right hemispheres, as well as in language-specific and language-related regions of interest (ROIs), with slightly higher CBF values in the left hemisphere. These results aligned with typical left hemisphere asymmetries reported in previous studies, providing a baseline for comparison with our DLD participants. Subsequent within-group comparisons for children with DLD revealed intriguing patterns. DLD002 exhibited significant differences in CBF between the left and right hemispheres, while DLD003 did not show typical left lateralization patterns (i.e., CBF was equal across hemispheres). Although global CBF patterns for DLD003 were similar to the group pattern, lateralization patterns differed, suggesting the global measures did not adequately capture aberrant blood flow for DLD003.

In sum, both DLD002 and DLD003 performed poorly on the CELF, yet they displayed distinct CBF patterns. DLD002 showed overall reduced CBF, and significant hemispheric lateralization differences compared to TD children (e.g., decreased CBF in the right hemisphere), aligning with previous findings on altered lateralization patterns in DLD. In contrast, DLD003 had somewhat elevated CBF patterns, with a lack of typical leftward asymmetry, suggesting that aberrancies in CBF, particularly in terms of lateralization, may be related to impaired language abilities and should be explored with larger sample sizes.

4.2. Aim 2: iFC Patterns

Aim 2 was to characterize intrinsic functional connectivity (iFC) patterns in children with DLD compared to TD children. To this end, we compared iFC patterns across the language-specific network and the language-related network between each of the DLD participants and the TD group (averaged). iFC patterns in the language network did not reveal any significant differences between the DLD participants and the group. However, within the language-related network, both participants exhibited distinct connectivity patterns compared to TD children. DLD002 displayed overconnectivity within language-related ROIs, while DLD003 demonstrated an overall pattern of underconnectivity with more anticorrelated regions. Thus, subsequent analysis focused on specific hub regions within the language network. DLD002 showed increased connectivity between hubs in the left inferior frontal gyrus, pars opercularis (IFG-PO), and left inferior frontal gyrus, pars triangularis (IFG-PT) and other frontal and temporal regions. These findings suggest potential recruitment of altered language networks in DLD002.

Conversely, DLD003 did not exhibit significant differences in connectivity patterns compared to TD children in these regions. However, within the language-related network, both DLD participants displayed differences in connectivity within the left caudate and regions such

as the left IFG-PT, left frontal operculum (FO), and left putamen (PUT). These findings are intriguing as recent research has strongly implicated the connection between subcortical structures within the basal ganglia and frontal regions in DLD (Abbott & Love, 2023; Ullman et al., 2024). Taken together with the results from Aim 1, the functional connectivity findings from this study suggest that altered network connectivity and neurovascular coupling could contribute to language impairment in DLD. In the final aim, we explored the relationship between these functional measures and language scores on the CELF.

4.3. Aim 3: CBF, iFC, and Language

Results from Aim 3 revealed significant associations between CBF within language-specific ROIs and CELF scores, moderated by sex. Older females with higher CBF tended to have better CELF scores, while older males with higher CBF tended to have worse scores. However, in language-related ROIs, no significant association was found between CBF and CELF scores, indicating a more nuanced relationship.

Analyses of FC patterns within language-specific and language-related ROIs did not significantly predict CELF scores in TD children, suggesting a complex interplay between brain function and language abilities. There was, however, a moderate positive correlation between CBF and FC patterns, which supports previous findings of positive relationship between FC and CBF. In the context of DLD, DLD002 demonstrated decreased CBF and increased FC within language networks, while DLD003 showed elevated CBF and reduced FC. These deviations from typical patterns suggest potential biomarkers of DLD, highlighting the importance of further investigation into the relationship between CBF, FC, and language abilities.

Overall, while CBF and FC measures in language-specific ROIs showed some association with language abilities in TD children, these relationships were not consistent across

all regions and were moderated by sex. Additionally, the lack of significant associations in language-related ROIs suggests a more complex relationship between brain function and language skills. Further research is needed to elucidate these relationships and their implications for understanding and treating DLD.

5. References

- Abbott, N., & Love, T. (2023). Bridging the Divide: Brain and Behavior in Developmental Language Disorder. *Brain Sciences*, 13(11), 1606. <https://doi.org/10.3390/brainsci13111606>
- Abraham, A., Pedregosa, F., Eickenberg, M., Gervais, P., Mueller, A., Kossaifi, J., Gramfort, A., Thirion, B., & Varoquaux, G. (2014). Machine learning for neuroimaging with scikit-learn. *Frontiers in Neuroinformatics*, 8. <https://doi.org/10.3389/fninf.2014.00014>
- Alsop, D. C., Detre, J. A., Golay, X., Günther, M., Hendrikse, J., Hernandez-Garcia, L., Lu, H., Macintosh, B. J., Parkes, L. M., Smits, M., Van Osch, M. J. P., Wang, D. J. J., Wong, E. C., & Zaharchuk, G. (2015). Recommended implementation of arterial spin-labeled perfusion MRI for clinical applications: A consensus of the ISMRM perfusion study group and the European consortium for ASL in dementia. *Magnetic Resonance in Medicine*, 73(1), 102-116. <https://doi.org/10.1002/mrm.25197>
- American Speech-Language-Hearing Association, T. (2005). Guidelines for manual pure-tone threshold audiometry. *ASHA*, 20 4, 297-301. <https://doi.org/10.1044/policy.GL2005-00014>
- Andersson, J. L., Hutton, C., Ashburner, J., Turner, R., & Friston, K. (2001). Modeling geometric deformations in EPI time series. *NeuroImage*, 13(5), 903-919.
- Ashburner, J. (2007). A fast diffeomorphic image registration algorithm. *NeuroImage*, 38(1), 95-113.
- Ashburner, J., & Friston, K. J. (2005). Unified segmentation. *NeuroImage*, 26(3), 839-851.
- Avants, B. B., Duda, J. T., Kilroy, E., Krasileva, K., Jann, K., Kandel, B. T., Tustison, N. J., Yan, L., Jog, M., & Smith, R. (2015). The pediatric template of brain perfusion. *Scientific data*, 2(1), 1-17.
- Avants, B. B., Epstein, C. L., Grossman, M., & Gee, J. C. (2008). Symmetric diffeomorphic image registration with cross-correlation: Evaluating automated labeling of elderly and neurodegenerative brain. *Medical Image Analysis*, 12(1), 26-41. <https://doi.org/https://doi.org/10.1016/j.media.2007.06.004>

- Baller, E. B., Valcarcel, A. M., Adebimpe, A., Alexander-Bloch, A., Cui, Z., Gur, R. C., Gur, R. E., Larsen, B. L., Linn, K. A., & O'Donnell, C. M. (2022). Developmental coupling of cerebral blood flow and fMRI fluctuations in youth. *Cell reports*, 38(13).
- 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.
- Berl, M. M., Mayo, J., Parks, E. N., Rosenberger, L. R., VanMeter, J., Ratner, N. B., Vaidya, C. J., & Gaillard, W. D. (2014). Regional differences in the developmental trajectory of lateralization of the language network. *Human Brain Mapping*, 35(1), 270-284.
- Bijsterbosch, J., Smith, S. M., & Beckmann, C. (2017). *An introduction to resting state fMRI functional connectivity*. Oxford University Press.
- Bishop, D. V., & Garsell, M. (2003). *Test for reception of grammar: Version 2: TROG-2 manual*.
- Bonakdarpour, B., Parrish, T. B., & Thompson, C. K. (2007). Hemodynamic response function in patients with stroke-induced aphasia: Implications for fMRI data analysis. *NeuroImage*, 36(2), 322-331. <https://doi.org/10.1016/j.neuroimage.2007.02.035>
- Botting, N. (2020). Language, literacy and cognitive skills of young adults with developmental language disorder (DLD). *International Journal of Language & Communication Disorders*, 55(2), 255-265. <https://doi.org/10.1111/1460-6984.12518>
- Brown, L., Sherbenou, R., & Johnsen, S. (1997). *Test of Nonverbal Intelligence—Third Edition*
- Buxton, R. B., Frank, L. R., Wong, E. C., Siewert, B., Warach, S., & Edelman, R. R. (1998). A general kinetic model for quantitative perfusion imaging with arterial spin labeling. *Magnetic Resonance in Medicine*, 40(3), 383-396. <https://doi.org/10.1002/mrm.1910400308>
- Calhoun, V. D., Wager, T. D., Krishnan, A., Rosch, K. S., Seymour, K. E., Nebel, M. B., Mostofsky, S. H., Nyalakanai, P., & Kiehl, K. (2017). *The impact of T1 versus EPI spatial normalization templates for fMRI data analyses* (1065-9471).
- Chai, X. J., Castañón, A. N., Öngür, D., & Whitfield-Gabrieli, S. (2012). Anticorrelations in resting state networks without global signal regression. *NeuroImage*, 59(2), 1420-1428.
- Chappell, M. A., Groves, A. R., Macintosh, B. J., Donahue, M. J., Jezzard, P., & Woolrich, M. W. (2011). Partial volume correction of multiple inversion time arterial spin labeling MRI data. *Magnetic Resonance in Medicine*, 65(4), 1173-1183. <https://doi.org/10.1002/mrm.22641>
- Chappell, M. A., Groves, A. R., Whitcher, B., & Woolrich, M. W. (2009). Variational Bayesian Inference for a Nonlinear Forward Model. *IEEE Transactions on Signal Processing*, 57(1), 223-236. <https://doi.org/10.1109/TSP.2008.2005752>

- Chen, B., Linke, A., Olson, L., Ibarra, C., Kinnear, M., & Fishman, I. (2021). Resting state functional networks in 1-to-3-year-old typically developing children. *Developmental cognitive neuroscience*, 51, 100991.
- Conti-Ramsden, N. B. Z., Emma Knox, Gina. (2001). Follow-up of children attending infant language units: Outcomes at 11 years of age. *International Journal of Language & Communication Disorders*, 36(2), 207-219.
- Crawford, J. R., Garthwaite, P. H., & Howell, D. C. (2009). On comparing a single case with a control sample: An alternative perspective. *Neuropsychologia*, 47(13), 2690-2695. <https://doi.org/https://doi.org/10.1016/j.neuropsychologia.2009.04.011>
- Crawford, J. R., & Howell, D. C. (1998). Comparing an individual's test score against norms derived from small samples. *The clinical neuropsychologist*, 12(4), 482-486.
- Dai, W., Garcia, D., De Bazelaire, C., & Alsop, D. C. (2008). Continuous flow-driven inversion for arterial spin labeling using pulsed radio frequency and gradient fields. *Magnetic Resonance in Medicine*, 60(6), 1488-1497. <https://doi.org/10.1002/mrm.21790>
- Desikan, R. S., Ségonne, F., Fischl, B., Quinn, B. T., Dickerson, B. C., Blacker, D., Buckner, R. L., Dale, A. M., Maguire, R. P., & Hyman, B. T. (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.
- Dollaghan, C., & Campbell, T. F. (1998). Nonword repetition and child language impairment. *Journal of speech, language, and hearing research*, 41(5), 1136-1146.
- Dolui, S., Wang, Z., Shinohara, R. T., Wolk, D. A., & Detre, J. A. (2017). Structural Correlation-based Outlier Rejection (SCORE) algorithm for arterial spin labeling time series. *Journal of Magnetic Resonance Imaging*, 45(6), 1786-1797. <https://doi.org/10.1002/jmri.25436>
- Dolui, S., Wolf, R., Nabavizadeh, S. A., Wolk, D. A., & Detre, J. A. (2017). Automated quality evaluation index for 2D ASL CBF maps. Poster presented at: 25th Annual Meeting and Exhibition of the International Society for Magnetic Resonance in Medicine,
- Dolui, S., Wolk, D. A., & Detre, J. A. (2016). SCRUB: a structural correlation and empirical robust bayesian method for ASL data. Proceedings of the International Society of Magnetic Resonance in Medicine,
- Dosenbach, N. U., Nardos, B., Cohen, A. L., Fair, D. A., Power, J. D., Church, J. A., Nelson, S. M., Wig, G. S., Vogel, A. C., & Lessov-Schlaggar, C. N. (2010). Prediction of individual brain maturity using fMRI. *Science*, 329(5997), 1358-1361.
- Duarte, J. V., Pereira, J. M., Quendera, B., Raimundo, M., Moreno, C., Gomes, L., Carrilho, F., & Castelo-Branco, M. (2015). Early disrupted neurovascular coupling and changed event

- level hemodynamic response function in type 2 diabetes: an fMRI study. *Journal of Cerebral Blood Flow & Metabolism*, 35(10), 1671-1680.
- Emerson, R. W., Gao, W., & Lin, W. (2016). Longitudinal study of the emerging functional connectivity asymmetry of primary language regions during infancy. *Journal of Neuroscience*, 36(42), 10883-10892.
- Eyler, L. T., Pierce, K., & Courchesne, E. (2012). A failure of left temporal cortex to specialize for language is an early emerging and fundamental property of autism. *Brain*, 135(3), 949-960.
- Fonov, V., Evans, A. C., Botteron, K., Almli, C. R., McKinstry, R. C., & Collins, D. L. (2011). Unbiased average age-appropriate atlases for pediatric studies. *NeuroImage*, 54(1), 313-327. <https://doi.org/10.1016/j.neuroimage.2010.07.033>
- Friston, K. J., Ashburner, J., Frith, C. D., Poline, J. B., Heather, J. D., & Frackowiak, R. S. (1995). Spatial registration and normalization of images. *Human Brain Mapping*, 3(3), 165-189.
- Friston, K. J., Williams, S., Howard, R., Frackowiak, R. S., & Turner, R. (1996). Movement-related effects in fMRI time-series. *Magnetic Resonance in Medicine*, 35(3), 346-355.
- Gao, W., Alcauter, S., Smith, J. K., Gilmore, J. H., & Lin, W. (2015). Development of human brain cortical network architecture during infancy. *Brain Structure and Function*, 220(2), 1173-1186.
- Gao, Y., Linke, A., Jao Keehn, R. J., Punyamurthula, S., Jahedi, A., Gates, K., Fishman, I., & Müller, R. A. (2019). The language network in autism: Atypical functional connectivity with default mode and visual regions. *Autism Research*, 12(9), 1344-1355.
- Gorgolewski, K., Burns, C. D., Madison, C., Clark, D., Halchenko, Y. O., Waskom, M. L., & Ghosh, S. S. (2011). Nipype: a flexible, lightweight and extensible neuroimaging data processing framework in python. *Frontiers in Neuroinformatics*, 5, 13.
- Greve, D. N., & Fischl, B. (2009). Accurate and robust brain image alignment using boundary-based registration. *NeuroImage*, 48(1), 63-72. <https://doi.org/10.1016/j.neuroimage.2009.06.060>
- Hallquist, M. N., Hwang, K., & Luna, B. (2013). The nuisance of nuisance regression: spectral misspecification in a common approach to resting-state fMRI preprocessing reintroduces noise and obscures functional connectivity. *NeuroImage*, 82, 208-225.
- Harris, C. R., Millman, K. J., van der Walt, S. J., Gommers, R., Virtanen, P., Cournapeau, D., Wieser, E., Taylor, J., Berg, S., Smith, N. J., Kern, R., Picus, M., Hoyer, S., van Kerkwijk, M. H., Brett, M., Haldane, A., del Río, J. F., Wiebe, M., Peterson, P., Gérard-Marchant, P., Sheppard, K., Reddy, T., Weckesser, W., Abbasi, H., Gohlke, C., & Oliphant, T. E.

- (2020). Array programming with NumPy. *Nature*, 585(7825), 357-362.
<https://doi.org/10.1038/s41586-020-2649-2>
- Hu, S., Wu, H., Xu, C., Wang, A., Wang, Y., Shen, T., Huang, F., Kan, H., & Li, C. (2019). Aberrant coupling between resting-state cerebral blood flow and functional connectivity in Wilson's disease. *Frontiers in Neural Circuits*, 13, 25.
- Jain, V., Duda, J., Avants, B., Giannetta, M., Xie, S. X., Roberts, T., Detre, J. A., Hurt, H., Wehrli, F. W., & Wang, D. J. (2012). Longitudinal reproducibility and accuracy of pseudo-continuous arterial spin-labeled perfusion MR imaging in typically developing children. *Radiology*, 263(2), 527-536.
- Jann, K., Hernandez, L. M., Beck-Pancer, D., McCarron, R., Smith, R. X., Dapretto, M., & Wang, D. J. J. (2015). Altered resting perfusion and functional connectivity of default mode network in youth with autism spectrum disorder. *Brain and Behavior*, 5(9), n/a-n/a.
<https://doi.org/10.1002/brb3.358>
- Jenkinson, M., Bannister, P., Brady, M., & Smith, S. (2002). Improved Optimization for the Robust and Accurate Linear Registration and Motion Correction of Brain Images. *NeuroImage*, 17(2), 825-841. <https://doi.org/https://doi.org/10.1006/nimg.2002.1132>
- Jenkinson, M., & Smith, S. (2001). A global optimisation method for robust affine registration of brain images. *Medical Image Analysis*, 5(2), 143-156.
[https://doi.org/https://doi.org/10.1016/S1361-8415\(01\)00036-6](https://doi.org/https://doi.org/10.1016/S1361-8415(01)00036-6)
- Kim, J. H., & Ress, D. (2016). Arterial impulse model for the BOLD response to brief neural activation. *NeuroImage*, 124, 394-408.
<https://doi.org/https://doi.org/10.1016/j.neuroimage.2015.08.068>
- Lanczos, C. (1964). Evaluation of Noisy Data. *Journal of the Society for Industrial and Applied Mathematics Series B Numerical Analysis*, 1(1), 76-85. <https://doi.org/10.1137/0701007>
- Lenroot, R. K., Gogtay, N., Greenstein, D. K., Wells, E. M., Wallace, G. L., Clasen, L. S., Blumenthal, J. D., Lerch, J., Zijdenbos, A. P., & Evans, A. C. (2007). Sexual dimorphism of brain developmental trajectories during childhood and adolescence. *NeuroImage*, 36(4), 1065-1073.
- Li, Z., Zhu, Y., Childress, A. R., Detre, J. A., & Wang, Z. (2012). Relations between BOLD fMRI-Derived Resting Brain Activity and Cerebral Blood Flow. *PLoS ONE*, 7(9), e44556. <https://doi.org/10.1371/journal.pone.0044556>
- Liang, X., Zou, Q., He, Y., & Yang, Y. (2013). Coupling of functional connectivity and regional cerebral blood flow reveals a physiological basis for network hubs of the human brain. *Proceedings of the National Academy of Sciences*, 110(5), 1929-1934.
<https://doi.org/10.1073/pnas.1214900110>

- Liégeois, F., Mayes, A., & Morgan, A. (2014). Neural Correlates of Developmental Speech and Language Disorders: Evidence from Neuroimaging. *Current Developmental Disorders Reports*, 1(3), 215-227. <https://doi.org/10.1007/s40474-014-0019-1>
- Lindquist, M. A., Meng Loh, J., Atlas, L. Y., & Wager, T. D. (2009). Modeling the hemodynamic response function in fMRI: Efficiency, bias and mis-modeling. *NeuroImage*, 45(1, Supplement 1), S187-S198. <https://doi.org/https://doi.org/10.1016/j.neuroimage.2008.10.065>
- Liu, F., Duan, Y., Peterson, B. S., Asllani, I., Zelaya, F., Lythgoe, D., & Kangarlu, A. (2018). Resting state cerebral blood flow with arterial spin labeling MRI in developing human brains. *European Journal of Paediatric Neurology*, 22(4), 642-651. <https://doi.org/https://doi.org/10.1016/j.ejpn.2018.03.003>
- Maenner, M. J., Shaw, K. A., & Baio, J. (2020). Prevalence of autism spectrum disorder among children aged 8 years—autism and developmental disabilities monitoring network, 11 sites, United States, 2016. *MMWR Surveillance Summaries*, 69(4), 1.
- McGregor, K. K. (2020). How We Fail Children With Developmental Language Disorder. *Language, Speech, and Hearing Services in Schools*, 51(4), 981-992. https://doi.org/10.1044/2020_lshss-20-00003
- Nieto-Castanon, A. (2020a). *Handbook of functional connectivity magnetic resonance imaging methods in CONN*. Hilbert Press.
- Nieto-Castanon, A. (2020b). *Handbook of functional connectivity magnetic resonance imaging methods in CONN*. Hilbert Press.
- Nieto-Castanon, A. (2022). Preparing fMRI data for statistical analysis. *arXiv preprint arXiv:2210.13564*.
- Nieto-Castanon, A., & Whitfield-Gabrieli, S. (2021). CONN functional connectivity toolbox (RRID: SCR_009550), Version 21. *Series CONN functional connectivity toolbox (RRID: SCR_009550), Version, 21*.
- Ogawa, S., Lee, T.-M., Kay, A. R., & Tank, D. W. (1990). Brain magnetic resonance imaging with contrast dependent on blood oxygenation. *Proceedings of the National Academy of Sciences*, 87(24), 9868-9872.
- Paniukov, D., Lebel, R., Giesbrecht, G., & Lebel, C. (2019). Cerebral Blood Flow Increases Across Early Childhood.
- Penny, W. D., Friston, K. J., Ashburner, J. T., Kiebel, S. J., & Nichols, T. E. (2011). *Statistical parametric mapping: the analysis of functional brain images*. Elsevier.

- Power, J. D., Mitra, A., Laumann, T. O., Snyder, A. Z., Schlaggar, B. L., & Petersen, S. E. (2014). Methods to detect, characterize, and remove motion artifact in resting state fMRI. *NeuroImage*, 84, 320-341. <https://doi.org/https://doi.org/10.1016/j.neuroimage.2013.08.048>
- R Core Team. (2023). *R: A Language and Environment for Statistical Computing*. In R Foundation for Statistical Computing. <https://www.R-project.org/>
- Rangaprakash, D., Tadayonnejad, R., Deshpande, G., O'Neill, J., & Feusner, J. D. (2021). FMRI hemodynamic response function (HRF) as a novel marker of brain function: applications for understanding obsessive-compulsive disorder pathology and treatment response. *Brain imaging and behavior*, 15(3), 1622-1640. <https://doi.org/10.1007/s11682-020-00358-8>
- Satterthwaite, T. D., Shinohara, R. T., Wolf, D. H., Hopson, R. D., Elliott, M. A., Vandekar, S. N., Ruparel, K., Calkins, M. E., Roalf, D. R., Gennatas, E. D., Jackson, C., Erus, G., Prabhakaran, K., Davatzikos, C., Detre, J. A., Hakonarson, H., Gur, R. C., & Gur, R. E. (2014). Impact of puberty on the evolution of cerebral perfusion during adolescence. *111*(23), 8643-8648. <https://doi.org/10.1073/pnas.1400178111>
- Simon, A. B., & Buxton, R. B. (2015). Understanding the dynamic relationship between cerebral blood flow and the BOLD signal: Implications for quantitative functional MRI. *NeuroImage*, 116, 158-167. <https://doi.org/10.1016/j.neuroimage.2015.03.080>
- Soni, N., Jain, A., Kumar, S., Pandey, C. M., & Awasthi, A. (2016). Arterial spin labeling magnetic resonance perfusion study to evaluate the effects of age and gender on normal cerebral blood flow. *Neurology India*, 64(Suppl 1). https://journals.lww.com/neur/fulltext/2016/64001/arterial_spin_labeling_magnetic_resonance.8.aspx
- Sours, C., Zhuo, J., Roys, S., Shanmuganathan, K., & Gullapalli, R. P. (2015). Disruptions in resting state functional connectivity and cerebral blood flow in mild traumatic brain injury patients. *PLoS ONE*, 10(8), e0134019.
- Taki, Y., Hashizume, H., Sassa, Y., Takeuchi, H., Wu, K., Asano, M., Asano, K., Fukuda, H., & Kawashima, R. (2011). Gender differences in partial-volume corrected brain perfusion using brain MRI in healthy children. *NeuroImage*, 58(3), 709-715. <https://doi.org/https://doi.org/10.1016/j.neuroimage.2011.07.020>
- Tustison, N. J., Avants, B. B., Cook, P. A., Zheng, Y., Egan, A., Yushkevich, P. A., & Gee, J. C. (2010). N4ITK: improved N3 bias correction. *IEEE transactions on medical imaging*, 29(6), 1310-1320.
- Ullman, M. T., Clark, G. M., Pullman, M. Y., Lovelett, J. T., Pierpont, E. I., Jiang, X., & Turkeltaub, P. E. (2024). The neuroanatomy of developmental language disorder: a systematic review and meta-analysis. *Nature Human Behaviour*, 1-14.

- Van Dijk, K. R., Sabuncu, M. R., & Buckner, R. L. (2012). The influence of head motion on intrinsic functional connectivity MRI. *NeuroImage*, 59(1), 431-438.
- Vanderwal, T., Kelly, C., Eilbott, J., Mayes, L. C., & Castellanos, F. X. (2015). Inscapes : A movie paradigm to improve compliance in functional magnetic resonance imaging. *NeuroImage*, 122, 222-232. <https://doi.org/10.1016/j.neuroimage.2015.07.069>
- Virtanen, P., Gommers, R., Oliphant, T. E., Haberland, M., Reddy, T., Cournapeau, D., Burovski, E., Peterson, P., Weckesser, W., Bright, J., van der Walt, S. J., Brett, M., Wilson, J., Millman, K. J., Mayorov, N., Nelson, A. R. J., Jones, E., Kern, R., Larson, E., Carey, C. J., Polat, İ., Feng, Y., Moore, E. W., VanderPlas, J., Laxalde, D., Perktold, J., Cimrman, R., Henriksen, I., Quintero, E. A., Harris, C. R., Archibald, A. M., Ribeiro, A. H., Pedregosa, F., van Mulbregt, P., Vijaykumar, A., Bardelli, A. P., Rothberg, A., Hilboll, A., Kloeckner, A., Scopatz, A., Lee, A., Rokem, A., Woods, C. N., Fulton, C., Masson, C., Häggström, C., Fitzgerald, C., Nicholson, D. A., Hagen, D. R., Pasechnik, D. V., Olivetti, E., Martin, E., Wieser, E., Silva, F., Lenders, F., Wilhelm, F., Young, G., Price, G. A., Ingold, G.-L., Allen, G. E., Lee, G. R., Audren, H., Probst, I., Dietrich, J. P., Silterra, J., Webber, J. T., Slavič, J., Nothman, J., Buchner, J., Kulick, J., Schönberger, J. L., de Miranda Cardoso, J. V., Reimer, J., Harrington, J., Rodríguez, J. L. C., Nunez-Iglesias, J., Kuczynski, J., Tritz, K., Thoma, M., Newville, M., Kümmerer, M., Bolingbroke, M., Tartre, M., Pak, M., Smith, N. J., Nowaczyk, N., Shebanov, N., Pavlyk, O., Brodtkorb, P. A., Lee, P., McGibbon, R. T., Feldbauer, R., Lewis, S., Tygier, S., Sievert, S., Vigna, S., Peterson, S., More, S., Pudlik, T., Oshima, T., Pingel, T. J., Robitaille, T. P., Spura, T., Jones, T. R., Cera, T., Leslie, T., Zito, T., Krauss, T., Upadhyay, U., Halchenko, Y. O., Vázquez-Baeza, Y., & SciPy, C. (2020). SciPy 1.0: fundamental algorithms for scientific computing in Python. *Nature Methods*, 17(3), 261-272. <https://doi.org/10.1038/s41592-019-0686-2>
- Whitfield-Gabrieli, S., & Nieto-Castanon, A. (2012). Conn: a functional connectivity toolbox for correlated and anticorrelated brain networks. *Brain connectivity*, 2(3), 125-141.
- Whitfield-Gabrieli, S., Nieto-Castanon, A., & Ghosh, S. (2011). Artifact detection tools (ART). *Cambridge, MA. Release Version*, 7(19), 11.
- Wiig, E. H., Semel, E., & Secord, W. (2013). *CELF 5*. Pearson/PsychCorp.
- Yan, W., Rangaprakash, D., & Deshpande, G. (2018). Aberrant hemodynamic responses in autism: implications for resting state fMRI functional connectivity studies. *NeuroImage: Clinical*, 19, 320-330.
- Ye, F., Du, L., Liu, B., Gao, X., Yang, A., Liu, D., Chen, Y., Lv, K., Xu, P., & Chen, Y. (2022). Application of pseudocontinuous arterial spin labeling perfusion imaging in children with autism spectrum disorders. *Frontiers in neuroscience*, 16, 1045585.

- Yerys, B. E., Herrington, J. D., Bartley, G. K., Liu, H.-S., Detre, J. A., & Schultz, R. T. (2018). Arterial spin labeling provides a reliable neurobiological marker of autism spectrum disorder. *Journal of Neurodevelopmental Disorders*, 10(1). <https://doi.org/10.1186/s11689-018-9250-0>
- Zhang, Y., Brady, M., & Smith, S. (2001). Segmentation of brain MR images through a hidden Markov random field model and the expectation-maximization algorithm. *IEEE transactions on medical imaging*, 20(1), 45-57. <https://doi.org/10.1109/42.906424>
- Zhu, J., Zhuo, C., Xu, L., Liu, F., Qin, W., & Yu, C. (2017). Altered coupling between resting-state cerebral blood flow and functional connectivity in schizophrenia. *Schizophrenia bulletin*, 43(6), 1363-1374.

Chapter 4

RATE OF SPEECH AFFECTS THE COMPREHENSION OF PRONOUNS IN CHILDREN WITH DEVELOPMENTAL LANGUAGE DISORDER

Preface

Chapter 3 revealed intriguing patterns of functional brain differences in children with DLD compared to typically developing (TD) children. When comparing these functional brain measures to language abilities, the study used a standardized measure of language, the CELF-5 Core Language Score (CLS), which is composed of 4 subtests that measure different aspects of language. Though standardized tests can be useful, especially when comparing performance across different age groups, they are limited in the amount of detail they can provide. In particular, they might not be sensitive to the nuances of everyday language interactions. For example, the subtests of the CELF are untimed and examiners will often wait for participants to respond before moving to the next test item, whereas real-time language processing (on the playground, for example) is temporally constrained. Thus, in the final chapter of this dissertation, we investigate real-time sentence processing in children with DLD, as a means of better understanding the source of language deficit.

Abstract

This study examined whether children with Developmental Language Disorder (DLD) have knowledge of binding principles (i.e., linking pronouns to their structurally licensed antecedent) during online and offline processing, and whether rate of speech impacted access to that knowledge. Fourteen children with DLD participated in two experiments, with sentences presented auditorily at either a regular or slow speech rate. Sentences were matched except to contain a pronoun, reflexive, or noun phrase (control) in the same syntactic position. Experiment (1) used a cross-modal picture priming paradigm to test online pronoun-antecedent linking abilities at both rates of speech. Children were instructed to make a binary decision during the uninterrupted auditory presentation of a sentence to a visually presented image (of the antecedent) at the offset of a pronoun, a reflexive, or a control noun. Response times between conditions (e.g., pronoun vs. control noun) were compared to determine whether participants showed evidence of priming (faster response times in the pronoun than control noun condition) at either speech rate. Experiment (2) used an auditory sentence-picture-matching task to test offline, final comprehension of similar sentences containing a pronoun or reflexive. Children were asked to point to the correct picture after hearing sentences presented at either speech rate. Accuracy was compared across both speech rates. For Experiment (1), children with DLD did not show evidence of real-time pronoun-antecedent priming at the regular speech rate. However, when sentences were slowed, they showed correct priming for the pronoun condition. For experiment (2), children with DLD performed at-chance when interpreting sentences with pronouns regardless of speech rate. While children with DLD have been shown to have difficulty processing sentences containing anaphors (such as pronouns), results suggest that this is not due to loss of intrinsic knowledge of binding principles. By slowing the rate of speech input, we showed that children with DLD do have access to that knowledge and can make the correct link

during online processing between a pronoun and its structurally licensed antecedent (Experiment 1) but need more time to do so. However, the effect of slowed speech input does not extend to offline, final comprehension (Experiment 2).

1. Introduction

Developmental Language Disorder (DLD; previously referred to as Specific Language Impairment or SLI) is a heterogeneous neurodevelopmental disorder that can disrupt expressive and/or receptive language abilities but cannot be attributed to hearing loss, intellectual disability, or neurological damage. DLD is estimated to affect around 7-10% of school-age children making it more prevalent than other neurodevelopmental disorders, such as autism spectrum disorder (ASD) (Norbury et al., 2016; Tomblin et al., 1997; Zablotsky et al., 2019). Despite its prevalence, there has been significant debate around the source of the deficit, especially regarding sentence level comprehension. The three most well represented arguments in the literature are that the deficits are specific to linguistic knowledge (underlying representations), language processing (such as lexical access or phoneme discrimination), or non-linguistic cognitive processes associated with language (such as working memory or processing speed) (Abbott & Love, 2023; Schwartz, 2017). Therefore, investigations into sentence comprehension impairments in DLD would need to isolate measures of language processing, including components of non-linguistic cognitive processes, from underlying linguistic representations to better understand the source of impairment. Previous studies approached this by comparing processing patterns between typically developing (TD) children and children with DLD on several different language constructions (Borovsky et al., 2013; Montgomery, 2000; Schelletter & Leinonen, 2003; Schwartz et al., 2016). Here, we focus on the processing of complex

sentences containing pronouns and reflexives (also known as anaphors) that must refer back to previous noun phrases (also known as antecedents) in children with DLD.

Generative rules of binding (Chomsky, 1982) state that syntactic principles dictate how pronouns and reflexives link to prior occurring noun phrases (i.e., antecedents). According to Principle A, demonstrated in sentence 1a below, the reflexive anaphor “*himself*” must only bind to an antecedent within the same local clause (e.g., ‘Finn’, as illustrated by the correct sub-index *j* and incorrect sub-index *i** for ‘Ollie’), whereas Principle B, demonstrated in sentence 1b below, states that the pronoun “*him*” must bind to an antecedent outside the local clause, in this case either ‘Ollie’ or some other previously mentioned noun phrase (e.g., ‘Vera’, ‘the doctor’, as illustrated by the correct sub-indices *i* or *k* and incorrect sub-index *j** for ‘Finn’).

Principle A (1a) Ollie_{*i*} thought [that Finn_{*j*} helped *himself*_{*i***j*}].

Principle B (1b) Ollie_{*i*} thought [that Finn_{*j*} helped *him*_{*i*/*j***k*}]¹.

Linking pronouns and reflexives to their structurally licensed antecedent requires intrinsic knowledge of binding relationships. However, prior research has produced discrepant results regarding the way in which children demonstrate this knowledge. Specifically, young children demonstrate different pronoun-antecedent linking abilities depending upon whether the ability is measured using real-time, *online* methods or interpretive, *offline* methods, as each measure captures different aspects of processing (Love et al., 2009; Schwartz et al., 2016).

Offline measures allow for additional metalinguistic reflection at all levels of sentence processing including syntactic, semantic, and pragmatic. Therefore, results from offline tasks measure conscious processing after all linguistic processes are complete (Sato & Vanek, 2023).

¹ The indices ‘*i*’, ‘*j*’, and ‘*k*’ represent a link between the pronoun and antecedent. The asterisk indicates a violation of binding principles. Note that ‘*k*’ refers to a pronoun that does not have an antecedent within the sentence.

In contrast, temporally sensitive *online* measures provide a glimpse into the moment-by-moment mapping of dependency relationships, thus revealing patterns of comprehension that offline measurements are unable to capture (Love et al., 2009; McKee et al., 1993). Love et al. (2009) demonstrated this difference using an online cross-modal picture priming paradigm (Swinney & Prather, 1989) and an offline sentence-picture-matching task to investigate intrinsic knowledge of pronominal binding relationships and final comprehension, respectively (Love et al., 2009). The authors found that when evaluated with online measures, TD participants as young as 5 years of age displayed adult-like knowledge of binding principles by correctly linking pronouns to antecedents. However, when the same children were tested using offline measures, the ability to correctly link a pronoun to its antecedent did not emerge until after 8 years of age, which replicates prior reports in the literature of a maturational effect of pronoun comprehension (Baauw & Cuetos, 2003; Chien & Wexler, 1990; McKee et al., 1993). These results suggest a different developmental trajectory for conscious and automatic processing of referential relationships, perhaps due to the additional offline demands of integrating all levels of linguistic input (syntactic, semantic, etc.), holding that information in memory, and making a final, interpretative decision about sentence meaning. Similar maturational patterns for TD children have been demonstrated with other language constructions such as relative clauses (Love, 2007), reflexives (McKee et al., 1993), and verb-phrase ellipses (Callahan et al., 2012).

Behavioral studies of binding processes in children with DLD are limited and have resulted in disparate conclusions about the underlying source of language impairment, likely owing to differences in methodology. For example, offline studies have revealed that children with DLD show different developmental trajectories for the acquisition of binding principles when compared to TD children, which has been interpreted as evidence for a deficit in linguistic

knowledge, and more specifically in underlying representations (Franks & Connell, 1996; Van Der Lely & Stollwerck, 1997). By contrast, Schwartz et al. (2016) tested binding processes in children with DLD using an online method and found that children with DLD are as accurate as TD children in linking pronouns to their structurally correct antecedents, but are slower to do so (Schwartz et al., 2016). Similarly, Girbau (2017) tested comprehension of direct object pronoun sentences in Spanish-speaking children with DLD using a cross-modal priming paradigm and found that they were slower to respond overall than TD children, but unlike Schwartz et al.'s (2016) findings, they were also less accurate than their TD peers (Girbau, 2017). Both authors concluded that children with DLD have deficits in processing speed, but it remains unclear whether poorer comprehension abilities are due to domain general processing speed deficits or deficits specific to language processing.

Slower processing of referential relationships suggests that slowing down the rate of speech input may improve the ability to link pronouns and reflexives to their structurally licensed antecedent in children with DLD. A slowed rate of speech has been shown to benefit those with language impairments (Baker & Love, 2023; Love et al., 2008; Pashek & Brookshire, 1982; Poeck & Pietron, 1981). However, slowed input has also been shown to disrupt real-time processing in language unimpaired individuals (Love et al., 2008). In Love et al.'s (2009) investigation of rate of speech effects in typically developing (TD) children, the authors explored how slowing down the rate of speech impacted the ability to link pronouns (e.g., *him*) to their structurally licensed noun phrase during real-time, online sentence processing and offline, final comprehension (Love et al. 2009). The experimental sentences in Love et al. (2009) contained two noun phrases, only one of which was the structurally licensed antecedent of a later appearing pronoun. In addition to their main pronoun sentence condition, the study also included a

reflexive condition; a linguistic structure of which typically developing children show early mastery (McKee et al., 1993). In Love et al. (2009), experimental sentences were designed as minimal pairs such that the sentences across all three conditions were identical except for the reference seeking element (pronoun, reflexive, or non-referential noun phrase, NP). Given that the purpose of the study was to test pronoun-antecedent linking, the authors did not directly test on-time reflexive-antecedent linking with these sentences (i.e., they only tested priming for the NP that was structurally linked to the pronoun - i.e., the first noun phrase, NP1). This focused design served two purposes, (1) it allowed the authors to control for additional processing demands introduced by adding a referent to the sentence and (2) it allowed the authors to test whether TD children would *violate* Binding Principle A by incorrectly linking a reflexive with an antecedent outside of its local clause.

The authors found that in the *online* experiment, TD children showed adult-like patterns of correct referential processing at a regular rate of speech, but when the rate of speech was slowed it disrupted their ability to make those co-referential links, similar to patterns found in neurotypical adults for other syntactically dependent relationships (Love et al., 2008). For the slowed rate of speech condition, where children should have linked the pronoun to the structurally licensed antecedent (NP1), children incorrectly linked the reflexive with NP1, indicating that at the slowed rate of speech, binding principles were incorrectly applied. Conversely, in the *offline* study, TD children demonstrated difficulty with pronoun-antecedent linking at the regular rate of speech, but with slowed speech input, final comprehension of sentences containing pronouns improved. For sentences with reflexives, on the other hand, TD children showed evidence of correctly interpreting sentences containing a reflexive at both speech rates. Based on these findings, and as reflected in Table 3.1, the authors concluded that

TD children showed age-appropriate real-time (online) referential linking for pronouns at the regular speech rate, but pronoun-anaphor linking required additional time (through slowed speech input) for successful offline (interpretive) comprehension.

Results from Love et al. (2009) provided insight into rate of speech effects for online vs. offline pronoun processing in typically developing children. Prior research has shown that children with DLD struggle for longer periods of time with correctly assigning pronouns to their antecedents (Baauw & Cuertos, 2003; van der Lely, 1996; Schwartz et al., 2016). It may be the case that children with DLD would benefit from a slowed rate of speech as it would allow for additional time to make the necessary binding links; that is if the linguistic knowledge for binding is available to them. To our knowledge, no studies have investigated this rate of speech manipulation on pronoun processing in DLD. If slowing down the rate of speech improves the ability to link pronouns to their structurally licensed antecedents in children with DLD, it will demonstrate intact knowledge of binding principles, suggesting that the deficit is not in linguistic knowledge or underlying linguistic representations as some theories suggest. Therefore, in the current study, we build on the typically developing findings from Love et al. (2009) by employing the same experimental design and materials to explore whether slowing down the rate of speech will improve online and offline pronoun-antecedent linking abilities in children with DLD.

1.1. The current study

The present study aims to test how rate of speech input impacts referential binding for pronouns during sentence comprehension in children with DLD. We used an online cross-modal picture priming paradigm (described below) to determine if children with DLD can correctly link pronouns back to their structurally defined antecedents in real-time with both regular and slow

speech input. Additionally, we investigated offline responses to the same stimuli using a sentence-picture-matching task at both rates of speech. For the *online* study (Experiment 1), we hypothesized that at a regular rate of speech, children with DLD would demonstrate impaired pronoun-antecedent linking beyond the age at which TD children are successful (i.e., no evidence of priming in the pronoun condition), but with a slowed rate of speech input, they would show on-time pronoun-antecedent linking (i.e., priming in the pronoun condition, further described in the Materials and Methods section below) upon hearing the pronoun. This pattern would indicate that children with DLD have intact linguistic representations but require more time to make the correct syntactic links. For the *offline* study (Experiment 2), we hypothesized that children with DLD would show impaired (at-chance) accuracy at the regular speech rate, with small gains in accuracy at the slowed speech rate. Like in Love et al. (2009), this study also included an additional reflexive condition in both experiments to help determine if underlying knowledge of binding principles for both reflexives (Principle A) and pronouns (Principle B) is intact in children with DLD. Prior research has shown that pronoun-anaphor linking takes longer to acquire than reflexive-anaphor linking (Love et al., 2009; Schwartz et al., 2016). Therefore, our hypotheses are focused on the pronoun condition, but we note here that any changes in reflexive-anaphor linking due to the rate of speech manipulation would provide insight into binding knowledge in children with DLD.

The purpose of this study is to build on previously published typically developing findings from Love et al. (2009) to better understand the source of language deficits in children with DLD. Important to the design of the online study, each experimental sentence had three versions that were identical minus the inclusion of either a pronoun, a reflexive, or an unrelated noun phrase (see Figure 4.2 in the Study Design and Stimuli section for example sentences). As

will be discussed, the measure of interest is reaction time differences between the matched pronoun and control sentences. By maintaining the structure and wording of the sentence triplets, we were able to isolate the linguistic process of interest, pronoun-anaphor linking, while reducing the effects of other cognitive processes, such as attention and memory. In doing so, this study will provide insight into whether children with DLD have intact knowledge of linguistic principles, or if their deficit stems from some other domain-general linguistic or non-linguistic cognitive process. In other words, this study investigates differences in *online* sentence processing and *offline* sentence comprehension. Table 4.1 lists our hypotheses for the pronoun condition at both regular and slow rates of speech for both the online (Experiment 1) and offline (Experiment 2) conditions, along with the findings from Love et al. (2009) in gray.

Table 4.1. A summary of findings from Love et al. (2009), which investigated whether typically developing (TD) children would show priming during pronoun-antecedent linking at regular and slow rates of speech (in gray) (Love et al., 2009). Next to the summary are the hypotheses for the current study investigating the same processes in children with developmental language disorder (DLD).

	Regular Rate		Slow Rate	
	TD (Love et al., 2009)	DLD (current study hypothesis)	TD (Love et al., 2009)	DLD (current study hypothesis)
Online (Response Times)	Evidence of priming in pronoun condition	Will not prime in pronoun condition	No evidence of priming in pronoun condition	Will prime in pronoun condition
Offline (Final Comprehension Accuracy)	Impaired (at- chance) accuracy in pronoun condition	Impaired (at- chance) accuracy in pronoun condition	Improved (above chance) accuracy in pronoun condition	Impaired (at- chance) performance with modest gains in accuracy in pronoun condition

2. Experiment 1: Online Processing via Cross-Modal Picture Priming

This first experiment in this study investigates how children with DLD process binding relations in real time by employing an online, cross-modal picture priming paradigm (Swinney &

Prather, 1989). Findings for typically developing children were previously published in Love et al. (2009) but have also been summarized in Table 4.1 above for reader convenience.

2.1. Materials and methods

2.1.1. Participants

Eighteen monolingual English-speaking children with DLD were recruited for the study. Data from 4 participants were removed due to not completing all 4 testing sessions. The remaining 14 participants ($M_{\text{age}} = 7.80$ years, $SD_{\text{age}} = 1.58$, 8 female) met inclusionary criteria for DLD based on clinical consensus, scoring less than 1.5 standard deviations below the mean on at least two out of the four core language index subtests of the Clinical Evaluation of Language Fundamentals, Version 4 (CELF-IV) (Semel et al., 2003), and scoring greater than 80 on the Test of Nonverbal Intelligence, Version 3 (TONI-III) (Brown et al., 1997). Participant demographics and diagnostic assessment scores are provided in Table 4.2. Participants also had normal or corrected-to-normal visual acuity and hearing and had no other reported neurodevelopmental disorders (e.g., ASD), genetic disorders (e.g., Down syndrome), or neurological impairments (e.g., head trauma, epilepsy, etc.). Participants were randomly assigned to either the regular rate of speech or the slow rate of speech condition. Following the data screening procedures described in more detail in the Analysis section below, there were 8 children with DLD in the regular rate of speech group ($M_{\text{age}} = 7.42$ years, $SD_{\text{age}} = 1.79$, 4 female) and 6 children with DLD in the slow rate of speech group ($M_{\text{age}} = 8.32$ years, $SD_{\text{age}} = 1.20$, 4 female). No significant differences in age, CELF-IV score, or TONI-III score were found between groups, and the age range was similar to Love et al. (2009), which used the same methodology to investigate pronoun binding relationships in TD children (see Table 4.2) (Love et al., 2009).

Participants were recruited from schools in the San Diego Unified School District and Del Mar School District as well as San Diego State University's (SDSU) Speech-Language Clinic. After the language and cognitive assessments were completed, the children returned for four testing sessions, each separated by at least three weeks and lasting approximately one hour (Experiment 1: 3 visits, Experiment 2: 1 visit). This study was approved under both SDSU and the University of California San Diego's (UCSD) IRB protocols and all participants were compensated for their time.

Table 4.2. Participant demographics and assessment scores [Mean (SD)]. ND = no data; CELF-4: Clinical Evaluation of Language Fundamentals, Version 4 (Semel et al., 2003); TONI-3: Test of Non-Verbal Intelligence, Version 3 (Brown et al., 1997); The CELF and the TONI are reported as scaled scores. The gray shaded region includes participant demographics for TD children tested by Love et al. (2009).

	TD Children	Children with DLD		
	Love et al., 2009	Regular (n=8)	Slow (n=6)	<i>p-value</i>
Age	7.43 (1.80)	7.42 (1.79)	8.32 (1.20)	0.28
Sex	21 females, 22 males	4 females, 4 males	4 females, 2 males	--
Handedness	ND	7 right, 1 left	4 right, 1 left, 1 both	--
CELF-4 Core Language Index	115.26 (10.10)	71.88 (9.48)	75.33 (15.81)	0.65
TONI-3	113.67 (12.10)	95.00 (13.14)	105.80 (16.24)	0.25

2.1.2. Study design and stimuli

For the online experiment, a cross-modal picture priming (CMPP) paradigm was used (Love, 2007; Love et al., 2009; Swinney & Prather, 1989). Materials were taken from a prior study by Love et al., (2009) and are described in more detail below. Each rate condition (regular or slow) was designed to be within-subjects; in other words, participants provided data for the anaphor (pronoun and reflexive) and control (non-referential noun phrase) conditions across all items, thus serving as their own controls.

As part of the CMPP paradigm, participants listened to sentences over headphones while seated in front of a computer screen (Figure 4.1). The children were told that they would be listening to sentences and that at some point during the sentence, a picture would appear, and

they would have to use a binary button box to make a decision about whether the picture was “alive” (right button press) or “not alive” (left button press). They were told to try their best to understand the sentences as they would occasionally be asked questions about them. The measure of interest was response time (and accuracy) during the binary decision task. In this CMPP paradigm, the principles of priming dictate that when the image, which is strategically presented at a point of interest in the sentence (e.g., where pronoun-antecedent linking should take place - at the offset of the pronoun), is related in some way to a noun (antecedent) in the sentence, participants should respond faster during the decision task than in a condition where there is no structural link (the control condition), demonstrating evidence of a priming effect, which reflects the access and processing of the antecedent at that point in time.

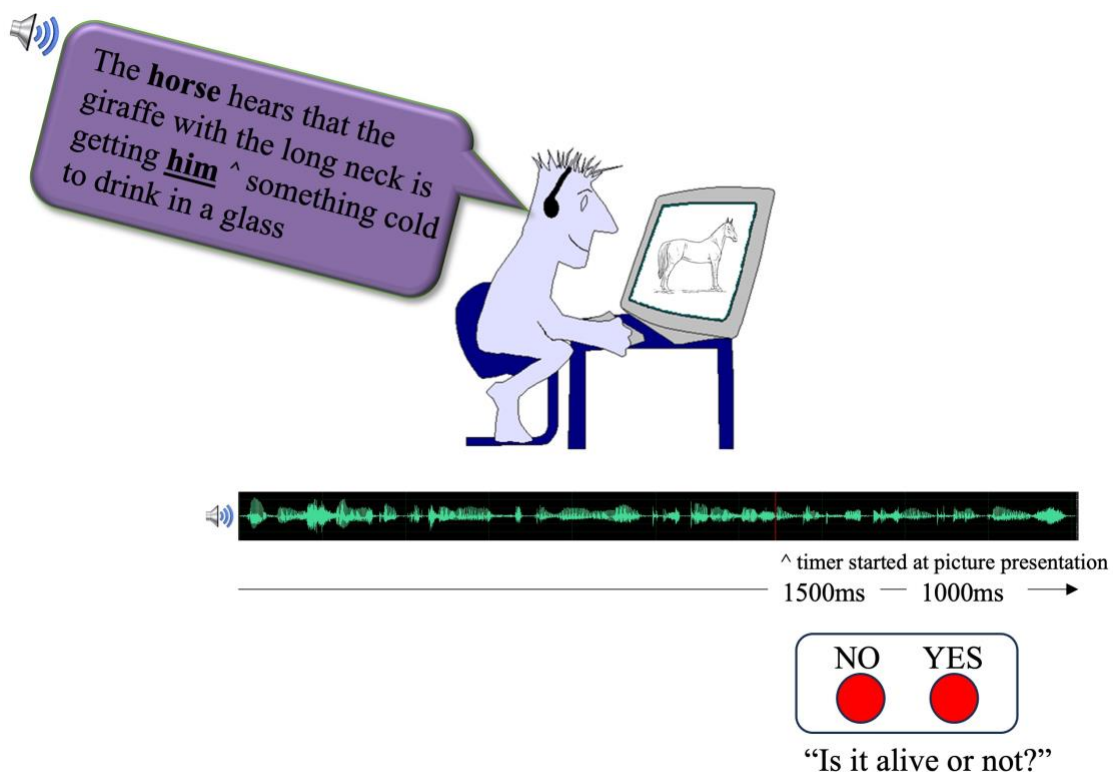


Figure 4.1. An illustration of the Cross Modal Picture Priming (CMPP) paradigm (Swinney & Prather, 1989). While listening to auditorily presented sentences, participants make a binary (alive or not alive) decision about the picture on the screen. The presentation of the picture begins approximately 1500ms after the sentence begins (noted by ^) and participants have

1000ms to make their decision before the image disappears from the screen and the next trial begins.

As described in Love et al. (2009), sentences contained multiple noun phrases. The noun phrases in the experimental sentences were animals, whereas filler sentences contained a mixture of animal and inanimate object names. The sentences for this study included 30 experimental sentences and 30 filler sentences. Each of the 30 experimental sentences were comprised of sentence triplets (10 per condition) that were identical in structure, wording, and length with the exception of the presence of either a pronoun (Principle B), a reflexive (Principle A), or an unrelated non-reference seeking noun phrase (Figure 4.2). For these experimental items, at the point in the sentence that the child should make a co-referential connection (e.g., pronoun offset) or after hearing the reflexive or unrelated noun, a picture would appear on the computer screen in front of them (noted by the ‘^’ in Figure 4.2). The children were instructed to respond as quickly and accurately as possible via a binary (alive/not alive) decision when the picture appeared. Importantly, reaction times to the same picture were compared across sentence triplets to gauge priming effects resulting from correct or incorrect linking of the reference seeking elements (pronoun vs control, reflexive vs control), to prior occurring noun phrases (NP1). Recall, that linking a reflexive to NP1 would violate Binding Principle A, as reflexives can only bind to antecedents within the local clause. Since NP1 is outside of the reflexive clause, the only appropriate structural link would be to the pronoun. Therefore, children should respond faster to the binary decision task when the image of NP1 appears at the offset of the pronoun rather than the reflexive. Following the pronoun, reflexive, or control noun phrase, there were at least seven syllables to ensure children would have time to process the sentence while simultaneously making a binary decision. All pronoun and reflexive sentences contained third-person singular,

masculine pronouns/reflexives, whereas all control sentences contained non-animal female nouns (e.g., the lady).

Given that the images presented for the experimental and control conditions are only of the first noun phrase (NP1, which is structurally licensed by the pronoun), our *a priori* hypothesis was that if children with DLD could make accurate binding links in real time, priming effects would be present in the pronoun (vs. control) condition only. Priming should not be seen in the reflexive condition (2b, in Figure 4.2, below) as binding for the reflexive should only occur with the second noun phrase (*giraffe*). This mismatch should result in increased reaction times for the reflexive condition when compared to the control condition. The control condition (2c, in Figure 4.2, below), with no intra-sentence referential links, was designed to provide a baseline measure of response times for sentences of this type, as children should not be making binding links to prior occurring noun phrases in the sentence. Quicker response times to the picture of NP1 in the pronoun condition compared to the control condition are interpreted as evidence of priming, and an indication of correct dependency linking, whereas quicker response times in the reflexive condition (compared to the control condition) are interpreted as evidence of incorrect priming, in other words, a link is made between the reflexive and the wrong NP.

- (2a) **Pronoun** The **horse_i** hears that the giraffe with the long neck is getting **him_i**, ^ something cold to drink in a glass.
 (2b) **Reflexive** The **horse_i** hears that the **giraffe_j** with the long neck is getting **himself_{j/i*}**, ^ something cold to drink in a glass.
 (2c) **Control** The **horse_i** hears that the giraffe with the long neck is getting **the nurse_{i*}**, ^ something cold to drink in a glass.

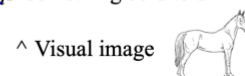


Figure 4.2. An example of experimental and control items. ‘The horse’ (NP1) is the correct antecedent for only the pronoun condition, noted by the *i*; *i** represents an incorrect link to ‘The horse’. The ‘^’ represents the point in the sentence that the image of NP1 appears on the screen. *j* indexes the antecedent-anaphor pair for the reflexive condition. Note that participants only saw images of NP1 for the experimental sentences, thus the reflexive is the incorrect anaphor for the visual image.

Filler sentences (n=30) of the same length and complexity as the experimental sentences were included. These sentences were designed to prevent participants from expecting an “alive” response for each picture or using strategies to complete the task. Examples of filler sentences can be seen in Figure 4.3, below. There were 10 that contained a pronoun or reflexive and 20 that were of another construction.

- (3a) The **camel**, thinks that the ostrich jumping over the bed will hurt him, ^ and everyone will have to stop playing.



- (3b) The alligator under the umbrella wonders if the fox ^ in the river is taking a bath this afternoon.



Figure 4.3. An example of filler items to elicit a “not alive” decision. The ‘^’ represents the point in the sentence that the image appears on the screen.

During each testing session, participants listened to 30 experimental sentences (3 versions per sentence: pronoun, reflexive, non-referential noun phrase) and 30 filler sentences, for a total of 180 items across three visits. Each experimental sentence had a pronoun, a reflexive, and a control version. These were counterbalanced across three scripts, with each script containing only one version of the experimental sentence. For example, referring to Figure 4.2, (2a) would appear in Script 1, (2b) in Script 2, and (2c) in Script 3 to ensure an equal number of exemplars across scripts and also to prevent any effects from repeating sentences in the same visit. In a given script, no more than 3 experimental sentences were presented in a row. Filler sentences were the same across all three scripts. After participants were trained on the CMPP task (procedure described in more detail below), the experiment began. The first six items presented during each visit were filler items to allow the participant to acclimate to the test, although they

were not informed of this. While every participant received all three scripts, one per visit, they were randomly assigned to different script presentation orders.

In the regular rate of speech input condition, sentences were recorded by a native English female speaker and were delivered at an average rate of 4.94 syllables per second. In the slow rate of speech condition, sentences were slowed (while maintaining pitch) to an average of 3.36 syllables per second (using the Cool Edit Pro v1.2 software package; Syntrillium Software, Phoenix, AZ). Participants only heard one rate of speech condition across all three visits. Those in the slow rate of speech condition often reported that the speaker sounded tired.

Stimuli were presented with an in-house software program (TEMPO; version 2.1.2) to control the presentation of the pictures and sentences. The same software was used to collect both reaction time and button press response choice. During the presentation of the sentence, at the predetermined onset of the presentation of the image, a millisecond-accurate computer timer was initiated. The timer terminated when the participant pressed the button to indicate their response on the binary decision task and their button selection and response time was recorded. Each picture remained on the screen for 1500ms or until the button press was made (whichever came first). Responses were allowed for an additional 1000ms after the picture disappeared, leaving a 2500ms window within which a participant could respond. Any response times longer than 2500ms were recorded as a no-response and counted as an error. There was a 3000ms gap between successive sentences.

2.1.3. Procedure

Participants were trained extensively in order to be able to complete the CMPP task (listening to and comprehending auditorily delivered sentences along with making a button press when shown pictures). Training was delivered in stages that increased in complexity to ensure

that participants were not overwhelmed. *First*, the experimenter presented cards with pictures on them, and participants were instructed to verbally respond “yes” or “no” to whether the image was alive (n=7) or not alive (n=7). If the child responded incorrectly, the experimenter would talk through the image until they responded correctly. *In the next stage*, the experimenter used the same set of images and the same task but instructed children to make their “yes” or “no” response using a button box instead of a verbal response. The experimenter continued to provide feedback as needed. *In the next to last training stage*, twenty images were presented on a computer screen in four blocks of five images each. In the first block, images remained on the screen for 1.5 seconds each and in subsequent blocks they remained on screen for .5 seconds each. This reduced presentation time was meant to encourage participants to respond as quickly as possible, while also maintaining accuracy. Children were instructed to decide whether the image was alive or not alive using a button box and they were trained until they responded correctly to all items. *The final* training protocol introduced children to the cross-modal experimental paradigm in which they simultaneously heard sentences and were told they would see an image during the presentation of the sentence. Their job was to press the correct button as quickly and accurately as possible while listening to the sentence that continued. Participants were trained to 100% response criterion. During this training, experimenters asked comprehension questions to ensure that the children were listening to the sentences. During the first visit, children completed the full training protocol, but during visits two and three, they only completed the final stage to refamiliarize them with the task.

After children completed the final stage of their training, the experimental session began with the six practice filler items followed by presentation of the experimental and remaining filler sentences. As described above, participants were allotted a total of 2500ms to make their

binary decision. The image remained on the screen for a maximum of 1500ms with the image immediately disappearing as soon as the participant made a response during that time. If no response was made by 1500ms, the image disappeared, but a decision choice and reaction time could be captured for an additional 1000ms, resulting in a stimulus onset asynchrony (SOA) of 2500ms. Sentences were separated by 3000ms. In addition to this task, the children were also periodically asked comprehension questions about the sentences that they heard to ensure that they were paying attention (18 per session, 3 attached to filler sentences). Comprehension questions were about nouns heard in the sentence or their location and were not meant to test pronoun-binding relationships. For example, after hearing a sentence like (2a) above, the participant would be asked question (4) below:

(4) Was the sentence you just heard about (A) a horse, (B) an elephant, or (C) a zebra?

Participants indicated their response by either saying their answer out loud or pointing to ‘A’, ‘B’, or ‘C’ on an answer sheet.

2.1.4. Analysis

Prior to analysis, 4 participants (3 from the slow rate of speech group and 1 from the regular rate of speech group) were removed from the initial pool of 18 for not completing all three testing sessions. For the remaining 14 participants, all responses to the experimental items that were less than 250ms (below the threshold of possible response times) or greater than 2500ms (i.e., non-responses; 4% data loss) or were incorrect (wrong button press, 12% data loss) were removed from further analyses. Following this screening, all 14 participants met our threshold of at least 50% of data points remaining. Accuracy on the binary decision task was calculated by taking the number of correct responses out of the total possible responses across all 3 visits (i.e., 90). A two-way mixed-design ANOVA was conducted using AFEX (Singmann H,

2023) in R (R Core Team, 2023) to assess differences in accuracy between rate (regular, slow) and within condition (pronoun, reflexive, control).

A univariate screening of reaction times was conducted to identify outliers for each participant per condition. Children with DLD often demonstrate more variable motor responses than TD children (Sack et al., 2022; Vuolo et al., 2017), which means that identifying outliers at the group level could bias the dataset to underrepresent children who are at the high or low ends of RT responses due to motor abilities. Thus, to control for motor variability in our participant's responses, we mean centered individual response times so that each participant essentially acted as their own control for motor responses. Response times that exceeded 2000ms were excluded from further analysis (1.5% data loss) as they do not represent automatic processing. We then calculated the means, 25th, and 75th Tukey hinges for reaction time (RT) by rate and condition for each participant was calculated using PROC Univariate in SAS 9.4 (SAS Institute Inc, 2014). The Tukey hinges were used to identify the upper and lower bounds of the distribution of RT for each participant by rate and condition. Extreme values for each participant were then winsorized to reduce their effects on mean RT values; outliers above the upper bounds were replaced with the values for the upper bounds and a similar procedure for outliers falling below the lower bounds was conducted. Table 4.3 shows the proportion of trials that were replaced for each participant.

Table 4.3. The proportion of trials replaced for each participant following the winsorizing procedure. Winsorizing is used to reduce the effects of extreme values on mean response time (RT).

Participant	Rate	Proportion of Trials Replaced
001	Regular	0.10
002	Regular	0.04
003	Slow	0.03
004	Regular	0.05
005	Regular	0.04
006	Slow	0.07
007	Regular	0.00
008	Regular	0.02
009	Slow	0.02
010	Slow	0.00
011	Regular	0.01
012	Regular	0.08
013	Slow	0.04
014	Slow	0.04

Mixed linear models with participants and sentence order (counterbalanced across all 3 visits) as random intercepts were used to examine the effects of rate (regular, slow), condition (pronoun, reflexive, control), and the interactions of rate $\times$ condition on reaction times. The model was estimated with SAS 9.4 (SAS Institute Inc, 2014) PROC MIXED. Post-hoc testing using least mean squares was used to examine significant main effects and the interaction for the model.

2.2. Results

Accuracy across all experimental conditions and participants for the binary decision task (alive or not alive) was 87.1%. As shown in Figure 4.4, below, overall accuracy for experimental sentences was well above chance (50%) across all conditions in both the regular ($t(7) = 6.02, p < 0.001$) and slow ($t(5) = 6.41, p = 0.001$) rate of speech conditions. Importantly, accuracy for filler items was 82%, demonstrating that children were actively making binary decisions throughout the study.

Results from a two-way mixed-effects ANOVA revealed no main effects of rate ($F(1,12) = 0.28, p > 0.05$) or condition ($F(2,24) = 0.88, p > 0.05$) on accuracy, nor was the rate $\times$ condition interaction significant ($F(2,24) = 1.79, p > 0.05$), indicating that rate and condition did not significantly impact overall accuracy during this task.

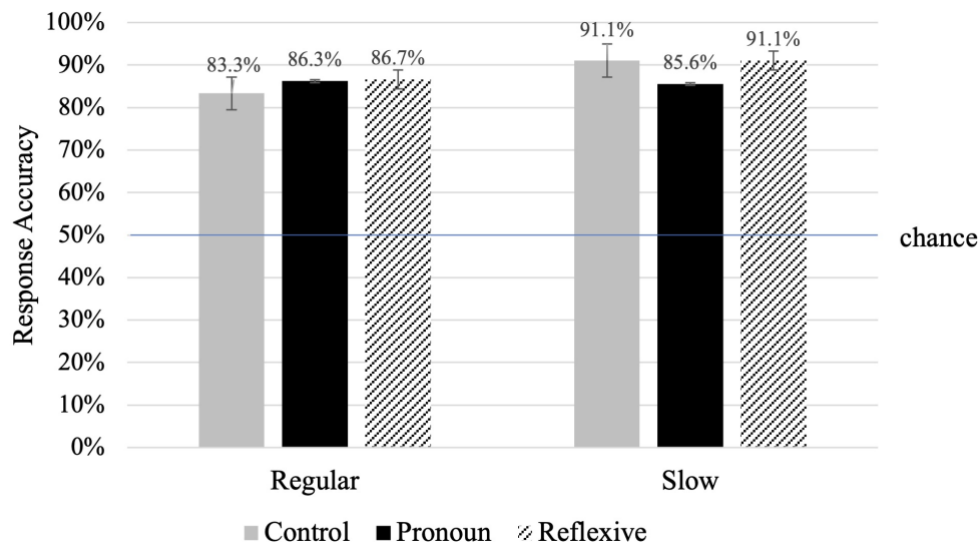


Figure 4.4. Accuracy (error bars are for standard error) for the binary decision task (alive = yes, not alive = no) following the target prime image. No significant differences between rate, condition, or their interaction were found. Chance is marked by the blue line at 50%.

Accuracy was also measured for the three-choice comprehension questions that were scattered throughout the online portion of the task to ensure participants were not simply ignoring the sentences to respond to the visual targets. For the regular rate of speech input, children with DLD answered the comprehension questions with an average accuracy of 60%, while for the slow condition they answered with an average accuracy of 69.1%. Response averages were above-chance (33%) for both the regular ($t(7) = 3.86, p = 0.006$) and slow ($t(5) = 5.93, p = 0.002$) rates of speech, suggesting that the children were attending to the auditory input.

Response times for the experimental data can be seen in Table 4.4. As a reminder, the visual probe in the sentences matched the first main clause noun phrase and appeared at the

offset of either the control noun phrase, the pronoun, or the reflexive in the second clause. Therefore, according to binding principles, the picture was the correct antecedent only for the pronoun condition and should facilitate linking the pronoun to the anaphor as indexed by faster response times.

A mixed linear model with participants and order of sentence presentation (which was counterbalanced across visits) as random intercepts was run to examine the effect of rate (regular, slow), condition (pronoun, reflexive, control), and the interaction of rate $\times$ condition on reaction time (RT). Results revealed a significant main effect of rate ($F(1,36) = 6.09, p = 0.01$), in which children with DLD responded on average about 173ms slower overall in the regular speech rate condition ($\bar{x}_{\text{response time}} = 1044\text{ms}$) compared to the slow speech rate condition ($\bar{x}_{\text{response time}} = 871\text{ms}; t(366) = -2.47, p = 0.014$).

Table 4.4. Mean response times (RT) in milliseconds and standard deviations (SD) for each condition by rate.

	Pronoun RT Mean (SD)	Reflexive RT Mean (SD)	Control RT Mean (SD)
Regular (n=8)	1043 (328.0)	1056 (342.4)	1033 (305.9)
Slow (n=6)	879 (278.8)	849 (260.3)	885 (291.7)

Results also revealed a significant rate $\times$ condition interaction ($F(2,712) = 9.87, p < 0.0001$). To further probe the significant interaction, post-hoc testing using least mean squares indicated that children with DLD were significantly faster to respond at the **regular rate of speech** in the control condition ($\bar{x}_{\text{response time}} = 1033\text{ms}$) compared to (a) the pronoun condition ($\bar{x}_{\text{response time}} = 1043\text{ms}; t(715) = -3.83, p = 0.0001$) and (b) the reflexive condition ($\bar{x}_{\text{response time}} = 1056\text{ms}; t(722) = -3.79, p = 0.0002$), which means there was no evidence of priming; that is, there was no correct priming for the pronoun condition (or incorrect priming for the reflexive

condition) at the normal speech rate. These results suggest that the process of pronoun-anaphor linking does not occur in real-time at the regular rate of speech input for children with DLD, as indexed by increased reaction times to the visual target for both the pronoun and reflexive conditions as compared to the control condition. There is also the additional possibility that the increased reaction times at the regular speech rate for the pronoun and reflexive conditions compared to the control condition could be the result of an interference effect created by the dual task nature of priming paradigms. However, this possibility is unlikely due to the minimal pair triplet design used in this study. As a reminder, each sentence triplet was identical except for the inclusion of an unrelated noun phrase (control), a pronoun, or a reflexive. At the offset of each condition, participants would see the same image and were asked to make a binary decision about whether the image was of something alive or not alive. Each participant contributed data to all conditions for each of the experimental sentences; that is, they heard all three versions of the sentences across three different visits with the order of sentence presentation randomized across each visit, allowing us to isolate pronoun-antecedent linking while controlling for additional effects of the dual task design.

Recall, that our *a priori* hypothesis was that unlike typically developing children, children with DLD would not show evidence of priming in the pronoun condition at the regular rate of speech (i.e., faster response times in the pronoun condition compared to the control condition) but would show evidence of priming in the pronoun condition at the slowed rate of speech. To explore our hypothesis, we examined the difference in reaction times to the pronoun and control conditions during the slow speech rate manipulation as compared to the regular rate condition (Figure 4.5).

Unlike the priming pattern at the regular rate of speech input described above, post-hoc analyses revealed the opposite pattern with the **slow rate of speech** input. Here, children with DLD were significantly faster to respond in the pronoun condition ($\bar{x}_{\text{response time}} = 879\text{ms}$) compared to the control condition ($\bar{x}_{\text{response time}} = 885\text{ms}$; $t(707) = 2.27$, $p = 0.02$) demonstrating evidence of priming.

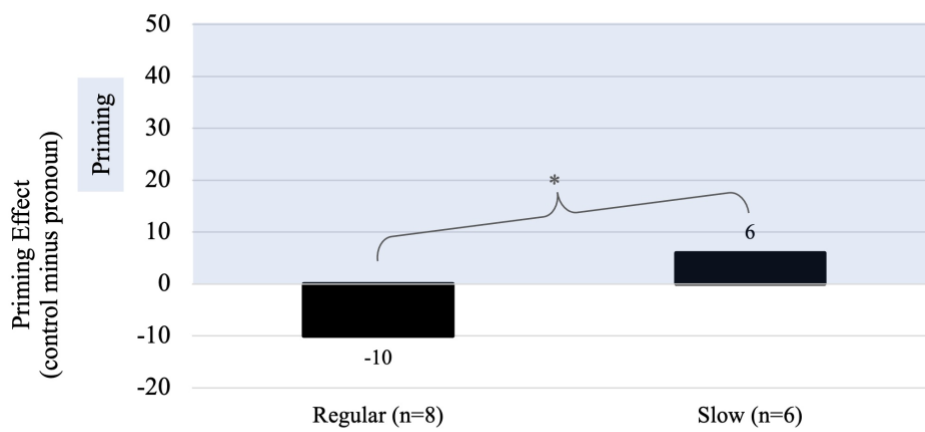


Figure 4.5. The priming effect (control minus pronoun) for the pronoun condition in both the regular and slow rate speech conditions. A positive difference indicates that the mean RT was faster in the pronoun condition, reflecting priming (noted by the highlighted region). *The change in RT from the regular to slow rate was significant at $p < 0.05$.

While not the direct focus of this investigation, we also explored whether children with DLD would show a rate effect while processing sentences containing reflexives, which did not reveal incorrect priming at the regular rate of speech input. At the slow rate of speech input, while we did not find statistically significant priming, the reaction time patterns indicated a reversal from the patterns found at the regular rate (see above; slow rate: reflexive $\bar{x}_{\text{response time}} = 849\text{ms}$; control $\bar{x}_{\text{response time}} = 885\text{ms}$; $t(701) = 0.99$, $p = 0.32$). As described in the discussion section, these patterns of results are consistent with those found with neurotypical children when processing sentences containing reflexives. Specifically, those prior studies showed compliance

with Principle A (no incorrect linking) at the regular rate of speech input and disrupted processing at the slowed rate of speech input.

Overall, results regarding pronoun-antecedent linking from experiment (1) showed no evidence of priming at the regular speech rate, but when the speech rate was slowed, children with DLD showed evidence of priming, suggesting that the linguistic knowledge needed to link pronouns to anaphors (Principle B) during online sentence processing is intact, but there is a delay in the speed at which this link is built.

2.3. Discussion: Experiment 1

Experiment (1) tested online response time patterns for linking pronouns and reflexives with the structurally licensed antecedent for the pronoun (the main clause noun phrase, NP1), across two different speech input rate conditions in children with DLD. Here, we were interested in whether children with DLD would show evidence of priming (indexed by quicker response times to pronouns than controls) when presented with a picture that correctly linked a pronoun with its antecedent; and if rate of speech input modulated this effect. As demonstrated in Love et al. (2009) using the same paradigm and materials, TD children showed evidence of pronoun priming (and thus, knowledge of Principle B) during online sentence processing at a regular rate of speech (Love et al., 2009). However, when speech was slowed, the priming effect went away, indicating that the speech rate impacted the real-time, automatic process of co-referential linking. For this study, we predicted the opposite; that at a regular rate of speech, children with DLD would not demonstrate priming effects, but when the speech rate was slowed, their response times would decrease indicating correct linking, as the slowed rate of input would allow for additional processing time to make the link between the pronoun and its antecedent.

Consistent with our predictions, we found that at a regular rate of speech, unlike patterns found with TD children, children with DLD did not show priming effects, suggesting that they

are unable to automatically link pronouns to their antecedents in real-time. However, when the speech input was slowed, children with DLD showed statistically faster response times in the pronoun condition compared to the control condition, indicating priming. This pattern differs from the results found for TD children in Love et al. (2009), who showed a breakdown in automatic linking with slow speech (Love et al., 2009). In fact, when looking at response times for the regular speech rate compared to the slow speech rate overall, results showed that in general, children with DLD were faster to respond in the slow rate condition than the regular rate condition. Though the important comparison of interest for this study is response times between the pronoun and control conditions within each rate of speech condition, the overall pattern further illustrates how slowed speech may facilitate real-time sentence processing in this group. Taken together, results suggest that children with DLD do in fact have knowledge of binding principles (since slowing down the sentence facilitated priming) and instead exhibit a language processing deficit in the speed at which they build these syntactic relationships.

We note here that children with DLD showed a similar pattern to TD children for processing of reflexive anaphors at the regular rate of speech; that is, they did not show evidence of incorrect priming upon encountering the reflexive anaphor. However, they differed in their priming patterns at the slow rate of speech. In Love et al. (2009), the authors found a marginally significant effect for priming of reflexives compared to control sentences and a significant effect when compared to pronouns, as TD children were quicker overall in responding in the reflexive condition (Love et al., 2009). The authors suggested that for TD children, the slow rate of speech caused breakdowns in the real-time linking that they demonstrated in the regular speech rate. However, for this study, the slow rate of speech facilitated children with DLD in making the *correct* pronoun-antecedent link while also causing them to incorrectly link the reflexive and the

antecedent for the pronoun, indicating that slowed speech input aids performance for linguistic processes that are not yet acquired and impairs those that are already established. This dissociation in the benefit of slow speech suggests that children with DLD have knowledge of binding principles but follow a different developmental trajectory than TD children. It may be the case that children with DLD need more time to implement certain language processes than typically developing children, which implies that younger children with DLD might benefit more from slowed speech than older children with DLD. Though the effect of age on anaphor-antecedent linking goes beyond the scope of this paper, an exploratory analysis of age effects can be found in Appendix A in consideration of this possibility.

Thus far, the CMPP results indicate difficulties for children with DLD in automatic processing of sentences containing pronominal anaphors. This approach, however, cannot indicate if the slow rate of speech ultimately helps children with DLD with final comprehension of these sentence constructions. We now turn to Experiment (2) which explores overt, offline comprehension of sentences containing pronouns.

3. Experiment 2: Offline Processing via Sentence-Picture-Matching

Experiment (2) used a sentence-picture-matching task to investigate offline processing of coreferential binding in children with DLD at both regular and slow rates of speech input. As previously discussed, prior research from Love et al. (2009) found that offline, TD children demonstrated at-chance comprehension accuracy at the regular speech rate for the pronoun condition, but showed significant improvement when the rate of speech was slowed. Given that children with DLD did not show evidence of intact pronoun-antecedent linking at regular rates of speech, we hypothesize that they will perform at-chance offline at regular rates of speech (with small gains with the slow rate of speech input). This hypothesis is based on the findings from

Love et al. (2009) that conscious, final comprehension abilities are generally acquired after real-time pronoun linking abilities are acquired (Love et al., 2009). In Experiment (1), children with DLD only showed evidence of priming in the pronoun condition once the rate of speech was slowed, indicating that they were unable to make co-referential links at regular rates of speech input during online, real-time sentence processing, which suggests they have not fully acquired the skill.

3.1. Materials and methods

3.1.1. Participants

The same group of participants tested in the online condition from Experiment (1) returned for 1 visit and were tested in this offline condition. They remained in the same regular (n=8) and slow (n=6) rate groups for Experiment (2) (see Table 4.2).

3.1.2. Study design and stimuli

The design, materials, and procedure are the same as those used in Love et al. (2009) and are described in more detail therein (Love et al., 2009). For the sake of brevity, we discuss the most relevant aspects here. Fifteen sentences from the online experiment were selected for this offline experiment, based upon their high degree of imageability. Sentences were modified from Experiment (1) to only contain one noun phrase so that it limited participants' ability to utilize pictorial context to interpret the referential links in the sentence. For each sentence, there were two versions, one with a pronoun and one with a reflexive, for a total of 30 items. Two images were created for each sentence; one correctly depicting a pronoun link and one correctly depicting a reflexive link (see Figure 4.6).

Experimental sentences were presented in a single session with the two versions presented at maximal distance. Sentences were recorded by a female native English speaker. In

the regular rate of speech input condition, sentences were delivered at an average rate of 5.00 syllables per second. In the slow rate of speech condition, sentences were slowed to an average of 3.19 syllables per second (maintaining pitch, using the Cool Edit Pro v1.2 software package; Syntrillium Software, Phoenix, AZ). Each sentence was paired with the two pictures on an 8.5 x 11-inch picture card, the position of the pictures was counterbalanced across items. Each picture corresponded with either the pronoun or reflexive interpretation of the sentence.

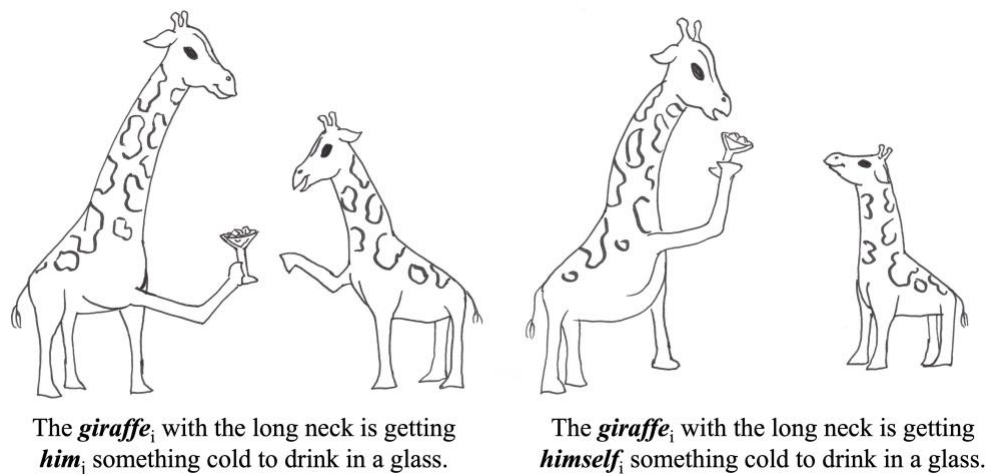


Figure 4.6. An example sentence and corresponding pictures for the sentence/picture matching task.

3.1.3. Procedure

Participants were instructed to listen carefully to the sentences they would hear and to select the picture that matched the sentence by pointing to it. During testing, sentences were presented to the participant via recorded audio files with the experimenter turning the picture cards before each recorded sentence was played. Children were familiarized with the task with a practice session consisting of four practice sentences before beginning the actual experiment.

3.1.4. Analysis

Data were analyzed using a mixed-effects logistic regression model for binary accuracy data (correct or incorrect) with rate (regular, slow) and condition (pronoun, reflexive) as fixed

effects and participant and sentence order as random effects. The model was estimated with SAS 9.4 (SAS Institute Inc, 2014) PROC MIXED. Post-hoc testing using least mean squares was used to examine significant main effects and the interaction for the model. F -statistics are reported for main effects and interactions and t -statistics are reported for follow-up comparisons.

3.2. Results

For the **comprehension accuracy data** (Figure 4.7), a mixed-effects logistic regression model indicated that children with DLD did not demonstrate an overall *rate effect* between the regular ($\bar{x}_{\text{accuracy}} = 61\%$) and slow ($\bar{x}_{\text{accuracy}} = 64\%$) rates of speech ($F(1,416) = 0.60, p = 0.44$). However, consistent with prior research, the results revealed a significant main effect of *condition* ($F(1,416) = 23.39, p < 0.0001$), indicating that across rates of speech, children with DLD were more accurate overall with sentences containing reflexives ($\bar{x}_{\text{accuracy}} = 73\%$) than sentences containing pronouns ($\bar{x}_{\text{accuracy}} = 52\%$); in fact, according to a one-sample t -test, performance in the pronoun condition was no different from chance (50%; $t(13) = 0.23, p = 0.82$). Importantly, further analysis revealed a significant *rate* $\times$ *condition* interaction ($F(1,416) = 5.42, p = 0.02$). This significant interaction arises from a large improvement in accuracy in the slow condition between pronoun ($\bar{x}_{\text{accuracy}} = 48\%$) and reflexive ($\bar{x}_{\text{accuracy}} = 81\%$) sentences ($t(416) = -4.74, p < 0.0001$); we note here that again, according to one-sample t -tests, performance for the pronoun condition was no different from chance for the regular ($t(7) = 0.52, p = 0.62$) or slow ($t(5) = -0.16, p = 0.88$) rate conditions. Overall, the slowed speech input helped improve comprehension accuracy for reflexives between the regular ($\bar{x}_{\text{accuracy}} = 67\%$) and slow ($\bar{x}_{\text{accuracy}} = 81\%$) conditions ($t(416) = -2.20, p = 0.03$).

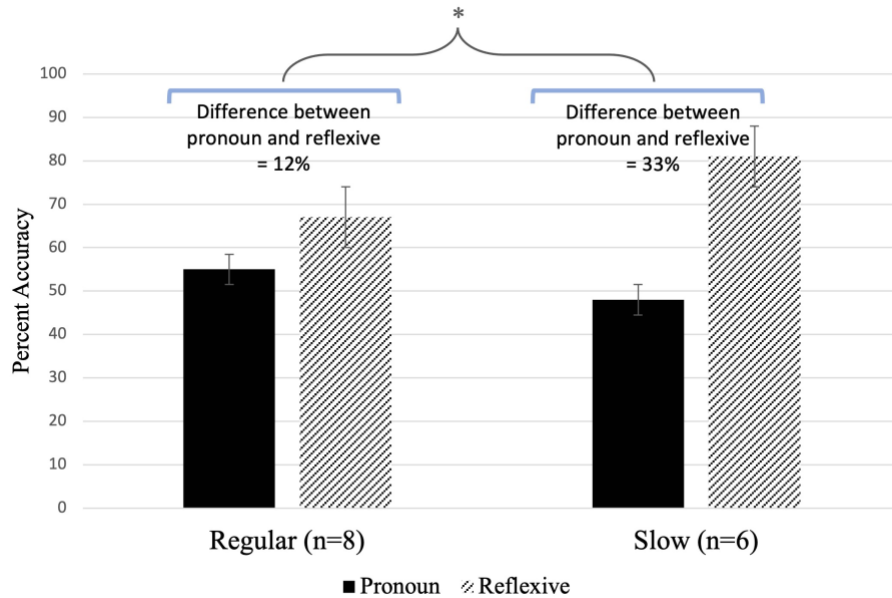


Figure 4.7. Percent accuracy (error bars are for standard error) for each rate condition. *indicates the significant rate x condition interaction effect for the difference in accuracy between the pronoun and reflexive conditions (blue brackets) when comparing the regular speech rate to the slow speech rate ($p = 0.02$).

Of interest to this study was the difference in accuracy in sentences containing pronouns between the regular and slow rate speech conditions. While children with DLD performed better in understanding sentences containing pronouns in the regular rate condition ($\bar{x}_{\text{accuracy}} = 55\%$) as compared to the slow rate condition ($\bar{x}_{\text{accuracy}} = 48\%$), the difference was not significant ($t(416) = 1.10, p = 0.27$). We remind the reader that accuracy was not significantly different from chance (50%) for either condition. This pattern is partially consistent with our predictions, as we anticipated that children with DLD would demonstrate difficulty with the offline task regardless of speech rate. However, we also predicted that they would demonstrate a slight improvement in pronoun processing with the slowed speech rate. Instead, we found a (non-significant) decline in pronoun accuracy at the slow rate. Results indicate that slowing down the rate of speech did not help with conscious access of the linguistic knowledge required for successful pronoun-

antecedent interpretation, despite evidence of real-time knowledge (i.e., priming with slow speech in Experiment 1) of binding principles.

3.3. Discussion: Experiment 2

For the offline experiment, we used a sentence-picture-matching task to investigate final comprehension of sentences with either pronouns or reflexives. Here, we predicted that children with DLD would show impaired (at-chance) performance for identifying the correct picture in the pronoun condition, regardless of speech rate, but would see modest gains in accuracy at a slowed rate of speech. Partially consistent with this prediction, we found that for the pronoun condition, children performed at-chance at both regular and slow rates of speech but did not show any significant gains in accuracy for the slow rate.

This pattern differs from the results found for TD children in Love et al. (2009). In their study, TD children demonstrated at-chance performance for the interpretation of pronouns at a regular rate of speech but improved when speech was slowed, suggesting that the slower speech rate facilitated final comprehension of sentences containing pronouns. The authors concluded that slowed speech may help with final comprehension of sentences containing pronouns only when the metalinguistic processes necessary to link pronouns and antecedents have not yet been fully mastered, suggesting that slow speech may be more beneficial to younger children whose language skills are still developing (see Appendix B for an exploratory analysis examining age effects in our participant group).

The focus of this paper was on pronoun-antecedent linking, but it is important to note differences for reflexive-antecedent processing since it can provide insight into whether children with DLD have knowledge of different binding principles. In the offline reflexive condition, while children performed above chance, they were more accurate for the slow rate of speech

compared to the regular rate of speech. The lack of ceiling effects in the data indicate that children with DLD have not yet fully mastered this ability, so when provided with more time, they perform better. Here the results suggest that children with DLD have intact knowledge of binding (Principle A) but may need more time to reflect on and make the link between the reflexive and antecedent.

4. Conclusion

In sum, our results demonstrate that children with DLD show evidence of priming (i.e., are faster) for online, real-time pronoun-antecedent linking when speech input is slowed but do not show evidence of priming (i.e., are slower) when sentences are presented at a regular rate of speech. This pattern of performance is the opposite of what was observed previously in TD children (Love et al., 2009). This suggests that children with DLD may have a delay in processing these co-referential relationships for pronouns that can be mitigated by slowing down the incoming auditory speech stream. However, when the same group of children were tested on these pronoun-antecedent relationships offline, they showed impaired (at-chance) interpretation of pronouns regardless of speech rate. This result is also different from that of TD children (Love et al., 2009), who showed improved accuracy in their final comprehension with a slowed rate of speech. Developmentally, the ability to link pronouns to their antecedents online is acquired before the ability to link them offline (Love et al., 2009; McKee et al., 1993; Schwartz et al., 2016). This likely has to do with the subconscious versus conscious properties involved in online processing versus offline final comprehension. Online processing measures the moment-by-moment mapping of words with their relationship to other words in the sentence, whereas offline processing measures final comprehension after all different levels of processing are complete. Thus, offline measures of accuracy encompass both sentence processing and sentence

comprehension. For children with DLD, slowing down speech may help with real-time mapping of pronoun-antecedent relationships, but it may not be enough to mitigate the additional demands of offline processing in terms of integrating all of the linguistic information, holding that information in memory, and making a final decision about the sentence meaning. In typically developing children, prior research has demonstrated a maturational effect of online vs offline pronoun-antecedent linking, such that online abilities are acquired before offline abilities, possibly due to the additional cognitive demands imposed by offline tasks (Love et al., 2009). Future studies with larger sample sizes of children with DLD across age ranges should be conducted to explore whether priming effects emerge at a later stage of development. Taken together, these results provide evidence that children with DLD do develop underlying knowledge of binding principles, which suggests that deficits in sentence processing may not be specifically linked to linguistic knowledge but instead are the result of other cognitive processes that impact language, such as delayed processing speed. The sentence triplet design used in our study allowed us to isolate pronominal binding while controlling for other factors such as sentence length and memory, which suggests that processing speed delays may more strongly impact language operations, though more work is needed to disentangle domain general processing from language-specific processing.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Contributions

NA: Formal Analysis, Writing – original draft, review & editing, Visualization; IN: Formal Analysis, Writing – original draft; TL: Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Supervision, Writing – review & editing.

Funding

This work was supported by NIH R01 DC03885 (T.L.) and T32-DC007361 (N.A., PI: T.L.).

Acknowledgments

We thank Dr. Matthew Walenski, Dr. Richard Schwartz, DeAnne Hunter, Dr. Niloofar Akhavan, Dr. Carolyn Baker, Brianne Bricker, Danielle Vignati, Maxwell Moholy, Carla Nerelli, Beth Hill, Nina Usuki, and Allyson Fisher for their contributions to various aspects of this project. We also thank all of our participants and their families.

Data Availability Statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Appendix A: Post-hoc Exploration of Age Effects on Online Processing (Experiment 1)

Like Love et al. (2009), this study includes children over a wide range of ages which means there may be differences across age in how children with DLD process sentences containing pronouns. Love et al. (2009) found that overall, older children were faster than younger children to respond during the decision task, but children as young as 5 years of age showed evidence of correct pronoun priming at the regular rate of speech input. Although our hypotheses did not include predictions about age-related differences, we acknowledge that for this study the youngest children may benefit more from the slow rate of speech condition, with that benefit diminishing as they get older. Such a relationship would indicate a delay in real-time knowledge of pronominal dependency relationships. To test this possibility, we re-ran our mixed effects model to include age (in years) as a continuous variable, along with the interactions between age $\times$ rate, age $\times$ condition, and age $\times$ rate $\times$ condition (again, acknowledging that the participants were not selected to ensure an equal number of ages across the range tested).

Results revealed a significant main effect of **age** ($F(1,332) = 10.76, p = 0.001$) in which older children were on average around 64ms slower to respond (across rate and condition) than younger children during the binary decision task ($t(1052) = 2.49, p = 0.013$). This pattern of age effects is reversed when compared to the results from Love et al. (2009), however, the reaction time differences are likely due to the significant age $\times$ condition interaction ($F(2,672) = 14.2, p < 0.0001$), and the significant age $\times$ rate $\times$ condition interaction ($F(2,672) = 8.40, p = 0.0002$). To further probe the interaction effects, we first examined the age $\times$ condition interaction. Here, an interesting pattern emerged. Starting around 9 years of age, there was an increase in mean RT in the reflexive condition ($t(1056) = 8.41, p < 0.0001$) which likely accounts for the overall slower response times for the older children. This pattern reverses for sentences containing pronouns;

that is there was a decrease in mean RT for children over 9 years of age ($t(1060) = 4.69, p < 0.001$). Interestingly, there were no significant effects of age on condition for children younger than 9 years. These results suggest that around 9 years children with DLD begin to demonstrate real-time knowledge of correct pronoun-antecedent linking as indexed by quicker response times to the pronoun condition, but as they demonstrate greater mastery of binding rules, they begin to experience processing delays when they encounter an incorrect antecedent-reflexive structure during real-time referential linking. The results for older children with DLD in this study are what we would expect for typically developing children (as young as 5 years of age), which shows that children with DLD do in fact have knowledge of binding rules during real-time sentence processing, but mastery of this knowledge is delayed and may be more variable when compared to typically developing children.

Next to probe the effect of **age** and the two **rates condition** on RT measures within each condition, we examined the three-way interaction between age $\times$ rate $\times$ condition that is detailed above. Again, an interesting pattern emerged here. Children younger than 9 years of age were significantly slower to respond during the binary decision task in the pronoun condition compared to the control condition at the regular rate of speech ($t(696) = -3.63, p = 0.0003$), but when the rate of speech was slowed, this pattern was flipped; that is, children younger than 9 years of age were significantly faster to respond in the pronoun condition compared to the control condition ($t(700) = 2.83, p < 0.005$). Finally, turning to the reflexive condition, a similar pattern of results was found. Children under 9 years of age, were faster to respond to sentences in the control condition than sentences in the reflexive condition for the regular speech rate ($t(702) = -3.99, p < 0.0001$), but when sentences were slowed, the pattern reversed (faster for sentences containing reflexives than control sentences; $t(697) = 2.43, p = 0.02$), indicating *incorrect*

priming of the antecedent. This pattern of results suggests that at the regular speech rate, children are unable to make the correct link between the pronoun and the antecedent but are able to recognize that the reflexive is not the correct anaphor. When speech is slowed, it aids in pronoun-antecedent linking but disrupts the ability to correctly process sentences containing reflexives.

To summarize, in our exploratory analysis, we examined whether differences would emerge across age in how children with DLD process referential relationships during real-time sentence processing, and how rate of speech impacted the process. We found a delineation by age in the ability to make syntactically dependent links between constituents. In our study, when sentences were presented at a regular speech rate, the younger children (under 9 years) were unable to make the necessary referential links between pronouns and antecedents (i.e., they failed to prime the structurally licensed antecedent), but were able to recognize that the reflexive anaphor was the incorrect link (i.e., they did not prime the incorrect antecedent). *This pattern changed when the speech rate was slowed*; the younger children demonstrated evidence of correct referential linking (e.g., priming) when sentences contained pronouns and incorrect referential linking when sentences contained reflexives (e.g., priming the incorrect antecedent) indicating that slowed speech improved pronoun-antecedent processing but impaired reflexive processing. These results suggest that young children with DLD may still be developing the real-time language processing skills necessary for pronoun-antecedent linking (as outlined by Binding Principle B), but have mastered the linguistic skills for real-time reflexive-antecedent linking (as outlined by Binding Principle A). After 9 years of age, results were more variable, but seem to suggest that rather than improving the ability to link pronouns to antecedents, slow

speech disrupts the process, which may indicate that around this age, children with DLD begin to develop automatic structural processing skills.

Taken together, these results provide preliminary evidence of a delay in the application of binding rules during real-time sentence processing until around 9 years of age, at which point they begin to demonstrate knowledge, but not yet mastery of pronoun-antecedent linking. Given the small sample size in this study and that we did not originally set out to test the effect of age on our findings, future studies should be conducted with larger sample sizes across a range of ages to determine the point at which children with DLD fully master this knowledge.

Appendix B: Post-hoc Exploration of Age Effects on Offline Processing (Experiment 2)

The maturational findings from the online portion of this study, along with the findings from Love et al., (2009) bring up the possibility that children with DLD may be delayed in their ability to correctly link pronouns and antecedents when compared to TD children. If offline final comprehension of sentences containing anaphors take longer to fully master than online, real-time processes (as demonstrated in Love et al., 2009), then it is a reasonable assumption that the developmental trajectory for children with DLD may be further delayed. Though we did not set out to specifically test for maturational changes in the interpretation of sentences containing pronouns, we ran an exploratory correlation analysis to test for a relationship between age and accuracy for each sentence condition at each rate of speech.

For the **pronoun** condition, results revealed a moderate correlation between age and accuracy at the regular rate of speech ($r = 0.27, p = 0.003$) suggesting that accuracy increased with age. When looking at accuracy for the pronoun sentences for each participant, results were somewhat variable, with some children doing better in the pronoun condition and other children doing better in the reflexive condition regardless of age, but nonetheless an interesting picture emerged. The children over 10 years of age had some of the highest accuracy scores for the interpretation of sentences containing pronouns, whereas the children under 10 were more variable suggesting that children with DLD may follow a delayed developmental trajectory for offline pronoun-antecedent linking when compared to TD children who seem to acquire these abilities around 8 years of age (Love et al., 2009). The correlations between age and accuracy for the other conditions did not reach significance. As noted previously, the ages of our participants were not carefully selected to test hypotheses about maturational differences, therefore, future

studies investigating pronoun processing in children with DLD should include carefully selected age ranges across larger sample sizes.

5. References

- Abbott, N., & Love, T. (2023). Bridging the Divide: Brain and Behavior in Developmental Language Disorder. *Brain Sciences*, 13(11), 1606. <https://doi.org/10.3390/brainsci13111606>
- Baaauw, S., & Cuetos, F. (2003). The interpretation of pronouns in Spanish language acquisition and breakdown: Evidence for the " Principle B Delay" as a non-unitary phenomenon. *Language Acquisition*, 11(4), 219-275. https://doi.org/10.1207/s15327817la1104_2
- Baker, C., & Love, T. (2023). The effect of time on lexical and syntactic processing in aphasia. *Journal of Neurolinguistics*, 67, 101142. <https://doi.org/10.1016/j.jneuroling.2023.101142>
- Borovsky, A., Burns, E., Elman, J. L., & Evans, J. L. (2013). Lexical activation during sentence comprehension in adolescents with history of specific language impairment. *Journal of Communication Disorders*, 46(5-6), 413-427. <https://doi.org/10.1016/j.jcomdis.2013.09.001>
- Brown, L., Sherbenou, R., & Johnsen, S. (1997). Test of Nonverbal Intelligence—Third Edition
- Callahan, S. M., Walenski, M., & Love, T. (2012). The processing and interpretation of verb phrase ellipsis constructions by children at normal and slowed speech rates. [https://doi.org/10.1044/1092-4388\(2011/10-0281\)](https://doi.org/10.1044/1092-4388(2011/10-0281))
- Chien, Y.-C., & Wexler, K. (1990). Children's knowledge of locality conditions in binding as evidence for the modularity of syntax and pragmatics. *Language Acquisition*, 1(3), 225-295. https://doi.org/10.1207/s15327817la0103_2
- Chomsky, N. (1982). *Some concepts and consequences of the theory of government and binding*. MIT press.
- Franks, S. L., & Connell, P. J. (1996). Knowledge of binding in normal and SLI children. *Journal of Child Language*, 23(2), 431-464. <https://doi.org/10.1017/S0305000900008874>
- Girbau, D. (2017). On-line processing and comprehension of direct object pronoun sentences in Spanish-speaking children with Specific Language Impairment. *Clinical Linguistics & Phonetics*, 31(3), 193-211. <https://doi.org/10.1080/02699206.2016.1224273>
- Love, T. (2007). The processing of non-canonically ordered constituents in long distance dependencies by pre-school children: A real-time investigation. *Journal of Psycholinguistic Research*, 36, 191-206. <https://doi.org/10.1007/s10936-006-9040-9>

- Love, T., Swinney, D., Walenski, M., & Zurif, E. (2008). How left inferior frontal cortex participates in syntactic processing: Evidence from aphasia. *Brain and Language*, 107(3), 203-219. <https://doi.org/10.1016/j.bandl.2007.11.004>
- Love, T., Walenski, M., & Swinney, D. (2009). Slowed speech input has a differential impact on on-line and off-line processing in children's comprehension of pronouns. *Journal of Psycholinguistic Research*, 38(3), 285-304. <https://doi.org/10.1007/s10936-009-9103-9>
- McKee, C., Nicol, J., & McDaniel, D. (1993). Children's application of binding during sentence processing. *Language and Cognitive Processes*, 8(3), 265-290. <https://doi.org/10.1080/01690969308406956>
- Montgomery, J. W. (2000). Relation of working memory to off-line and real-time sentence processing in children with specific language impairment. *Applied Psycholinguistics*, 21(1), 117-148. <https://doi.org/10.1017/S0142716400001065>
- Norbury, C. F., Gooch, D., Wray, C., Baird, G., Charman, T., Simonoff, E., Vamvakas, G., & Pickles, A. (2016). The impact of nonverbal ability on prevalence and clinical presentation of language disorder: Evidence from a population study. *Journal of Child Psychology and Psychiatry*, 57(11), 1247-1257. <https://doi.org/10.1111/jcpp.12573>
- Pashek, G. V., & Brookshire, R. H. (1982). Effects of rate of speech and linguistic stress on auditory paragraph comprehension of aphasic individuals. *Journal of speech, language, and hearing research*, 25(3), 377-383. <https://doi.org/10.1044/jshr.2503.377>
- Poeck, K., & Pietron, H.-P. (1981). The influence of stretched speech presentation on token test performance of aphasic and right brain damaged patients. *Neuropsychologia*, 19(1), 133-136. [https://doi.org/10.1016/0028-3932\(81\)90052-X](https://doi.org/10.1016/0028-3932(81)90052-X)
- R Core Team. (2023). *R: A Language and Environment for Statistical Computing*. In R Foundation for Statistical Computing. <https://www.R-project.org/>
- Sack, L., Dollaghan, C., & Goffman, L. (2022). Contributions of early motor deficits in predicting language outcomes among preschoolers with developmental language disorder. *International Journal of Speech-Language Pathology*, 24(4), 362-374. <https://doi.org/10.1080/17549507.2021.1998629>
- SAS Institute Inc. (2014). *SAS (Version 9.4)*. In SAS Institute, Inc. Cary, NC, USA.
- Sato, S., & Vanek, N. (2023). Contrasting online and offline measures: Examples from experimental research on linguistic relativity. In *The Routledge handbook of experimental linguistics* (pp. 217-234). Routledge.
- Schelleter, C., & Leinonen, E. (2003). Normal and language-impaired children's use of reference: syntactic vs pragmatic processing. *Clinical linguistics and phonetics*. <https://doi.org/10.1080/0269920031000080000>

- Schwartz, R. G. (2017). *Handbook of Child Language Disorders* (2nd ed.). Psychology Press. <https://doi.org/10.4324/9781315283531>
- Schwartz, R. G., Hestvik, A., Seiger-Gardner, L., & Almodovar, D. (2016). Processing binding relations in specific language impairment. *Journal of speech, language, and hearing research*, 59(6), 1384-1394. https://doi.org/10.1044/2016_JSLHR-L-15-0107
- Semel, E., Wiig, E., & Secord, W. (2003). Clinical evaluation of language fundamentals (CELF-4). the psychological corporation. *San Antonio, TX*.
- Singmann H, Bolker B., Westfall J., Aust F., and Ben-Shachar M. (2023). *afex: Analysis of Factorial Experiments*. In (Version R package version 1.3-0) <<https://CRAN.R-project.org/package=afex>>
- Swinney, D., & Prather, P. (1989). On the comprehension of lexical ambiguity by young children: Investigations into the development of mental modularity. In *Resolving semantic ambiguity* (pp. 225-238). Springer.
- Tomblin, J. B., Records, N. L., Buckwalter, P., Zhang, X., Smith, E., & O'Brien, M. (1997). Prevalence of Specific Language Impairment in Kindergarten Children. *Journal of speech, language, and hearing research*, 40(6), 1245-1260. <https://doi.org/10.1044/jslhr.4006.1245>
- Van Der Lely, H. K. J., & Stollwerck, L. (1997). Binding theory and grammatical specific language impairment in children. *Cognition*, 62(3), 245-290. [https://doi.org/10.1016/s0010-0277\(96\)00783-4](https://doi.org/10.1016/s0010-0277(96)00783-4)
- Vuolo, J., Goffman, L., & Zelaznik, H. N. (2017). Deficits in coordinative bimanual timing precision in children with specific language impairment. *Journal of speech, language, and hearing research*, 60(2), 393-405.
- Zablotsky, B., Black, L. I., Maenner, M. J., Schieve, L. A., Danielson, M. L., Bitsko, R. H., Blumberg, S. J., Kogan, M. D., & Boyle, C. A. (2019). Prevalence and trends of developmental disabilities among children in the United States: 2009–2017. *Pediatrics*, 144(4). <https://doi.org/10.1542/peds.2019-0811>

Acknowledgements

Chapter 4, in full, is a reprint of material that is currently under revised review for publication as it may appear in *Frontiers in Language Sciences*, Abbott, N., Nip, I. and Love, T. (2024). Rate of Speech Affects the Comprehension of Pronouns in Children with Developmental Language Disorder The dissertation author was the primary researcher and author of this paper.

Chapter 5

GENERAL DISCUSSION AND CONCLUSION

This dissertation examined the neurobiological underpinnings of language processing by investigating how alterations in brain structure and function affect language behavior. **Chapter 1** looked at cerebral blood flow (CBF) patterns in people with post-stroke aphasia (PWA). PWA have overt, structural brain damage to regions of the brain associated with language. In adults with aphasia, the language system and associated neural networks are already developed. Thus, changes in language abilities likely reflect compromised neural tissue and neural function, which provides a unique window into the neural underpinnings of language processing. In **Chapter 1**, we emphasized the importance of characterizing baseline cerebral blood flow (CBF) values in PWA. By taking an individualized approach to exploring CBF patterns throughout the whole brain, we found regions of aberrant brain function (e.g., reduced CBF) that weren't otherwise accounted for by the lesion.

There is a tight coupling between CBF and neural activity, as discussed in **Chapters 1-3**. When neurons fire, there is an increase in CBF to the region to supply the neurons with the necessary fuel to perform the action. If neurons are not receiving adequate blood flow, then this can impact their function. In **Chapter 2** and **Chapter 3** of this dissertation, we explored the possibility of altered blood flow dynamics in children with DLD. Unlike PWA, children with DLD do not have overt damage to the brain, yet language abilities are significantly impacted. In **Chapter 2**, we discussed a number of key brain regions that have been implicated in DLD both structurally and functionally. These included regions such as the inferior frontal gyrus, superior temporal gyrus, and striatum (comprised of the caudate and putamen). We then argued for exploring underlying factors that support brain function, namely CBF and functional connectivity (FC) patterns, to better inform future investigations of brain and behavior in DLD.

In **Chapter 2**, we examined these measures (CBF and FC), in two children with DLD compared to a larger typically developing (TD) group. We found contrasting patterns of CBF in each child with DLD (significantly decreased CBF compared to slightly elevated CBF). Interestingly, when CBF was compared to FC patterns, each child with DLD showed an inverse relationship (e.g., decreased CBF and increased FC v. increased CBF and decreased FC). In the TD children we found that these measures were positively correlated with one another, indicating that an inverse relationship may be a potential biomarker of DLD. Though more work is needed to better understand these results, they are especially compelling as they align well with reports from other neurologically impaired populations of inverse relationships between the measures. In particular, more work is needed to understand how they relate to language impairment. In this chapter, we utilized a standardized measure of language, the CELF-CLS, which may not be sensitive to the subtle nuances of language, such as the speed at which language must be processed. Thus, in **Chapter 4**, we explored real-time, online syntactic dependency linking as well as offline syntactic linking at two different rates of speech, regular and slow.

Results from the online portion of the study indicated that when presented with sentences at a regular speech rate, children with DLD were unable to make the necessary link between a pronoun and its syntactically licensed antecedent (a previously referred to noun phrase in this case). However, when the speech rate was slowed, they were able to make the appropriate link. In the offline portion of the study, the children struggled to make the link, regardless of speech rate. The pattern of results suggests that children with DLD do in fact have knowledge of linguistic principles (i.e., syntactic binding principles) during real-time sentence processing, but need more time to make the links. Taken together with the other results from this dissertation, it may be the case that reduced CBF or inefficient neural networks impact processing speed in

children with DLD. This underscores the importance of investigating the underlying properties that support brain function in impaired-language populations in conjunction with both standardized and more carefully constrained experimental measures of language abilities. In doing so, we can continue to elucidate the neural underpinnings of language and eventually identify biomarkers of language impairment across the lifespan.