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Structural Neural Connectivity Correlates of Early Language and Reading Development and Prenatal Alcohol Exposure

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Structural Neural Connectivity Correlates of Early Language and Reading Development and Prenatal Alcohol Exposure

by

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Abstract

Reading and language difficulties are common in children and can have long-lasting effects. Studying the brain's structural connectivity from an early age can provide insight into the roots of reading and language development and may help with early identification and interventions. Prior studies examining the structural neural correlates of language and pre-reading/reading abilities have mainly focused on older, typically developing children. Unfortunately, little research has been done on preschool children, despite this being a critical learning period. Additionally, the effects of adverse early environments such as prenatal alcohol exposure (PAE) on these associations remain unclear. This thesis aimed to gain a better understanding of the associations between brain structural networks and early language and reading abilities in young children, and the impact of PAE on these associations.

Brain imaging data were previously collected using diffusion weighted imaging (DWI) in two cohorts of children from Canada and South Africa. Children completed skills assessments. DWI images were processed, and structural connectivity was assessed using graph theory. The associations between early language and structural connectivity, and the effect of PAE on these associations were analyzed. We found that 1) phonological processing skills were associated with connectivity in a network consisting of reading and language regions in preschool aged children, 2) PAE negatively moderated the relationship between pre-reading skills and network measures in preschool aged children, and 3) PAE-related alterations to language abilities and brain-language associations are present during the toddler years.

Our findings expand the current literature, supporting the idea that the structural brain correlates of reading and language are present early, and showing that PAE moderates them. These moderation effects imply that reading and language deficits in children with PAE begin early,

suggesting that the roots of reading and language (dis)ability are present well before children go to school. This highlights the need for early diagnosis and interventions to support positive outcomes for children. Our findings provide a better understanding of the neural correlates of pre-reading and language from an early age and can lay the groundwork for earlier interventions for reading and language disabilities.

Preface

This thesis presents original work investigating the structural connectivity correlates of early pre-reading and language skills in young children, and how prenatal alcohol exposure moderates these associations. All studies in this thesis received ethics approval from the University of Calgary Conjoint Health Research Ethics Board (CHREB) (REB13-0020, REB14-2266, REB21-1846).

Chapter 1 provides an overview of the key concepts related to the thesis questions and presented studies including language, reading, brain development, neuroimaging, graph theory analysis, and prenatal alcohol exposure. All figures used in chapter 1 were created by the thesis author unless stated otherwise. Chapters 2-4 were collaborative research projects done under the supervision of Dr. Catherine Lebel.

Chapter 2 characterizes how the structural brain network properties are associated with pre-reading language measures, specifically phonological awareness and naming speed, in young Canadian children (2-6 years). This study has been published as: Ghasoub, M., Perdue, M., Long, X., Donnici, C., Dewey, D., & Lebel, C. (2024). Structural neural connectivity correlates with pre-reading abilities in preschool children. Developmental Cognitive Neuroscience, 65, 101332. https://doi.org/10.1016/j.dcn.2023.101332. The following is the author's contributions: Mohammad Ghasoub: Conceptualization, Data curation, Formal analysis, Methodology, Visualization, Writing – original draft, Writing – review & editing. Meaghan Perdue: Conceptualization, Methodology, Writing – review & editing. Xiangyu Long: Methodology, Writing – review & editing. Claire Donnici: Data curation, Writing – review & editing. Deborah Dewey: Conceptualization, Writing – review & editing. Catherine Lebel: Conceptualization,

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Chapter 3 determined how prenatal alcohol exposure moderates the associations of structural network connectivity with pre-reading language measures in early childhood (2-6 years). This study has been published as: Ghasoub, M., Perdue, M., Long, X., Donnici, C., Kar, P., Gibbard, B., Tortorelli, C., McMorris, C., Dewey, D., & Lebel, C. (2024). The brain's structural connectivity and pre-reading abilities in young children with prenatal alcohol exposure. Developmental Cognitive Neuroscience, 70, 101467. https://doi.org/10.1016/j.dcn.2024.101467. The following is the author's contribution statement: Mohammad Ghasoub: Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis, Data curation, Conceptualization. Meaghan Perdue: Writing – review & editing, Methodology. Xiangyu Long: Writing – review & editing, Methodology. Claire Donnici: Writing – review & editing, Data curation. Preeti Kar: Writing – review & editing, Data curation. W Ben Gibbard: Writing – review & editing, Funding acquisition, Conceptualization. Chris Tortorelli: Writing – review & editing, Funding acquisition, Conceptualization. Carly McMorris: Writing – review & editing, Methodology, Funding acquisition, Conceptualization. Deborah Dewey: Writing – review & editing, Methodology. Catherine Lebel: Writing – review & editing, Supervision, Resources, Project administration, Funding acquisition, Conceptualization.

Chapter 4 examines how prenatal alcohol exposure moderates the associations of structural language network connectivity with receptive and expressive communication skills in South African children at ages 2-3 years old. This study has been published as: Ghasoub, M., Scholten,

C., Geeraert, B., Long, X., Joshi, S., Wedderburn, C. J., Roos, A., Subramoney, S., Hoffman, N., Narr, K., Woods, R., Zar, H. J., Stein, D. J., Donald, K., & Lebel, C. (2025). The Effects of Prenatal Alcohol Exposure on Structural Brain Connectivity and Early Language Skills in a South African Birth Cohort. Neurobiology of Language, 6, nol_a_00161. https://doi.org/10.1162/nol_a_00161. The following is the author's contributions to this manuscript: Mohammad Ghasoub: Conceptualization: Equal; Formal analysis: Lead; Validation: Lead; Visualization: Lead; Writing – original draft: Lead; Writing – review & editing: Lead. Chloe Scholten: Data curation: Supporting; Validation: Supporting; Writing – review & editing: Supporting. Bryce Geeraert: Data curation: Supporting; Validation: Supporting; Visualization: Supporting; Writing – review & editing: Supporting. Xiangyu Long: Formal analysis: Supporting; Methodology: Supporting; Writing – review & editing: Supporting. Shantanu Johsi: Conceptualization: Supporting; Data curation: Supporting; Writing – review & editing: Supporting. Catherine J. Wedderburn: Conceptualization: Supporting; Writing – review & editing: Supporting. Annerine Roos: Data curation: Supporting; Writing – review & editing: Supporting. Sivenesi Subramoney: Data curation: Supporting; Writing – review & editing: Supporting. Nadia Hoffman: Data curation: Supporting; Writing – review & editing: Supporting. Katherine Narr: Conceptualization: Supporting; Writing – review & editing: Supporting. Roger Woods: Conceptualization: Supporting; Writing – review & editing: Supporting. Heather J. Zar: Conceptualization: Supporting; Writing – review & editing: Supporting. Dan J. Stein: Conceptualization: Supporting; Writing – review & editing: Supporting. Kirsten Donald: Conceptualization: Equal; Data curation: Supporting; Funding acquisition: Equal; Supervision: Supporting; Writing – review & editing: Supporting. Catherine Lebel: Conceptualization: Equal; Funding acquisition: Lead; Supervision: Lead; Writing – review & editing: Equal.

Chapter 5 provides an overall discussion and interpretation of the findings, highlighting the key results integrated from the three studies as well as the limitations and future directions of the work done.

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Dedication

To the almighty god, for every blessing; to my family, for every sacrifice; and to my homeland, for every hope it instilled in me.

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Figure 4.3 PAE moderated the Expressive Communication–graph theory metric associations for (A) global efficiency, (B) nodal degree, and (C) betweenness centrality in the right hemisphere network.

List of Abbreviations

AAL – Automated Anatomical Labeling atlas

AD – axial diffusivity

ADHD – attention deficit hyperactivity disorder

ANG – angular gyrus

APrON – Alberta Pregnancy Outcomes and Nutrition

ASD – autism spectrum disorder

ASSIST – alcohol, Smoking, and Substance

Involvement Screening Test

B_0 – static magnetic field

B1 – added magnetic field

BSID-III – Bayley Scales of Infant and Toddler

Development, Third Edition

DCHS – Drakenstein Child Health Study

DTI – Diffusion tensor imaging

DWI – Diffusion weighted imaging

e – eigenvectors

EEG – electroencephalography

EPI – echo planar imaging

FA – fractional anisotropy

FASD – fetal alcohol spectrum disorder

FDR – False discovery rate correction

FFG – fusiform gyrus

fMRI – functional magnetic resonance imaging

G – amplitude

H^+ – hydrogen proton

HES – Heschl's gyrus

IFGoperc – inferior frontal gyrus opercular

IFGtriang – inferior frontal gyrus triangular

ITG – inferior temporal gyrus

LING – lingual gyrus

MD – mean diffusivity

MRI – magnetic resonance imaging

Ms – milliseconds

NEPSY-II – Developmental Neuropsychological

Assessment-Second Edition

NMV – net magnetization vector

NPC – neural progenitor cells

PAE – prenatal alcohol exposure

PP – Phonological Processing

PTE – Prenatal tobacco exposure

RAN – rapid automatized naming

RD – radial diffusivity

s/mm^2 – seconds per square millimeter

SES – socioeconomic status

SN – Speeded Naming

STG – superior temporal gyrus

T1 – H^+-lattice time constant

T2 – H^+-H^+ relaxation time constant

γ – gyromagnetic ratio

Δ – diffusion time

δ – duration of diffusion

λ – eigenvalues

Chapter 1: Introduction

1.1 Early language and reading skills

Language and reading are considered some of the most crucial communication skills. Though they are often synonymous with each other and share many features, both skills differ in their development and purpose. Language is a foundational skill that develops naturally and is highly specialized in humans, which distinguishes them from other species. Reading is also specialized in humans but is an acquired skill that humans gained and developed over time as an extension of language. Both skills play an important role in day-to-day life, and the development of each skill influences the other (Demir-Lira et al., 2019). Additionally, language and reading skills share brain regions and pathways, which is thought to be due to reading being acquired by humans later on from an evolutionary perspective (Alagöz et al., 2025; Wilcox et al., 2022). Moreover, language and reading development are bidirectional with other foundational and academic skills, including executive functioning, writing, and mathematics, making their healthy development pivotal for typical cognitive and behavioral development (Cirino et al., 2019; Erbeli et al., 2021; Peng, 2023).

1.1.1 Language categories

Language has three main domains that are crucial in early childhood development: receptive, expressive, and pragmatic (Wilcox et al., 2022). Receptive language is the domain of understanding and comprehending language communicated by others. Examples of receptive language include object recognition, conversation comprehension, and understanding the meaning of words. Expressive language is the accurate expression and production of words, such as object naming, using sounds to communicate emotions, and speaking to communicate using

words and sentences. Both receptive and expressive language develop early and are seen from infancy; however, they have different developmental trajectories, and receptive language develops earlier. Pragmatic language, often referred to as social language, is the ability to understand and use language in the appropriate context such as metaphors, sarcasm, nonverbal communication, and emotional aspects of language.

1.1.2 Language development

Language is thought to develop naturally, meaning that unlike other forms of communication such as reading and writing, it does not require formal instruction to develop. However, it requires environmental and biological events including language exposure/interaction, as well as proper brain development in order to develop appropriately (Richardson, 2025). The concept of language being innate was popularized by Noam Chomsky, who argued that humans are "hard-wired" for language and that humans are predisposed to acquire language (Chomsky, 2009). While still debated in the field, several factors favor the nativist view of language. First, language has a critical period, when both biological and environmental events must occur in order for language to develop properly, as evidenced by studies of children who were isolated and unexposed to language and consequently failed to acquire it (Richardson, 2025). These cases support the argument that humans are predisposed to language development during a specific time window and in turn, support the nativist view. Additionally, the concepts of universal grammar and poverty of stimulus (i.e., children receive insufficient language input to fully develop their skills) highlight that children understand several language structures without formal instruction, suggesting that children have an innate capacity for language (Wilcox et al., 2022). Moreover, children make grammatical mistakes when they first begin to speak but

typically go on to master these concepts despite not receiving formal instruction, or even correction, further supporting the innate nature of language development (Chomsky, 2009).

1.1.3 Language development across early childhood

Humans utilize language to fulfill several needs, including learning, meeting their own necessities and goals, controlling behavior, contacting and constructing interpersonal relationships with others, as well as expressing themselves. Children begin to show signs of language development from infancy; during the first few months of life, they recognize voices and react when spoken to, as well as use their own voices to display discomfort (Feldman, 2019; Kujala et al., 2023; Morse & Cangelosi, 2017; Wilcox et al., 2022). By the first year, children begin to respond to names and simple directions, along with babbling and producing their first word. Toddlers begin to use more complex language, where they have better recognition of objects and are able to communicate using short concise sentences. Then, during the preschool stage, children begin to have a better understanding of what is said to them as well as being understood by others. Finally, as children transition to school and get older, they can understand and speak more complex and complete sentences as well as understand nonliteral language such as idioms and sarcasm, demonstrating increased development of pragmatic language skills.

1.1.4 Reading development

Language plays a wide foundational role in communication skills development, and some components of language such as oral language are associated with stronger reading skills (Chang et al., 2020; Honig, 2007). Unlike language, reading requires formal explicit instruction to develop and improve. Reading also does not have a critical period where learning is required to

obtain the skill; however, early reading acquisition is necessary for better academic outcomes. Notably, reading and language have a bidirectional relationship, where better language skills are associated with better reading skills and vice versa (Chang et al., 2020; Honig, 2007).

1.1.5 Reading categories

There are five major components of reading: phonological awareness, decoding, vocabulary, fluency, and comprehension (Wilcox et al., 2022). Phonological awareness refers to the ability to recognize and manipulate sound unit of words (i.e., phonemes) (Eden & Flowers, 2009; Vander Stappen & Reybroeck, 2018). Decoding is the concept of matching phonemes with their corresponding letters (i.e., graphemes) and is important particularly during the early stages of reading acquisition. Vocabulary is an important part of reading and is significantly linked to both reading and language skills (Lee, 2011). Infant vocabulary is a significant indicator of later language skills such as reading comprehension, accuracy, and phonological skills (Duff et al., 2015). Moreover, vocabulary size is also a predictor of language and reading skills; although, this relationship is bi-directional (Lee, 2011). Reading fluency refers to the ability to read with speed, accuracy and appropriate expression. Skilled readers are fluent readers, and fluency is important as it lessens the cognitive demand on the working memory, thereby freeing up working memory capacity for improving other components of reading such as comprehension (Ergül et al., 2022). Reading comprehension is the ability to comprehend and interpret the meaning of sentences and is considered the main goal of reading acquisition. Comprehension develops later as children become more skilled with the other four components of reading. Reading begins to develop early, starting with a child's ability to recognize objects and manipulate phonemes (i.e., sound unit of words), to the ability to recognize letters and numbers,

then automatic recall of words in a fast and accurate manner (i.e., fluency), and finally comprehension. These skills improve with age as children become more skilled with explicit instruction and practice.

1.1.6 Pre-reading abilities

Reading difficulties often go undiagnosed until children are already in school and struggling, which impacts various aspects of their academic, social, and mental wellbeing. However, reading begins to develop early and is dependent on pre-reading skills (Gabrieli, 2009). Phonological awareness includes sound knowledge at the phoneme level and the child's ability to manipulate phonemes by segmenting or combining them (Chard & Dickson, 1999) and is one of the most important pre-reading skills and has been studied extensively (Eden & Flowers, 2009; Vander Stappen & Reybroeck, 2018). Phonological awareness skills in young children predict future reading performance (Kibby et al., 2014; Lafrance & Gottardo, 2005; Nelson et al., 2012). Additionally, phonological awareness is a target for several reading interventions for individuals with reading difficulties (Perdue et al., 2022).

Rapid automatized naming (also known as naming speed) is another important pre-reading skill; it encompasses processing speed and phonological access/retrieval ability. Rapid automatized naming can be first assessed based on the ability to rapidly identify objects and colors in young children, then letters and/or numbers identification in older children (Vander Stappen & Reybroeck, 2018). Individuals with poor reading skills tend to perform worse at naming speed tasks than skilled readers (Eden & Flowers, 2009; Elliot & Grigorenko, 2014). Moreover, letters and/or number identification assessments are stronger predictors of reading than object identification. Phonological awareness tends to be a better predictor of reading during the early

years of learning while rapid automatized naming becomes a better predictor later (Cohen et al., 2018; Kirby et al., 2003). However, unlike phonological awareness, rapid automatized naming is less amenable to remediation through interventions (de Jong and Vrielink, 2004).

1.1.7 Factors influencing language and reading

Several biological and environmental factors are associated with language and reading skills in children. Biologically, lateralization towards the left hemisphere is associated with better language and reading skills (Purves et al., 2001). Additionally, reading disorders have a strong genetic component where genetic factors account for approximately 40-70% of variations in reading disorders (Erbeli et al., 2021). There are also sex differences in language and reading, where females tend to acquire better language and reading skills than males in early childhood (Manu et al., 2023). The presence of these sex differences in adolescents and adults, however, is inconsistent, with some studies showing that a gap between females and males remains with age while others report a decrease (Manu et al., 2023; Rice & Hoffman, 2015).

Reading disorders show high familial heritability, with children who have a family history of dyslexia being at 40–60% risk of developing reading difficulties, compared to 10–12% in the general population. Twin studies estimate that genetic factors account for approximately 40–80% of the variance in reading abilities. Specific genes associated with reading disorders, such as DYX1C1,

Several social and environmental factors also play a role in early childhood. Socioeconomic status is related to language development in childhood, where children from lower

socioeconomic status to tend to have poorer language and reading skills (Schwab & Lew-Williams, 2016). Parental education and involvement in reading positively influence children's reading comprehension skills (Hoff et al., 2024). Children from low socioeconomic status backgrounds tend to have lower reading and pre-reading scores compared to children with high socioeconomic status (Noble et al., 2006). Early home literacy environment is also associated with future reading outcomes (Torppa et al., 2022). Moreover, household stability and parent-child interaction predict the child's future language skills (Vernon-Feagans et al., 2012). Furthermore, environmental effects on language and reading can occur even earlier, particularly in the prenatal stage, where prenatal exposure to teratogens such as alcohol can affect language development through their detremenital impacts on brain development (Hendricks et al., 2019; Landi et al., 2017).

1.1.8 Language and reading disorders

Developmental language disorders and delays are prevalent, affecting approximately 7% of children (Black et al., 2015). Additionally, language difficulties are prevalent and comorbid with several neurodevelopmental disorders such as autism spectrum disorder, attention-deficit hyperactivity disorder, and learning disabilities; although, the causality is not well understood (Andreou et al., 2025; Nitin et al., 2022). Reading disabilities affect approximately 10% of Canadians and account for 80% of known learning disabilities (Kohli et al., 2018; Shaywitz & Shaywitz, 2008). Most reading difficulties go undiagnosed until children have been struggling for several years, which can have a substantial long-lasting effect on many aspects of their life. Childhood reading deficits are associated with unsatisfactory academic achievement and poor mental health (Livingston et al., 2018). Thus, early recognition and treatment is important.

1.2 Brain Development

1.2.1 Prenatal neurodevelopment

Brain development is a complex process that begins in early pregnancy and continues postnatally, consisting of several stages that occur in sequence but also overlap with each other (Eisenstat et al., 2023; Kandel et al., 2012). The main stages of brain development can be categorized as neurulation, neurogenesis and proliferation, gliogenesis, neuronal migration, programmed cell death, synaptogenesis, myelination, and synaptic pruning. Most of these are complete before birth, while other stages predominantly occur postnatally (figure 1.1). These stages are guided and regulated by several signalling molecules, which are important for each neurodevelopmental stage to materialize (Kandel et al., 2012). During the embryonic stage, around the third week post conception, the embryo undergoes a major transformation process called gastrulation. In gastrulation, a three-layered structure is formed in which each layer has stem cells that will eventually make up distinct structures of the fetus (Sanes et al., 2019). These three layers are called the endoderm, mesoderm, and ectoderm. The endoderm will eventually form the gut and respiratory tract, the mesoderm will form the bones, muscles, and vascular system, while the ectoderm will make up the skin and the central nervous system (Eisenstat et al., 2023). By the end of gastrulation, signalling molecules from the mesoderm and notochord differentiate the dorsal part of the ectoderm into the neuroectoderm. This is located at what is known as the neural plate, giving rise to the neural progenitor cells (NPC), the building blocks of the central nervous system. Then, the neural plate undergoes further adaptations, folding into a cylindrical structure known as the neural tube. This stage is known as neurulation. Neurulation is crucial for typical neurodevelopment, and failure to enclose the neural tube results in neural tube

defects such as spina bifida (Kandel et al., 2012). The neural tube eventually gives rise to the main components of the central nervous system. The posterior segment of the neural tube makes up the spinal cord, while the anterior segment make up the forebrain, midbrain, and hindbrain. Following neurulation and around the fifth week of pregnancy, early stages of proliferation and neurogenesis begin, where NPCs divide and proliferate symmetrically (giving rise to more NPCs) and then asymmetrically later on (giving rise to a NPC and a neuron). Gliogenesis begins shortly after neurogenesis and they continue simultaneously. The produced neurons then migrate to their specific location in the brain in an orderly fashion, a stage known as neuronal migration (Eisenstat et al., 2023). During neurogenesis, an overabundance of neurons are produced. Consequently, the first regressive process of brain development, known as programmed cell death (i.e., apoptosis) begins. Apoptosis is necessary to remove the unused neurons to better organize the brain and maximize its efficiency. The remaining neurons' cell bodies comprise the gray matter component of the brain. Afterwards, once the neurons are at their target location, they begin to form connections with other neurons through synaptogenesis (Eisenstat et al., 2023; Kandel et al., 2012). The synapse is the main communication structure in the brain, and is comprised of the axon terminals, synaptic cleft, and dendrites. Synaptogenesis is regulated by adhesion molecules which are crucial for proper synapse development. The neurons begin to form connections with each other by extending their axons to reach their target neurons. Around the same time, the axons undergo further significant morphological changes that are dependent on glial development, in another stage called myelination (Eisenstat et al., 2023; Kandel et al., 2012). Myelinated axons make up the white matter pathways of the brain. Myelination begins prenatally but largely takes place postnatally. Up until birth, the brain continues to undergo

major changes, with the formation of brain connections and circuits as well as rapid morphological changes such as cortical folding (i.e., gyrification) occurring in the third trimester.

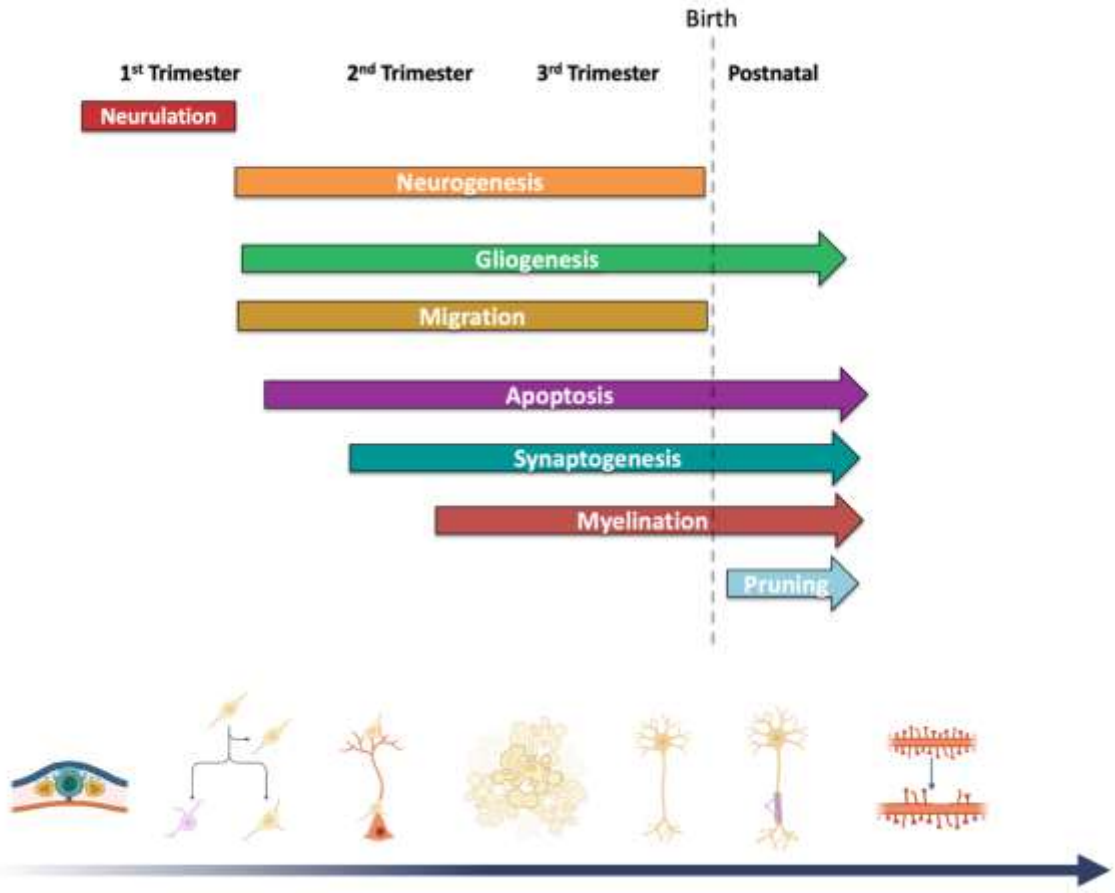

Figure 1.1 Timeline of the major neurodevelopmental stages that underlie the neurological and behavioral characteristics of humans, beginning from neurulation around the third week of pregnancy and continuing postnatally throughout childhood and early adulthood. This figure was partially created and edited with BioRender and OpenAI with granted permission (BioRender.com; OpenAI, GPT-4).

1.2.2 Postnatal neurodevelopment

By the time the fetus is born, most of the early neurodevelopmental stages have occurred. However, the brain continues to grow and undergo significant changes throughout development. At around age 6 years, the child brain is almost 90% of the adult size (Grigorenko, 2017). Neurogenesis predominantly takes place prenatally, with two known exceptions in the olfactory bulb and the dentate gyrus of the hippocampus, where new neurons can be created even in adulthood (Kumar et al., 2019). Glial cells on the other hand continue to develop extensively after birth throughout development and even in adulthood. Postnatal brain development is characterized by two key processes, synaptic pruning and myelination (figure 1.1).

Synaptic pruning, the second key regressive brain development stage, is observed early in the postnatal brain and continues into early adulthood (Eisenstat et al., 2023; Sanes et al., 2019). During synaptogenesis, the brain generates an excess number of synapses, many of which go underutilized. Through exposure to environment and learning, the brain begins to undergo refinement by removing the underutilized synapses to maximize its efficiency. This process peaks during early childhood around the first 6 years of life and intensifies from childhood to early adolescence (Eisenstat et al., 2023; Kandel et al., 2012).

Myelination is the process by which glial cells coat axons with a white fatty substance called myelin, which serves as protection for the axons and speeds up communication between neurons (Eisenstat et al., 2023; Sanes et al., 2019). Propagation of neural signals along myelinated axons conduction is known as saltatory conduction. Electrochemical impulses in unmyelinated axons travel at a typical conduction speed of around 10 m/s, whereas in myelinated axons, conduction speed is up to 150 m/s. This highlights the importance of myelination for effective neural communication (Kandel et al., 2012). Oligodendrocytes are the main glial cells responsible for myelination in the brain, while Schwann cells play a similar role in the spinal cord. Myelination

occurs rapidly during the first two-three years of life and continues into early adulthood as evidenced by human neuroimaging studies (Lebel et al., 2008).

1.3 Magnetic Resonance Imaging (MRI)

Magnetic resonance imaging (MRI) is a safe and non-invasive imaging technique that can be used to study the brain (Johansen-Berg & Behrens, 2014). MRI has a high spatial resolution and does not require the use of radiation or tracer injection, making it the ideal imaging technique for research studies of brain structure and function. MRI has been used extensively over the past few decades to investigate many aspects of neurodevelopment such as regional brain volume, white matter microstructure, cortical morphology, gyrification, and connectivity, including in both typically developing brains as well as in neurodevelopmental and neurological disorders.

1.3.1 Principles of MRI

MRI is able to generate and record signal from a body of interest by manipulating positively charged hydrogen ions (protons; H^+) due to their abundance in the body (Johansen-Berg & Behrens, 2014). These protons are constantly spinning, which generates a magnetic field. This magnetic field has an orientation as well as an intrinsic angular momentum called the nuclear spin. H^+ nuclei have spin of ½ since they have one proton and no neutron (Johansen-Berg & Behrens, 2014).

1.3.2 MRI acquisition

At rest, the H^+ are in different orientations and, therefore, cancel each other out and generate no net magnetic field (Grover et al., 2015). In the presence of a strong external magnetic field, the

magnetic fields of H^+ align, with their vertical component in either parallel or antiparallel direction, with more H^+ aligned parallel to the strong magnetic field as this is a lower energy state than antiparallel (Grover et al., 2015). However, H^+ do not align perfectly with B0, and this slight misalignment causes hydrogen atoms to precess at a frequency defined by the Larmor equation ($f = \gamma B_0$), where f is the precessional frequency of H^+ and γ is the gyromagnetic ratio. In the context of MRI, the scanner generates a strong, static magnetic field known as B_0. Common field strengths for MRI scanners are 1.5, 3, and 7.0 Tesla. A stronger B_0 field results in a greater proportion of H+ aligning parallel to B_0 orientation rather than antiparallel, increasing the amount of signal we can record from a body of interest. The summation of all the magnetic moments of the individual hydrogen nuclei is called the net magnetization vector (NMV) (McMahon et al., 2011). The NMV is much smaller in magnitude than B_0, thus it is difficult to measure when aligned with the main magnetic field's orientation. To measure NMV, an additional magnetic field is introduced (B1) that tilts the NMV to the transverse plane. This process is known as excitation (Grover et al., 2015). B1 is applied at a frequency matched to the precessional frequency of H^+ (i.e., Larmor frequency) to create resonance. When B1 is applied, H^+ are precessing together in phase, but local variations in magnetic field strength experienced by H^+ causes precession at slightly different frequencies, resulting in signal decay over time. After excitation, NMV returns towards the B_0 orientation in an exponential decay manner, known as relaxation. There are two processes that characterize relaxation (Grover et al., 2015; McMahon et al., 2011): the first is longitudinal regrowth, which describes the process of the NMV returning to alignment with B_0 and returning to its full magnitude. The second is known as transverse decay which refers to the process of magnetization in the transverse plane decreasing to a magnitude of 0. Longitudinal regrowth is quantified by the H^+-lattice time constant (T1),

which is the amount of time it takes for the NMV to return to 63% of its full magnitude. Transverse decay is quantified by the H^+-H^+ relaxation time constant (T2) which describes the amount of time it takes for the curve to reach only 37% of its maximum. T2 decay happens much faster than longitudinal regrowth, since it is easier to transfer energy between hydrogen atoms than getting rid of it. T1 and T2 also differ among tissues. For instance, white matter has a T1 of 1000 ms and T2 of 60 ms, while gray matter has a T1 of 1800 ms and T2 of 100 ms (Dale et al., 2015).

Magnetic field gradients are used to limit the amount of tissue affected by the B1 field to a slice and encode spatial information into our recorded signal based on the physical location of H^+ protons within that slice. This frequency-encoded signal is recorded by receiver coils placed near the tissue of interest and stored in mathematical space called k-space. In traditional acquisitions, k-space encodes recorded signals line by line, representing spatial frequencies present in MRI images (McMahon et al., 2011). The basic contrast and overall brightness of an image is stored at the center of k-space while the fine details and sharpness of an image is held in the periphery. Then, brain images are reconstructed using the Fourier Transform, a mathematical function that takes spatial frequencies and adds them together at appropriate amplitudes to produce the brain images seen on the scanner computer (Grover et al., 2015; McMahon et al., 2011).

1.4 Diffusion weighted imaging

1.4.1 Principles of DWI

Diffusion weighted imaging (DWI) is a neuroimaging technique commonly used to study the brain's white matter due to its sensitivity to white matter microstructure (Beaulieu, 2002). Diffusion imaging takes advantage of the fact that water diffusion in white matter is directionally

dependent (anisotropic). By measuring diffusion in different directions, DWI can provide a comprehensive picture of water movement in 3 dimensions in each voxel within the brain (Johansen-Berg & Behrens, 2014). Measurements from DWI can provide a better understanding of the neural basis underlying early reading and language skills in children.

DWI utilizes water diffusion properties to assess tissue microstructure. Diffusion is random motion (Brownian motion), meaning that in the absence of barriers, each water molecule has an independent and equal probability of moving in any direction (Johansen-Berg & Behrens, 2014). This is opposed to flow, where the movement has a net bulk motion such as blood flow in brain blood vessels (Le Bihan, 2012). There are several factors that influence diffusion, including temperature, molecule size, surface, concentration gradient, as well as the diffusion medium (Beaulieu, 2002). In white matter, diffusion is anisotropic and directionally dependent due to the presence of packed myelinated axons, and, therefore, diffusion is more likely to occur along the orientation of axons (Beaulieu, 2002). Meanwhile, water diffusion in the gray matter is less anisotropic due to the presence of fewer coherently-oriented barriers, while cerebrospinal fluid (CSF) is mostly isotropic (figure 1.2). Thus, DWI is ideal for studying white matter properties given its ability to trace long-range fiber bundles/tracts and quantify features of microstructure based on measurement of diffusivity and anisotropy.

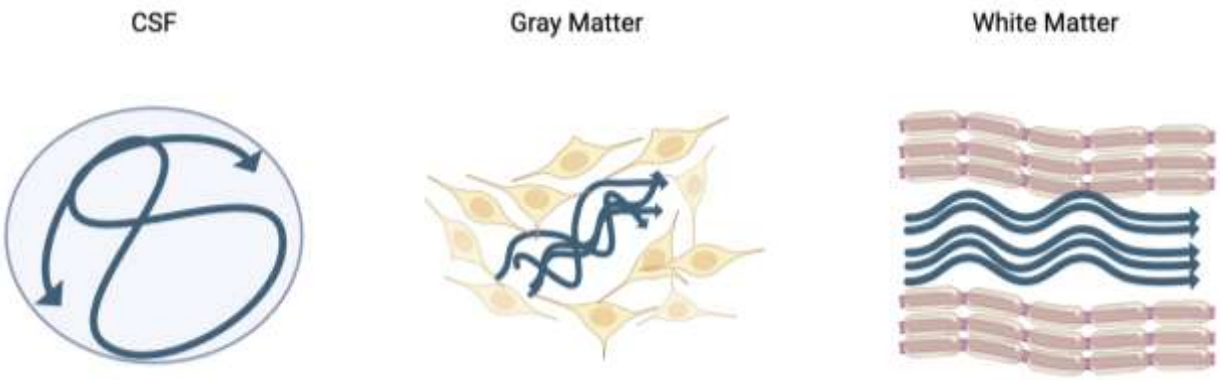

Figure 1.2 Illustration of water diffusion properties comparisons between cerebrospinal fluid (CSF), gray matter, and white matter tissues. Water diffusion is isotropic in CSF given the absence of barriers, less isotropic in gray matter due to presence of incoherent barriers, and anisotropic in white matter due to the presence of densely packed axons. This figure was generated from BioRender (BioRender.com)

1.4.2 DWI acquisition

To acquire standard DWI images, first, a diffusion-encoding gradient is applied to cause H+ to precess at different phases in their cycle based on their spatial location (Johansen-Berg & Behrens, 2014). After waiting for a period of time, a 180° pulse is applied to refocus the H^+ dephasing caused by MRI magnetic field inhomogeneities before applying a second diffusion gradient to the phase information that had been encoded by the first gradient. Due to the water diffusion properties, encoding gradients and reversing them in a given direction causes a signal loss that is used to measure diffusion. This is a common DWI acquisition method known as spin-echo sequence. Diffusion sensitivity is measured by the b-value, measured in s/mm² and can be calculated using the following equation: $b = \gamma^2 \cdot G^2 \cdot \delta^2 \cdot (\Delta - \delta/3)$, Where γ is the gyromagnetic ratio, G represents the amplitude, δ is the duration, and Δ is the diffusion time (beginning of

phase encoding to beginning of reversal phase encoding) (Beaulieu, 2002; Johansen-Berg & Behrens, 2014). Typically, a b-value of 750-1000 s/mm² is used in most research studies. Increasing b-value increases the sensitivity to detecting diffusion and can improve the quality and specificity. However, this results in less signal available to measure, resulting in noisier images unless compensation methods are applied such as increasing voxel size, consequently impacting spatial resolution.

1.4.3 DTI

Diffusion tensor imaging (DTI) is a type of DWI often used to study white matter microstructural properties (Soares et al., 2013). By measuring diffusion in enough unique different directions, water diffusion properties can be modeled and fitted to an ellipsoid (elongated sphere), represented mathematically by a 3x3 symmetric matrix, also known as tensor (Johansen-Berg & Behrens, 2014; Soares et al., 2013). In white matter, signal diffusion loss is high when measuring in the primary direction of axon orientation, and low when measuring in perpendicular direction. The diffusion represented by the tensor can be fully characterized by its three orthogonal eigenvalues ($\lambda1$, $\lambda2$, $\lambda3$) and their eigenvectors (e1, e2, e3). The eigenvalues represent the magnitude of diffusion along the longest, middle, and shortest axes of the ellipsoid, and the eigenvectors represent the directionality of these axes (diffusion) (Beaulieu, 2002; Johansen-Berg & Behrens, 2014; Soares et al., 2013).

To calculate a tensor, diffusion must be assessed in a minimum of 6 directions. However, it is more common to use 30 measurements or more to get more information about diffusion properties and improve image quality. Generally, the more directions are obtained, the more

accurate and better represented the overall diffusion is in an area (Beaulieu, 2002; Johansen-Berg & Behrens, 2014; Soares et al., 2013).

Once the tensor is calculated, several measures that indirectly infer information about white matter microstructural properties such as fractional anisotropy (FA; a measure of water movement directionality), axial diffusivity (AD; water diffusion along the axons), radial diffusivity (RD; water diffusion perpendicular to the axons), and mean diffusivity (MD; overall water movement) can be computed. The putative trajectories of axonal fibers can also be reconstructed from diffusion MRI data, typically by assessing the primary orientation of the tensor in each voxel using tractography (Alexander et al., 2007; Qiu et al., 2015).

1.4.4 Tractography

Once DWI data is acquired and processed (e.g., the tensor is calculated), it can be used to connect voxels and model where tracts exist to reconstruct and visualize fiber bundles (Soares et al., 2013; Qiu et al., 2015). The main principle of tractography is essentially reconstructing the white matte pathways based on the water diffusion directionality such as moving from one voxel to another and drawing from the diffusion tensor in that voxel to determine where to step next, until reaching a threshold such as minimum fractional anisotropy or maximum change in angle between steps (Johansen-Berg & Behrens, 2014). There are different types of tractography, with probabilistic and deterministic tractography being the two most commonly used techniques. In probabilistic tractography, a probability distribution of the preferred direction of water diffusion is fitted at each voxel (i.e., tensor) to determine the likelihood that a streamline will disseminate in any direction (Soares et al., 2013). Thus, probabilistic tractography models the uncertainty of preferred direction estimate, and provides confidence bounds on the trajectory of the

reconstructed pathway. In deterministic tractography, the process involves seeding a specific voxel and then propagating a streamline that follows the principal direction of water diffusion in each voxel until some termination criterion is reached (Soares et al., 2013). Thus, deterministic tractography uses a point estimate of the preferred direction of diffusion in each voxel.

1.5 Brain regions and pathways supporting language and reading

1.5.1 Brain regions of language and reading

Several brain regions have been implicated in supporting language and reading in humans (Martin et al., 2015) (figure 1.3). Some of the major regions identified include:

I. Triangular and opercular parts of the inferior frontal gyrus: encompasses Broca's area and are associated with phonological and semantic processing.
II. Angular gyrus: Integration hub for audio and visual components of reading and language.
III. Superior temporal gyrus: encompasses Wernicke's area. Associated with retrieval and comprehension of language and reading.
IV. Heschl's gyrus: Contains the primary auditory cortex. Associated with speech and other auditory components of reading and language.
V. Inferior temporal gyrus: Important for visual components of reading and language such as object recognition and comprehension.
VI. Lingual gyrus: Involved in several visual processes such as letter recognition and visual memory.
VII. Fusiform gyrus: comprises the visual word form area, Important for facial recognition (predominately right hemisphere) as well as word identification (predominantly left hemisphere).

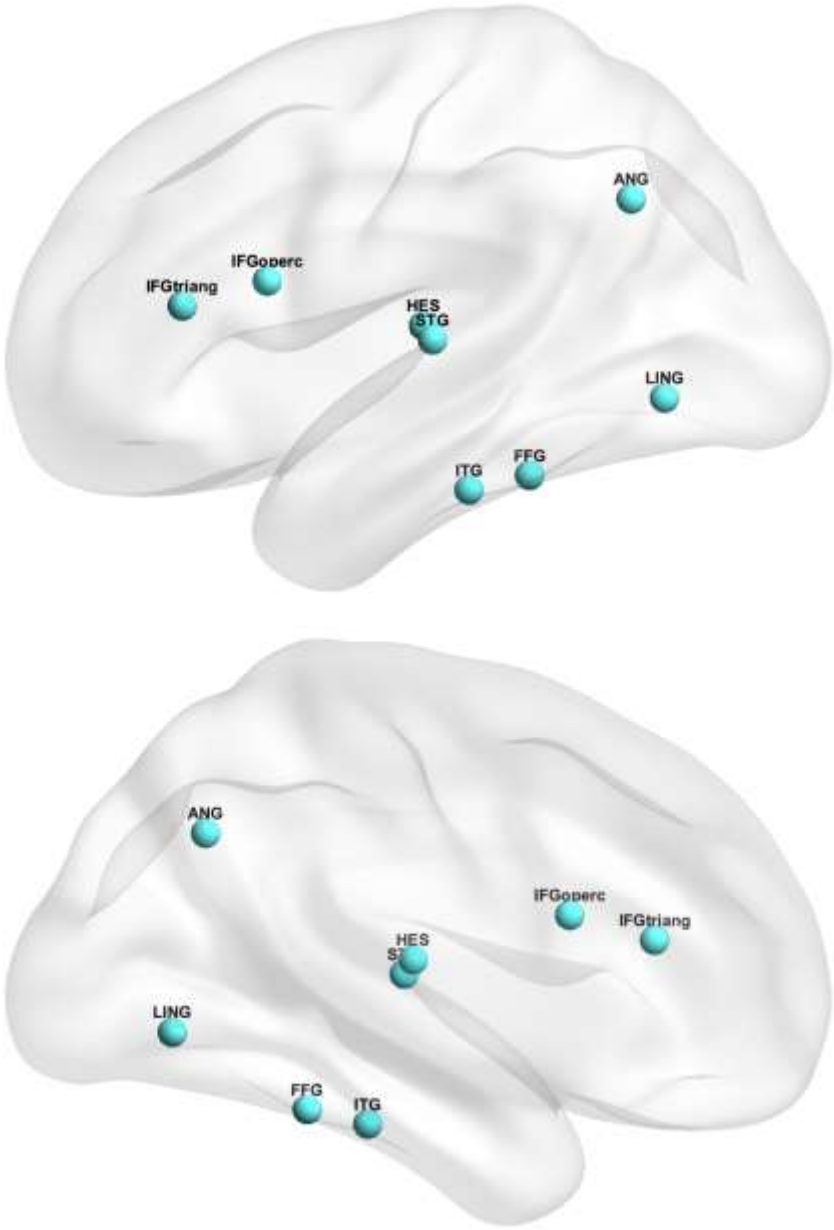

Figure 1.3 Sagittal view of brain regions associated with reading and language processing. The opercular and triangular parts of the inferior frontal gyrus (IFGoperc; IFGtriang); the lingual gyrus (LING); fusiform gyrus (FFG); angular gyrus (ANG); Heschl's gyrus (HES); superior temporal gyrus (STG); and inferior temporal gyrus (ITG).

1.5.2 White matter pathways supporting language and reading

DWI has been used extensively in research to identify major white matter pathways implicated in language and reading processing in both typical and atypical development (figure 1.4). Diffusion studies consistently show differences in white matter microstructural properties between typical readers and individuals with reading disabilities (Cui et al., 2016). They also provide evidence for different developmental trajectories in typical readers and non-typical readers (Houston et al., 2014; Lebel et al., 2019).

Some of the major tracts identified include (figure 1.4):

I. Arcuate fasciculus: a major white matter pathway connecting Broca's and Wernicke's areas that is implicated in phonological processing and fluency.
II. Uncinate fasciculus: white matter pathway that links the limbic system structures in the temporal lobe with the inferior frontal lobe and is involved in lexical and semantic processing as well as naming.
III. Superior longitudinal fasciculus: large white matter bundle connecting all four lobes of the brain and is involved in language processing and comprehension.
IV. Inferior longitudinal fasciculus: Connects the occipital and temporal lobes, and is associated with reading as well as object recognition
V. Inferior fronto-occipital fasciculus: Long white matter pathway between the frontal, occipital, and the temporal lobes, involved in semantic processing and word retrieval

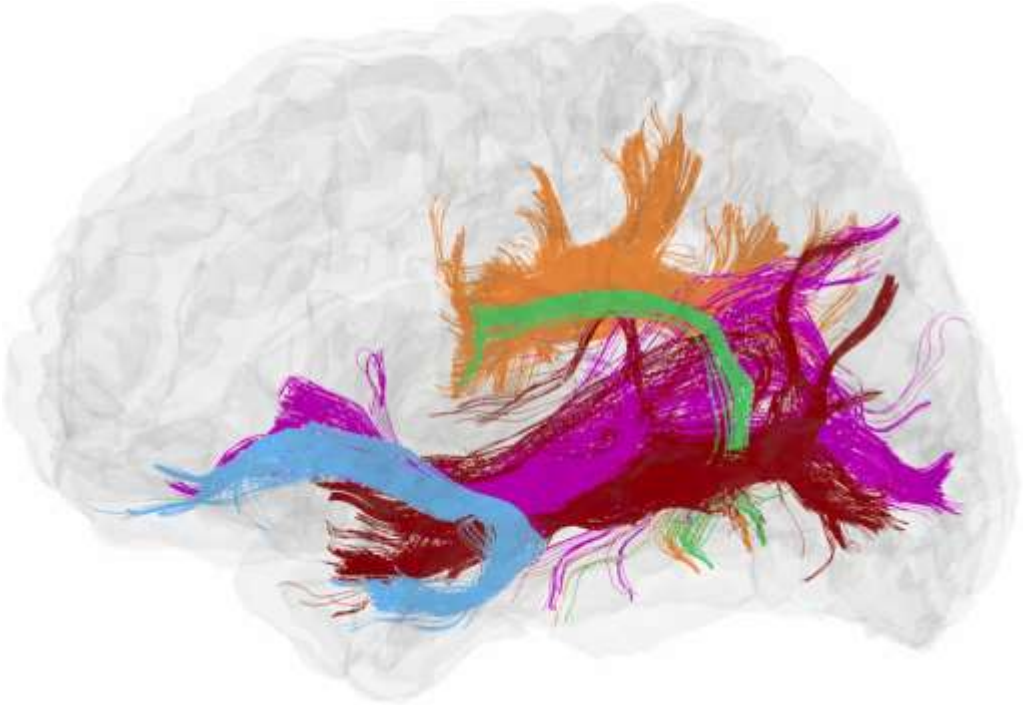

Figure 1.4 Sagittal view of white matter pathways implicated in reading and language. arcuate fasciculus (blue); uncinate fasciculus (green); superior longitudinal fasciculus (orange); inferior fronto-occipital fasciculus (pink); and inferior longitudinal fasciculus (red). Note: this figure was previously published by author in an article titled "Associations between white matter asymmetry and communication skills in children with prenatal alcohol exposure" published in Drug and Alcohol Dependence.

1.6 Graph theory analysis

Graph theory analysis is a technique in network neuroscience that mathematically represents brain regions and the functional and/or structural connectivity between them as graphs (Bullmore & Sporns, 2009). Graphs consist of brain regions (nodes) and the connectivity between them (edges) and create a comprehensive map known as a connectome (Fornito, 2016). Graph theory has been used to map neural networks from the cellular levels of neurons and synapses to the

brain systems level. Characteristics of neural networks can be delineated from graph theory measures at both the local (i.e., between neighboring regions) and global (i.e., between all network regions) levels. Functional connectomes can be assessed using techniques such as functional magnetic resonance imaging (fMRI) and electroencephalography (EEG) (Abbott, 2016). Structural connectomes can be assessed using DWI (Fornito, 2016) (figure 1.5). This is done by preprocessing diffusion MRI images and parcellating the brain into predefined regions using an anatomical atlas (e.g., AAL 90). Then, a connectivity threshold is set to determine which regions are connected or not before a connectivity matrix representing the brain regions and their connectivity is made. The connectivity matrix can either be binary or weighted. Weighted connectivity matrices are created by defining a connectivity threshold based on a DTI metric (e.g., FA), where the weights of the edges that pass the threshold are equal to the mean FA of the streamlines connecting the nodes (Mehraram et al., 2020). Binary connectivity matrices binarize the relationship between regions where 1 indicates that two regions are connected while 0 indicates no connectivity between regions. Binary connectivity matrices do not consider the different strengths (i.e., weights) of connectivity between various regions of the network, while the weighted connectivity matrices show the variability in weighted connectivity in all edges of a network (Mehraram et al., 2020).

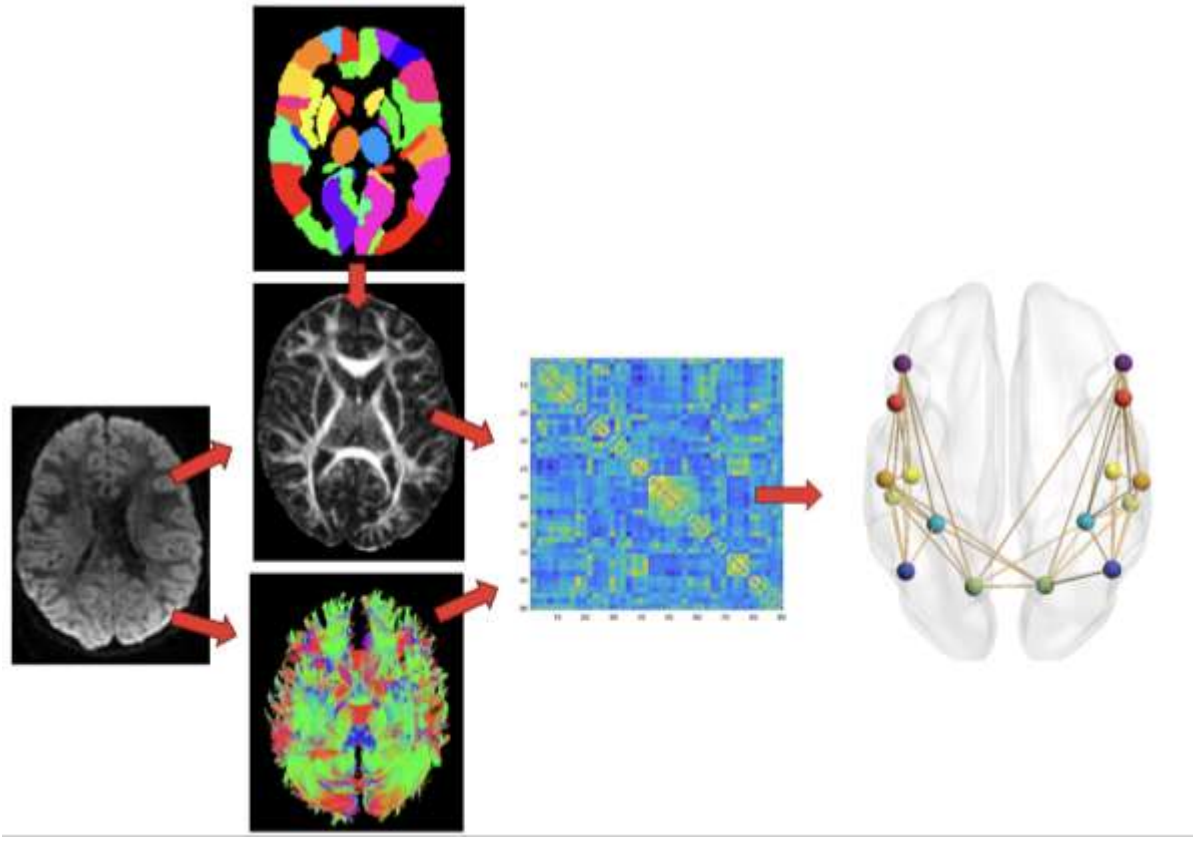

Figure 1.5 processes included in diffusion-based structural connectome. DWI scans are first preprocessed to generate whole brain tractography as well as FA maps. FA maps are then parcellated using a brain atlas to define brain regions. Following this, whole brain tractography and parcellated FA maps are combined and processed to generate a connectivity matrix, consisting of the parcellated brain regions (nodes) and the white matter fibers connecting them (edges). The connectivity matrix can then be used to delineate graph theory measures to infer the structural connectome properties.

1.6.1 Graph theory measures

Once the connectivity matrices are created, measures of network organization can be calculated to indirectly infer network properties such as clustering coefficient, nodal degree, local efficiency, and global efficiency (Bullmore & Sporns, 2009; Fornito, 2016). Clustering

coefficient is the density of connectivity between nodes and is a measure of local properties. Nodal degree is a measure of global network connectivity and refers to how many connections (edges) project to/from each region (node). Local efficiency is a measure of how efficient the transfer of information is between local neighboring nodes. Global efficiency measures the integration of information globally across the network and measures the efficiency of the transfer of information between two nodes. These measures have been used to better understand the brain architecture, look at the efficiency of information transfer between different brain regions, and examine the implications of lesions and damage to specific anatomical regions (Farahani et al., 2019).

1.6.2 Graph theory correlates of early reading and language abilities

Previous studies examining the neural correlates of language mainly focused on functional connectivity and on older, school-aged children and adolescents. In school-aged children, one study found the connectivity strength between central and peripheral nodes in the structural connectome of reading to be associated with reading efficiency and phonemic decoding, while local efficiency was found to be associated with phonemic decoding (Lou et al., 2021). They also examined rapid naming, however it was not associated with any graph theory measures (Lou et al., 2021). Moreover, another study found stronger academic performance is associated with overall better organization of white matter connectome (Bathelt et al., 2018). Nonetheless, the extent to which these network properties are present in preschool aged children and how they relate to emerging reading and language skills remains understudied.

1.7 Prenatal Alcohol Exposure (PAE)

Prenatal alcohol exposure (PAE) is the largest known cause of developmental disorders in Canada (Popova et al., 2017). Children with PAE can go on to develop a range of neurological, physiological, and behavioral challenges. These challenges may also meet the criteria for fetal alcohol spectrum disorder (FASD) diagnosis, the neurodevelopmental disorder associated with PAE (Pei et al., 2021).

1.7.1 PAE prevalence and social determinants of health

Alcohol consumption during pregnancy and the adverse risks associated with it are universal; however, some regions and populations are more impacted and tend to have high prevalence rates of PAE. The global prevalence of PAE is estimated to be around 10%, with countries such as Ireland, Belarus, and South Africa having some of the highest rates of reported alcohol consumption during pregnancy (Eisenstat et al., 2023). Meanwhile, countries with the lowest rates of PAE are in the eastern Mediterranean region, where alcohol consumption is generally not socially acceptable. Moreover, FASD prevalence rates also vary, as not all children with PAE go on to have an FASD diagnosis. In Canada, PAE prevalence rate is 10%, however, less than 4% of those with PAE meet the diagnostic criteria for FASD diagnosis (Cook et al., 2021). Countries with the highest rates of FASD include South Africa, Croatia, and Ireland (Eisenstat et al., 2023; Lange et al., 2017). South Africa, particularly the Western Cape region, reports the highest rates of FASD globally (Eisenstat et al., 2023). It is important to note that differences in diagnostic criteria for FASD in different countries may also account in part for the global prevalence differences as well as access to diagnosis.

Despite the increase in awareness about the adverse risks of alcohol exposure during pregnancy, PAE prevalence rates remain high. While the majority of people stop drinking alcohol once they become aware of their pregnancy, a significant number continue to consume alcohol. It is estimated that around 25% of pregnant individuals engage in binge drinking (Peltier et al., 2025). To better understand this, it is important to examine the social determinants of health of PAE and FASD. As opposed to the previous thinking, FASD is not completely preventable due to the various reasons why PAE occurs in the first place. In some cases, PAE occurs in unplanned pregnancies (May & Gossage, 2011). In other cases, PAE can be attributed to trauma and historical events. Intimate partner violence and domestic abuse are common risk factors for PAE (Flannigan et al., 2022). Additionally, Intergenerational trauma is one of the major social determinants of PAE and FASD (Flannigan et al., 2022). As mentioned, some communities report higher prevalence rates of PAE, and these communities have been historically marginalized and discriminated against, such as the Black population in South Africa as a result of apartheid, and Indigenous population in North America as a result of residential schools (Eisenstat et al., 2023). Although studying the biological mechanisms underlying the neurodevelopmental deficits associated with PAE is important, these social factors should be taken into consideration for a more comprehensive understanding of the issue.

1.7.2 Challenges in PAE research

Despite its high prevalence and known adverse effects, PAE remains relatively understudied for several reasons. The misconception that PAE is completely preventable has made PAE research a low priority. Other reasons include stigma surrounding alcohol consumption during pregnancy which leads to PAE being underreported in some communities, making it difficult to study, and

contributing to lack of understanding the etiology of the disorder (Eisenstat et al., 2023; Flannigan et al., 2022). Further, marginalized communities are often neglected in research, and have an increased risk of FASD. Another reason is the heterogeneity in the amount, frequency, and duration of exposure which can influence the adverse neurological and behavioral effects (Eisenstat et al., 2023). Additionally, many children with PAE studied in North America are in adoptive or foster care; therefore, much of their confounding early environment information is not available. Moreover, many of the children with PAE have postnatal adverse childhood experiences, making it difficult to distinguish between the prenatal and postnatal effects (Eisenstat et al., 2023; Flannigan et al., 2022). PAE is also highly comorbid with several neurodevelopmental disorders, including attention deficit hyperactivity disorder and learning disabilities, adding more challenges in studying the direct effects of PAE on behavior and cognition as it is difficult to distinguish whether the comorbid conditions are caused by PAE, or if they would have occurred in the absence of PAE due to genetic and/or other environmental factors. Furthermore, prenatal polysubstance abuse is common, and alcohol is often not the only teratogen the fetus is exposed to. Other substances such as tobacco, cocaine, and cannabis are frequently used, which further adds to the challenges of studying PAE (Popova et al., 2023). Nevertheless, despite these challenges, it is important to continue investigating PAE to provide a better understanding of its teratogenic effects and examining early interventions to address these effects.

1.7.3 Biological mechanisms of PAE

PAE can cause aberrant brain development through a variety of biological mechanisms that impact a range of neurodevelopmental and cognitive outcomes. Alcohol can cross the placenta,

where it then hinders the development of glial and neural stem cells and impairs regular cellular mechanisms such as cell proliferation and differentiation that are essential for neurodevelopment (Caputo et al., 2016; Goodlett & Horn, 2001; Veazey et al., 2013). Evidence from animal studies shows that PAE in prenatal mice hinders neural tube formation and causing craniofacial dysmorphologies in mice during the first trimester, as well as abnormal neurogenesis, gliogenesis, synaptogenesis, cell migration, angiogenesis, and myelination (Almeida et al., 2020; Godin et al., 2011; Veazey et al., 2013). Furthermore, whole brain network organization is significantly altered in rats exposed to alcohol prenatally (Tang et al., 2020).

In human children, PAE is associated with a range of structural and functional neurological deficits, including brain volume reductions, and atypical connectivity between brain regions (Fan et al., 2016; Gautam et al., 2015; Lebel et al., 2011; Nardelli et al., 2011). These alterations have been observed early in utero (Stuempflen et al., 2023). It is worth noting that these developmental alterations likely vary with the amount of alcohol consumed and the timing of exposure, and these alterations have been observed even with low amounts of PAE (Long & Lebel, 2022).

1.7.4 Early language and reading skills in children with PAE

Language and reading difficulties are common amongst individuals with PAE (Glass et al., 2017; Glass et al., 2015; McGee et al., 2009; Wyper & Rasmussen, 2011), and communication is one of the key neurobehavioral domains assessed for FASD diagnosis. Studies have shown that children with PAE perform worse on phonological awareness (Adnams et al., 2007; Glass et al., 2015), reading comprehension (Lindinger et al., 2022), and expressive and receptive language assessments (Hendricks et al., 2019; Wyper & Rasmussen, 2011) than children without exposure.

However, other studies report no differences in expressive and receptive language (Hendricks et al., 2020). These mixed findings likely reflect the heterogeneity of PAE and how its effects on language and reading can differ between individuals, possibly due to other social and environmental factors (Flannigan et al., 2022; Mantha et al., 2013; McLachlan et al., 2017). Nevertheless, early language skills and impairments in toddlers and pre-school aged children with PAE remain to be fully defined, and further research is required.

1.7.5 White matter correlates of language and reading abilities in PAE

Alterations have been found in brain pathways associated with language and reading processing in children with PAE (Fan et al., 2016; Ghazi Sherbaf et al., 2019; Gomez et al., 2022; Kar et al., 2021; Lebel et al., 2008; Roos et al., 2021), but very few studies have directly examined the associations between brain structure and reading performance. One study found significant correlations between superior fronto-occipital fasciculus MD values and both reading and receptive vocabulary scores in school-aged children with FASD (Treit et al., 2013). A more recent study by Yu et al. (2022) found significant associations between reading performance and the FA of both the superior and inferior longitudinal fasciculus. They also found significant differences between adolescents with and without FASD in the association between the inferior longitudinal fasciculus degree of lateralization and phonemic decoding performance. However, some studies found nominally significant associations between white matter language pathways and pre-reading and communication skills in children with PAE (Ostertag et al., 2023; Scholten et al., 2024).

1.7.6 Structural connectome studies in individual with PAE

The effects of PAE on the structural connectome remain to be fully understood, and only two studies prior to this thesis have explored the structural connectome in children with PAE. One study in neonates found no significant differences between PAE and unexposed groups at the global level; while at the regional level, neonates with PAE had lower connectivity in parietal regions and higher connectivity in frontal, occipital, and temporal regions compared unexposed neonates (Roos et al., 2021). In another study, Long et al. (2020) found an overall decrease in structural connectivity, particularly in the attention, somatomotor, and default-mode networks in children and adolescents with PAE compared to an unexposed group. Children with PAE also had significantly different graph theory network metrics compared to unexposed children at both global and local level. Decreased connectivity in individuals with PAE may play a role in the behavioral and cognitive deficits observed in children with PAE. Nevertheless, the extent to which these structural connectivity alterations play a role in pre-reading abilities and early language skills remain to be fully understood. Studying the brain's structural connectivity correlates of early language skills from an early age in children with and without PAE can provide additional insight into the roots of reading abilities in the developing brain.

1.8 Thesis Rationale

This thesis aimed to provide a comprehensive understanding of the structural brain connectivity and the roots of reading abilities in the developing brain, with implications for the identification of and early intervention for reading and language disabilities. Prior work has shown that the structural neural correlates of early language skills (e.g., pre-reading skills) are strong predictors

of future reading ability. However, these studies have mostly focused on older, school aged, typically developing children. Additionally, the extent to which PAE alters these associations remains underexamined. Moreover, most of these studies were conducted in regions with high income such as North America, while little research has been done in low-income countries with high PAE prevalence.

In this thesis, we aimed to address these gaps in the literature and to identify how the developing brain's structural connectivity is associated with language skills from an early age. Additionally, it contributes insight into the language deficits commonly seen in children with PAE and how their brain networks supporting reading and language may differ from children without PAE. Research studies examining structural brain connectivity and early language skills in preschool aged children with PAE are scarce, and in this thesis, we aimed to help determine how PAE moderates these associations during this critical learning period. This is significant given that PAE is one of the most prevalent yet understudied causes of neurodevelopmental disorders in Canada (i.e., FASD) and is characterized by a variety of cognitive, behavioral, and emotional difficulties, including reading and language deficits. It is also associated with high incarceration and substance abuse rates in the population.

Moreover, identifying early markers and sensitive periods of brain and language development can guide early interventions to enhance reading and language abilities of children with language and reading problems (including children with PAE) during these periods, where possible. Early recognition and treatment are important since childhood reading and language deficits are associated with unsatisfactory academic achievement and poor mental health. Furthermore, most studies investigating the neural correlates of reading and language in PAE largely come from Western countries. This thesis integrates data collected in both Calgary and South Africa,

providing more robustness and diversity and supporting the international relevance of this work. Taking all of this into account, the findings of this thesis will significantly contribute to understanding the processes of early language development and structural connectivity during a crucial learning period, as well as how PAE might influence and disrupt these processes, using datasets collected in two countries and consequently lay the groundwork for early diagnosis and interventions for reading and language deficits.

The thesis has **3 key aims**:

1. Characterize how structural brain network properties are associated with pre-reading language measures, specifically phonological awareness and naming speed, in young children (2-6 years).
2. Determine how PAE moderates the associations of structural network connectivity with pre-reading language measures in early childhood (2-6 years).
3. Determine how PAE moderates the associations of structural language network connectivity with receptive and expressive communication skills in children at ages 2-3 years.

Based on previous studies, we **hypothesized** that:

1. Increased structural connectivity would be associated with better pre-reading skills in young children.
2. PAE negatively moderates the associations between structural network connectivity and pre-reading skills such that associations between connectivity and pre-reading skills will be weaker in the PAE group.

3. PAE negatively moderates the associations of structural network properties with receptive and expressive communication skills such that associations will be weaker in the PAE group.

Chapter 2: Structural neural connectivity correlates with pre-reading abilities in preschool children

2.1 Abstract

Pre-reading abilities are predictive of later reading ability and can be assessed before reading begins. However, the neural correlates of pre-reading abilities in young children are not fully understood. To address this, we examined 246 datasets collected in an accelerated longitudinal design from 81 children aged 2–6 years (age = 4.6 ± 0.98 years, 47 males). Children completed pre-reading assessments (NEPSY-II Phonological Processing and Speeded Naming) and underwent a diffusion magnetic resonance imaging (MRI) scan to assess white matter connectivity. We defined a core neural network of reading and language regions based on prior literature, and structural connections within this network were assessed using graph theory analysis. Linear mixed models accounting for repeated measures were used to test associations between children's pre-reading performance and graph theory measures for the whole bilateral reading network and each hemisphere separately. Phonological Processing scores were positively associated with global efficiency, local efficiency, and clustering coefficient in the bilateral and right hemisphere networks, as well as local efficiency and clustering coefficient in the left hemisphere network. Our findings provide further evidence that structural neural correlates of Phonological Processing emerge in early childhood, before and during early reading instruction.

2.2 Background

Reading disorders affect approximately 10% of children and account for almost 80% of known learning disorders (Kohli et al., 2018). These disorders include deficits in comprehension, fluency, and phonological deficits (Elliott and Grigorenko, 2014). Most reading disorders go undiagnosed until children have been struggling in school for years, which can have a substantial impact on their lives. Early recognition and diagnosis are important for early intervention. However, reading develops early, and pre-reading skills begin to emerge early in development and are strong predictors of future reading performance (Gabrieli, 2009). Phonological awareness and rapid automatized naming (RAN) are two key pre-reading skills (Eden and Flowers, 2009, Vander Stappen and Reybroeck, 2018). Phonological awareness includes sound knowledge at the phoneme level and the manipulation of phonemes by segmenting or combining phonemes and words (Chard and Dickson, 1999). Phonological awareness skills in children as young as 3 years old predict future reading performance (Kibby et al., 2014, Lafrance and Gottardo, 2005, Nelson et al., 2012). RAN (also called naming speed) encompasses processing speed and phonological access/retrieval abilities and can be assessed based on the ability to rapidly identify objects, colors, letters, and/or numbers (Vander Stappen and Reybroeck, 2018, Wolf and Bowers, 1999). Individuals with poor reading skills tend to perform worse at RAN than skilled readers (Eden and Flowers, 2009, Elliott and Grigorenko, 2014). Both phonological awareness and RAN are great indicators of future reading ability, however, phonological awareness tends to be a better predictor during the preschool and early school years, whereas RAN emerges as a stronger predictor later in childhood as children become more proficient at reading (Cohen et al., 2018, Kirby et al., 2003, Taibah and Haynes, 2011). This shift likely reflects a transition from relying on phonemic decoding to fluent sight-word recognition as

children progress in reading. The relative importance of these predictors may also interact with other factors such as socioeconomic status (Romeo et al., 2022).

Reading involves the recruitment of several brain regions with distinct functions that communicate with each other, thereby forming a brain network (Wilcox et al., 2022). Multiple functional and structural neuroimaging studies have revealed a largely left-lateralized reading network involving the inferior frontal/precentral gyri, superior temporal gyrus/sulcus, temporo-parietal cortex, and occipito-temporal cortex (Wilcox et al., 2022). The inferior frontal gyrus (including Broca's area) is involved in working memory, phonological processing, and phonemic integration, and the inferior frontal and precentral gyri are involved in motor planning and articulation. The superior temporal gyrus (including the primary auditory cortex (Heschl's Gyrus) and Wernicke's area) plays an important role in phonological retrieval and semantic processing. Adjacent temporo-parietal cortex regions (including the angular and supramarginal gyri) are important for integrating the audiovisual inputs of reading for decoding print (Martin et al., 2015, Wilcox et al., 2022). The occitpito-temporal cortex (including fusiform, lingual, and inferior temporal gyri) is associated with the visual component of reading and is important for rapid word recognition, fluency, and orthographic processing. Activation in these regions has been consistently shown to be associated with reading in adults and even young children and emerging readers (Benischek et al., 2020, Houdé et al., 2010, Martin et al., 2015). Moreover, these regions have been shown to be sensitive to changes in response to reading interventions in children with reading disorders (Perdue et al., 2022).

Studying the brain's structural connections (i.e., white matter) and how they relate to early pre-reading skills in young children has already helped provide an understanding of the processes underlying reading development by highlighting microstructural properties and brain

connections that underlie reading, as well as identifying atypical patterns of connectivity between regions that are associated with reading difficulties (Ben-Shachar et al., 2007, Perdue et al., 2022). This line of research complements functional connectivity studies, which have shown how synchronized dynamic activation of brain regions correlates with reading performance (Martin et al., 2015). Prior studies consistently show positive associations between phonological awareness and white matter fractional anisotropy values in language and reading pathways including the arcuate, uncinate, and inferior fronto-occipital fasciculi in children (Keller and Just, 2009, Reynolds et al., 2019, Saygin et al., 2013, Walton et al., 2018), as well as negative associations with mean diffusivity values (Reynolds et al., 2019, Walton et al., 2018). These associations are consistent with findings in adult studies (Vandermosten et al., 2012, Welcome and Joanisse, 2014). Recent studies also suggest widespread relationships between white matter structure and phonological awareness, along with more limited relationships between white matter and reading, thus providing additional support for using pre-reading skills as a target for investigating the brain-behavior relationships that underly reading (Koirala et al., 2021).

In addition to studying white matter microstructure in relation to pre-reading skills, characteristics of structural brain networks can be quantified. Graph theory analysis mathematically represents brain regions and the functional and/or structural connectivity between them as graphs (Bullmore and Sporns, 2009). Characteristics of neural networks can then be delineated from graph theory measures at both the local (i.e., between neighboring regions) and global (i.e., between all network regions) levels. Studying these connectivity measures using graph theory is useful for quantifying network properties and gaining insight into the complexity of brain organization. Additionally, as opposed to studying individual regions or pathways, connectome-based studies can provide additional information by looking at the

network as a whole, which may be more sensitive to changes that can't be seen by studying isolated individual regions and pathways.

Brain networks have provided useful information about the neural correlates of reading in older children and adolescents, but brain networks and pre-reading skills have not been well-studied in younger children. School-aged children with reading difficulties have decreased functional global and local efficiency in the whole brain compared to typical readers (Vourkas et al., 2011). School-aged children with reading difficulties also show abnormally high global efficiency in the right hemisphere and lower clustering in left hemisphere fronto-temporal language regions compared to typical readers, indicating a higher reliance on bilateral networks and reduced efficiency in the typical left-lateralized reading network (Mao et al., 2021). Moreover, a longitudinal study showed that higher correlations between functional connectivity and phonological awareness in young children predicted later reading performance (Yu et al., 2018). A recent study examining functional connectivity in both Chinese adults and school-aged children found that adults had increased functional connectivity in semantic-visual processing regions (I.e., inferior occipital cortex) and lower functional connectivity in phonological awareness processing regions (I.e., inferior frontal and superior temporal gyri) compared to children (Zhou et al., 2021). These findings suggest a shift in the brain from reliance more on phonological processing regions at younger ages to semantic-visual processing regions at older ages (Zhou et al., 2021). In pre-school children (in a sample overlapping the one used here), pre-reading performance was associated with stronger functional connectivity between key reading brain regions including the angular gyrus as well as Broca's and Wernicke's areas, suggesting that functional brain connectivity correlates of pre-reading skills are apparent even before formal

reading instruction begins (Benischek et al., 2020). This evidence linking functional connectivity and pre-reading abilities motivates investigation of the underlying structural networks.

In school-aged children, Lou et al. (2021) found the structural connectivity strength between central and peripheral nodes in the structural connectome of reading regions (e.g., inferior frontal and occipital, middle and superior temporal, supramarginal, precentral, and Heschl's gyri) was associated with reading efficiency and phonemic decoding, while local efficiency was associated with phonemic decoding. They also found no associations of RAN with any graph theory measures (Lou et al., 2021). Another study in school-aged children found stronger academic performance associated with overall better organization of the white matter connectome (Bathelt et al., 2018). These studies show that structural network properties underlie reading in older children, but the extent to which these network properties are present in early childhood and how they relate to emerging reading skills is unclear.

In this study, we investigated how the brain's structural reading network properties, modeled with graph theory, were associated with pre-reading abilities (phonological awareness and RAN) using an accelerated longitudinal design in a large cohort of children aged 2-6 years. We hypothesized that stronger structural connectivity in the language network would be associated with better pre-reading skills. Studying these associations in this early period of development addresses current gaps in the literature in this age period and contributes to the existing body of work linking reading and brain structure in older children and adults. Moreover, studying these language measures and brain development at an early stage may lay the foundation for future work examining early interventions for reading deficits.

2.3 Methods

2.3.1 Participants and pre-reading assessments

A total of 246 datasets collected using an accelerated longitudinal design were included in the analysis; these were from 81 children aged 3.0–6.9 years (47 males/34 females) were included in the analysis. Participants were recruited from the Alberta Pregnancy Outcomes and Nutrition (APrON) study, and from the Calgary community. The average age at the time of scan was 4.6 ± 0.98 years (table 2.1). The dataset included 29 participants with one scan only, 9 with 2 scans, and 43 with ≥ 3 scans (figure 2.1). All participants were born at ≥ 35 weeks' gestation, spoke English as their primary language, and had no diagnosed genetic disorders, intellectual impairments, motor disorders, developmental disorders, or brain injuries. Participants were within the age range of early pre-reading (3–6 years), however, reading abilities were not assessed for this study, and so children were not necessarily all pre-readers. The study was approved by the University of Calgary's Conjoint Health Research Ethics Board (REB13–0020). Written consent was obtained from each child's legal guardian and verbal assent was obtained from the children.

Table 2.1 Participants demographics and pre-reading scores.

Participant demographics	**Overall** **N = 81**
Sex	Males (47)
Ethnicity	White (85.2%)
Household Income (per year)	> $100,000 CAD (72.8%)

Total dataset	**N = 246**
Age (years)	
Mean (SD)	4.6 (0.98)
Median [Min, Max]	4.4 [3.0, 6.9]
Phonological Processing (PP) Standard Score	
Mean (SD)	11.5 (2.91)
Median [Min, Max]	12.0 [1.0, 18.0]
Speeded Naming (SN) Scaled Score	
Mean (SD)	11.9 (2.76)
Median [Min, Max]	12.0 [4.0, 19.0]

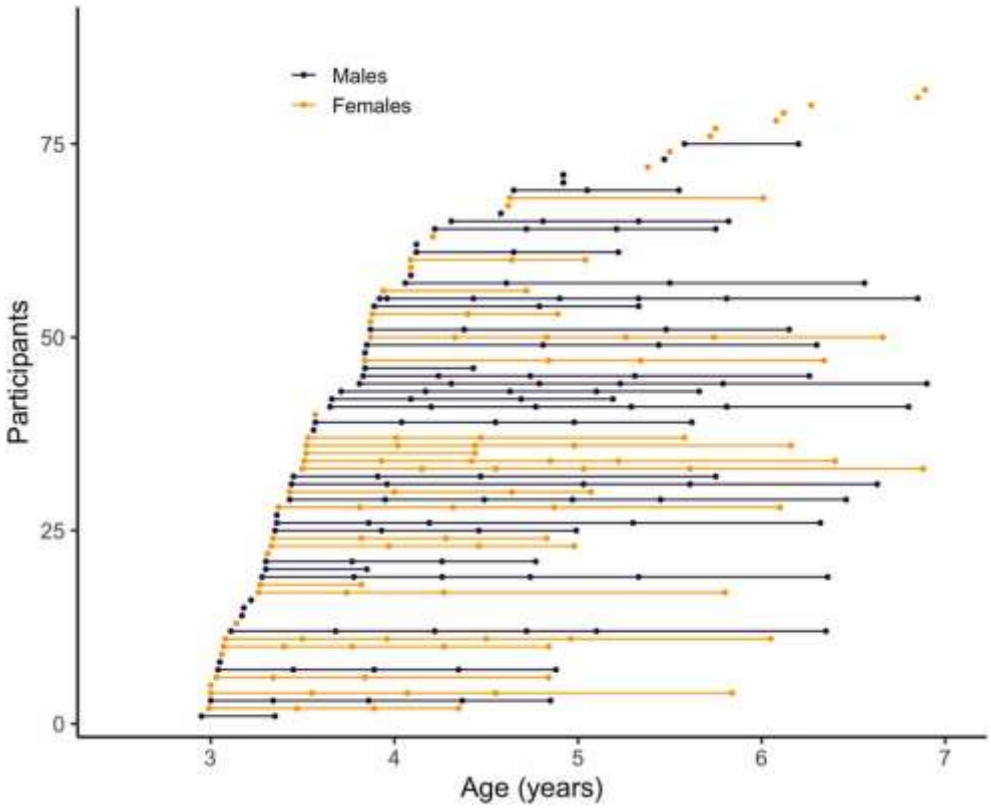

Figure 2.1 Distribution of participant ages at each study visit (n = 246, females are shown in orange and males in purple). Each participant (n = 81) is represented in a row and each circle represents one study visit.

Pre-reading skills were assessed at each visit using the age-normed Phonological Processing (PP) and Speeded Naming (SN) subtests from the Developmental Neuropsychological Assessment-Second Edition (NEPSY-II; Korkman et al., 2007). The PP subtest is used to assess children's ability to segment and manipulate phonemes and words; the SN subtest is used to assess children's ability to rapidly identify pictured shapes and colors. Each assessment took approximately 5–10 minutes to complete depending on the child's abilities, and were mostly acquired on the same day as the scan, but always within two weeks.

2.3.2 Image acquisition and preprocessing

Children underwent a diffusion MRI scan on the same research-dedicated General Electric 3 T MR750w system with a 32-channel head coil at the Alberta Children's Hospital in Calgary, Canada. Diffusion tensor imaging (DTI) data were acquired using single shot spin echo echo-planar imaging sequence of 1.6 × 1.6 × 2.2 mm resolution (resampled to 0.78 × 0.78 × 2.2 mm on scanner), TR = 6750 ms; TE = 79 ms, 30 gradient encoding directions at b = 750 s/mm2, and 5 images at b = 0 s/mm2, scan time 4:03 min (See Reynolds et al., 2020 for further details).

DTI images were preprocessed using ExploreDTI (Leemans, 2009). Raw DICOM images were converted to NIFTI format, and b-matrices were generated. Preprocessing steps included flip/permute images, correction for signal drift, Gibbs ringing correction, head motion correction, and correction for eddy current distortions. Diffusion tensor was calculated to extract fractional anisotropy (FA) values, and whole brain tractography was performed with seedpoint resolution = 2 × 2 × 2 mm3, seed FA threshold = 0.15, fiber length range = 50–500 mm, angle threshold = 30°, step size = 1.

2.3.3 Graph theory analysis

To create structural DTI-based connectomes, the Automated Anatomical Labeling atlas (AAL; Tzourio-Mazoyer et al., 2002) was used to parcellate the brain into 90 regions, excluding the cerebellum. AAL gray matter regions were dilated by 3 mm to ensure white matter tracts could reach the AAL regions using FSL (Jenkinson et al., 2012), and whole brain tractography was used to generate connectivity matrices of the brain regions of interest in ExploreDTI (Leemans et al., 2009). Each connection was weighted by the average FA values within the connected fiber

tracts. The brain regions parcellated from the AAL 90 represents the nodes of the graph while the average FA values of the tracts connecting the nodes represent the edges.

We selected a specific network of brain regions that have been consistently shown to be associated with language and reading (Hertrich et al., 2020, Martin et al., 2015, Turker et al., 2019) for analysis: opercular part of the inferior frontal gyrus, the triangular part of the inferior frontal gyrus, the lingual gyrus, the fusiform gyrus, the angular gyrus, Heschl's gyrus, the superior temporal gyrus, and the inferior temporal gyrus (figure 2.2). The connectivity matrix of those regions was extracted from the whole brain matrix and the following analyses were conducted.

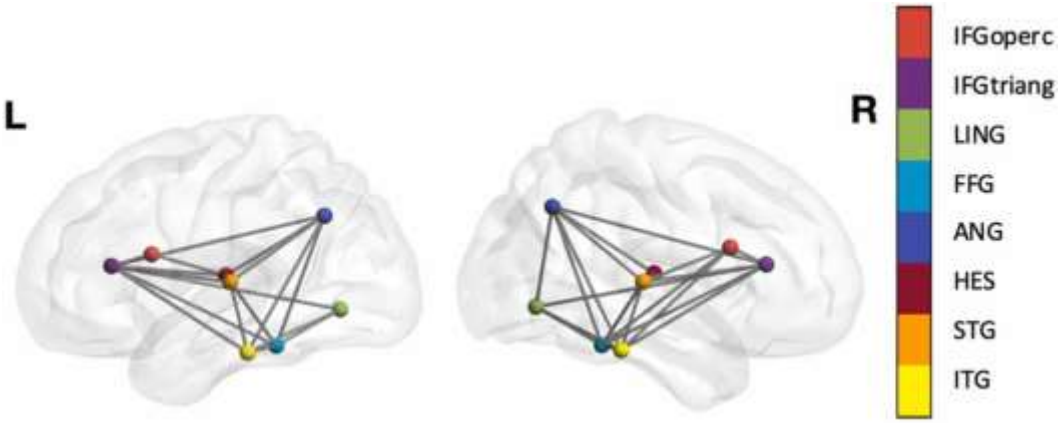

Figure 2.2 16 Regions of interest (8 from each hemisphere) in the network: opercular part of the inferior frontal gyrus (IFGoperc), the triangular part of the inferior frontal gyrus (IFGtriang), the lingual gyrus (LING), the fusiform gyrus (FFG), the angular gyrus (ANG), Heschl's gyrus (HES), the superior temporal gyrus (STG), and the inferior temporal gyrus (ITG). Networks were visualized using BrainNet Viewer (Xia et al., 2013).

Graph theory measures of network connectivity (local efficiency, global efficiency, clustering coefficient, and nodal degree) were calculated using the Brain Connectivity Toolbox (Rubinov and Sporns, 2010). These measures were selected given their relationship with reading skills in older children (Mao et al., 2021, Vourkas et al., 2011). Global efficiency measures how efficient the transfer of information is across the whole network. Local efficiency measures how efficient the transfer of information is between local neighboring nodes. In the context of white matter connectomes, efficiency refers to the connections between gray matter regions through their white matter pathways, where higher efficiency refers to shorter distances (edges) between brain regions (nodes) and therefore higher integration of information and communication across the network. The clustering coefficient is the density of connections between regions and is a measure of functional specialization within regions. Nodal degree is the number of connections (edges) projecting to/from each region. Metrics were calculated from the bilateral networks (16 ×16 matrix), and left and right networks (8 ×8 matrix), given the evidence of bilateral and right hemisphere contributions to reading and language processing early in development (Benischek et al., 2020, Reynolds et al., 2019), and the well-established importance of the left hemisphere for reading throughout life.

2.3.4 Statistical analysis

Statistical analysis was conducted in R (R Core Team, 2021). To account for varying number of scans by participants, linear mixed-effect models were used to test associations between pre-reading scores and graph theory measures with participant included as a random factor with the equation: pre-reading score ~ graphic metric + age + sex + graphic metric*age + [1|Subject]. Graph theory metrics, age, sex, and the interaction between age and graph theory measures were

fixed effects in the model, and subjects were included as a random effect to account for repeated measures. Maximum likelihood estimation was used. Separate models were used to test each graph theory metric from each network (bilateral, left, and right). False discovery rate correction (FDR) at $q < 0.05$ was used to correct for 24 multiple comparisons (2 pre-reading assessments x 4 graph theory metrics x 3 brain networks = 24).

2.4. Results

2.4.1. Pre-reading assessments

2.4.1.1 Phonological processing

Mixed effect analysis showed Phonological Processing (PP) scores were significantly associated with average global efficiency (b= 88.6, p = 0.007, q= 0.028), local efficiency (b= 160.27, p = 0.002, q= 0.024), and clustering coefficient (b= 95.06, p = 0.013 q= 0.045), in the bilateral network and right hemisphere network (b= 71.13, p = 0.015, q= 0.045; b= 126.30, p = 0.004, q= 0.028; b= 88.51, p = 0.002, q= 0.024, respectively), as well as average local efficiency (b=136.56, p = 0.005, q= 0.028) and clustering coefficient (b= 95.65, p = 0.006, q= 0.028, respectively) in the left hemisphere network (table 2.2). All associations survived FDR correction for multiple comparisons.

Table 2.2 Associations between graph theory measures and Phonological Processing.

	Graph Theory Metric			**Graph Theory Metric X Age**		
Bilateral Network						
	Beta (CI)	t_{239}	*p-value*	*Beta (CI)*	t_{239}	*p-value*
Global Efficiency	88.6 (25.0, 152.2)	2.74	**0.007** **q= 0.028**	-20.1 (−33.9, −6.3)	-2.87	**0.004**

Local Efficiency	160.3 (57.2, 263.4)	3.06	**0.002** **q= 0.024**	-34.2 (56.4, −12.0)	-3.04	**0.003**
Clustering Coefficient	95.1 (20.0, 170.1)	2.5	**0.013** **q= 0.045**	-20.7 (−37.2, −4.2)	-2.48	**0.014**
Nodal Degree	1.5 (−0.3, 3.3)	1.68	0.095	-0.3 (−0.7, 0.1)	-1.73	0.085
Left Network						
	Beta (CI)	t_{239}	*p-value*	*Beta (CI)*	t_{239}	*p-value*
Global Efficiency	60.1 (−2.75, 122.86)	1.88	0.061	-13.9 (−27.5, −0.3)	-2.01	**0.045**
Local Efficiency	136.6 (41.5, 231.7)	2.83	**0.005** **q= 0.028**	-32.3 (−52.7, −11.9)	-3.12	**0.002**
Clustering Coefficient	95.7 (28.2, 163.2)	2.79	**0.006** **q= 0.028**	-22.8 (−37.0, −8.7)	-3.17	**0.002**
Nodal Degree	0.5 (−1.9, 2.9)	0.43	0.666	-0.1 (−0.7, 0.4)	-0.48	0.635
Right Network						
	Beta (CI)	t_{239}	*p-value*	*Beta (CI)*	t_{239}	*p-value*
Global Efficiency	71.1 (14.1, 128.2)	2.46	**0.015** **q= 0.045**	-12.4 (−24.7, −0.2)	-2.00	**0.046**
Local Efficiency	126.3 (40.9, 211.8)	2.91	**0.004** **q= 0.028**	-24.3 (−42.2, −6.5)	-2.69	**0.008**
Clustering Coefficient	88.5 (33.0, 144.0)	3.14	**0.002** **q= 0.024**	-19.4 (−31.4, −7.4)	-3.18	**0.002**

Nodal Degree	1.7 (−0.7, 4.0)	1.39	0.167	-0.3 (−0.8, 0.3)	-0.96	0.340

The age-by-graph theory metric interactions were significant for global efficiency ($p = 0.004$), local efficiency ($p = 0.003$), and clustering coefficient ($p = 0.014$) in the bilateral network as well the left ($p = 0.045$, $p = 0.002$, $p = 0.002$, respectively), and right hemisphere ($p = 0.046$, $p = 0.008$, $p = 0.002$, respectively) networks.

In order to visualize the age-by-graph theory metric interactions found with PP, we split the data by the median age (4.44 y) and observed that younger children displayed a more positive relationship between PP and graph theory metrics than older children (figure 2.3).

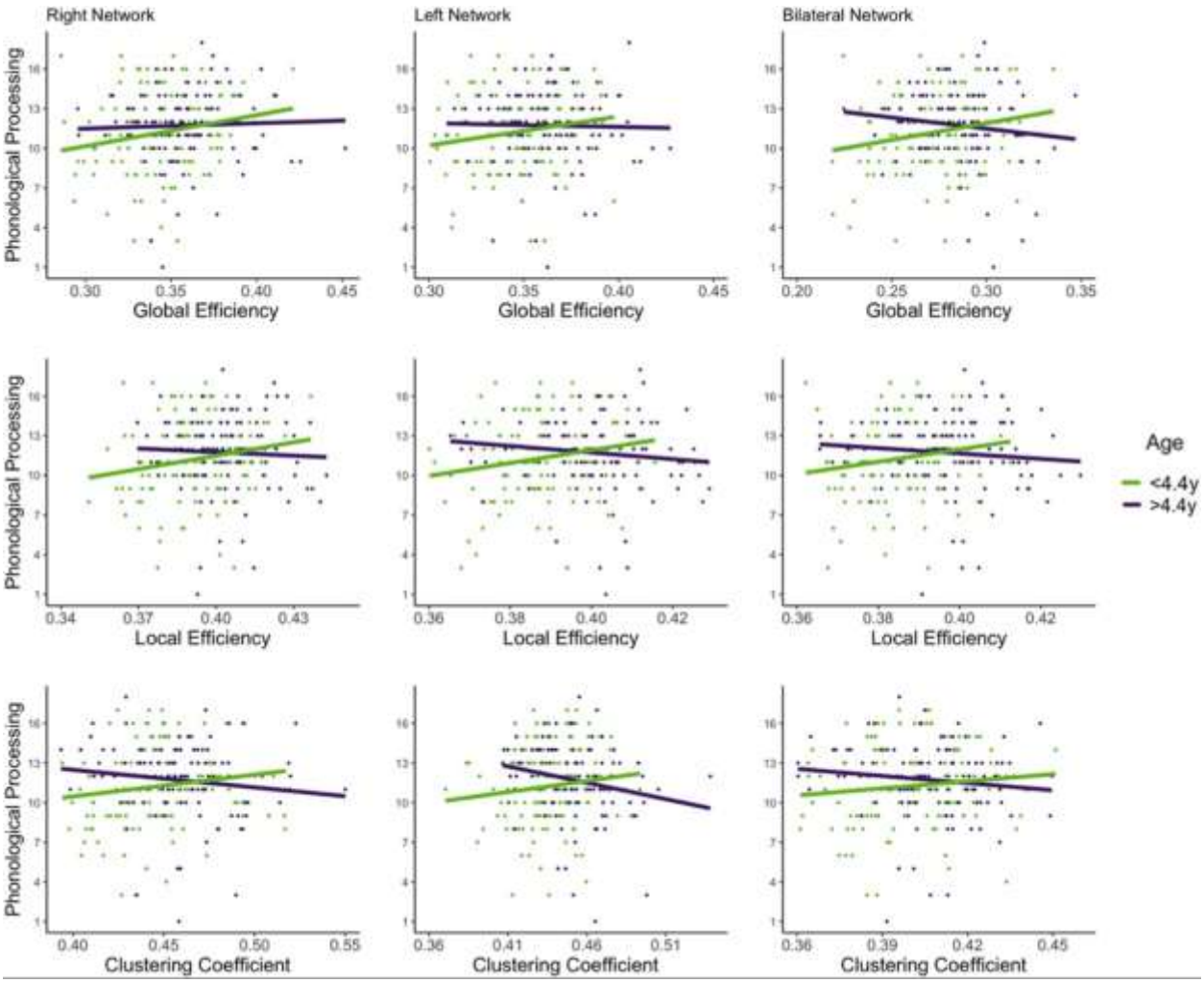

Figure 2.3 To visualize the significant age-by-graph theory metric interactions for Phonological Processing, we used a median split at age 4.4 years. This figure shows phonological processing-brain interactions for: global efficiency (top row), local efficiency (middle row), and clustering coefficient (bottom row) in each hemisphere (first and second columns) and bilaterally (third column) by age group. Age groups were split at the median (4.4 years) with older children shown in purple and younger children shown in green. In all cases, the relationship was stronger in younger children than older children.

2.4.1.2. Speeded naming

No significant associations were found between Speeded Naming (SN) scores and graph theory metrics in any of the networks (all $p > .2$) (table 2.3).

Table 2.3 Associations between graph theory measures and Speeded Naming.

	Graph Theory Metric			**Graph Theory Metric X Age**		
Bilateral Network						
	Beta (CI)	t_{239}	*p-value*	*Beta (CI)*	t_{239}	*p-value*
Global Efficiency	-13.5 (−76.3, 49.4)	-0.42	0.674	3.6 (−10.3, 17.2)	0.52	0.604
Local Efficiency	46.4 (−56.0, 148.9)	0.89	0.373	-8.3 (−30.4, 13.8)	-0.74	0.461
Clustering Coefficient	33.3 (−40.7, 107.3)	0.89	0.376	5.8 (−22.1, 10.5)	-0.70	0.483
Nodal Degree	-0.8 (−2.5, 0.9)	-0.90	0.368	0.2 (−0.2, 0.6)	0.96	0.339
Left Network						
	Beta (CI)	t_{239}	*p-value*	*Beta (CI)*	t_{239}	*p-value*
Global Efficiency	36.0 (−25.5, 97.5)	1.15	0.250	-4.70 (−18.0, 8.6)	-0.70	0.487

Local Efficiency	60.7 (−33.5, 154.8)	1.27	0.206	-8.14 (−28.4, 12.1)	-0.79	0.429
Clustering Coefficient	34.7 (−31.6101.0)	1.03	0.303	-4.9 (−18.9,9.0)	-0.70	0.486
Nodal Degree	0.7 (−1.6, 3.0)	0.59	0.559	-0.1 (−0.6, 0.4)	-0.27	0.790
Right Network						
	Beta (CI)	t_{239}	*p-value*	*Beta (CI)*	t_{239}	*p-value*
Global Efficiency	15.3 (−41.0, 71.7)	0.54	0.592	-4.6 (−16.7, 7.4)	-0.76	0.450
Local Efficiency	36.9 (−47.4, 121.2)	0.86	0.389	-10.6 (−28.3, 7.1)	-1.18	0.239
Clustering Coefficient	24.2 (−31.1, 79.4)	0.86	0.389	-5.2 (−17.1, 6.8)	-0.85	0.398
Nodal Degree	-0.03 (−2.3, 2.3)	-0.02	0.983	-6.79e-03 (−0.5, 0.5)	-0.03	0.979

2.5 Discussion

Here, we show that structural connectome properties of the language network are associated with phonological awareness in children aged 2–6 years. Our findings extend previous studies of brain structure and reading in older children and show that these associations are present even in younger children before and during the early stages of formal reading instructions. This key pre-reading skill is positively associated with structural connectivity at both the global and local

levels in young children. Associations between brain metrics and phonological awareness were stronger in younger children, suggesting that these relationships may weaken slightly with age, although these associations were not significant. No significant associations with naming speed were found, though these associations may emerge in older children or in different networks, as the reading becomes more proficient.

Stronger structural connectivity, measured by higher global efficiency, local efficiency, and clustering coefficient in the reading network, was associated with better PP scores in preschool children, supporting our hypothesis. This shows that structural brain connectivity underlies emerging reading skills even before and during the earliest stages of formal reading instruction. Structural connectivity in individual white matter pathways is associated with pre-reading skills in young children (Saygin et al., 2013, Walton et al., 2018, Wang et al., 2021); our findings show that the organization of the reading network is also associated with phonological awareness. Our findings are in good agreement with previous studies in school-aged children showing higher structural network efficiency associated with better reading and academic performance (Bathelt et al., 2018, Lou et al., 2021). This also adds to previous findings in an overlapping sample showing better pre-reading abilities to be associated with stronger functional connectivity (Benischek et al., 2020). Thus, stronger functional and structural connectivity are associated with better phonological awareness performance. Pre-reading skills are predictors of future reading ability (Kibby et al., 2014), and network properties are altered in children with reading disabilities (Vourkas et al., 2011), and in response to reading intervention (Horowitz-Kraus et al., 2015, Richards et al., 2018). Together with our findings, this suggests that these network properties changes are evident even in young children, and altered structural network connectivity may also underlie future reading ability/disability.

PP scores were positively associated with structural connectivity properties in both hemispheres as well as the bilateral network. Language and reading processing in the brain are generally left-lateralized (Schlaggar and McCandliss, 2007), and while macrostructural lateralization is present even in young children, lateralization of microstructural and functional brain properties tends to increase across early childhood (Reynolds et al., 2019). Thus, our findings likely reflect reduced hemispheric specialization in early childhood, where both hemispheres are important for pre-reading skills. These findings are supported by functional studies showing associations in right hemisphere regions in young children (Benischek et al., 2020), as well as an age-related decrease in right hemisphere activation during language tasks across childhood (Holland et al., 2007, Olulade et al., 2020). More longitudinal data examining age-related changes in network connectivity and reading will help further understand the role of the right hemisphere in these skills as children mature.

Our findings from this large longitudinal sample of young children motivate graph theory structural connectivity as a plausible predictor of later reading outcomes, similar to prior findings using other brain metrics in longitudinal studies of early childhood. Longitudinal studies found increased brain activity correlated with reading fluency in school aged children (McNorgan et al., 2011; Ozernov-Palchik et al., 2023). Additionally, functional connectivity correlates of pre-reading skills (I.e., phonological processing) during the pre-reading period predicted later reading development (Jasińska et al., 2021; Yu et al., 2018). Similar positive trend associations between reading development in school aged children and white matter properties (Moulton et al., 2019, Vanderauwera et al., 2018) were found in longitudinal studies. Accordingly, our findings complement these studies and further demonstrate the emergence of these neural correlates and their prediction of pre-reading skills before and during the early stages of learning.

In future research, we will examine if the structural connectome of reading networks predicts future reading ability.

The associations between structural network properties and PP weakened with age; younger children had more positive associations between PP scores and graphic metrics than older children. The decreasing associations with age may be due to changes in reading network connectivity and specialization over the course of development. In general, the brain undergoes pruning and specialization that support cognitive processing, and these maturation/specialization processes have also been seen in brain connectivity (Battista et al., 2018). Our findings are consistent with prior studies showing that connectivity in phonology-related regions decreases with age, while connectivity in semantic and orthography-related regions increases with age, (Liu et al., 2018; Zhou et al., 2021). Preschool aged children rely more on decoding and phonological processing during the early stages of reading instruction and word recognition later (Hogan et al., 2005), which may manifest in these age-brain interactions.

Speeded Naming scores were not associated with structural network properties. This is interesting given that RAN is a predictor of future reading skills (Norton and Wolf, 2012). However, previous studies suggest that phonological awareness is a better predictor of reading ability early, while naming speed becomes a stronger predictor later (Cohen et al., 2018, Kirby et al., 2003, Taibah and Haynes, 2011). This likely reflects the shift from children relying on phonemic decoding of words letter by letter, to rapidly recalling words as they become proficient readers. Moreover, letter/number identification assessments of naming speed tend to be a better predictor of reading than the object identification assessments that our sample have completed (Araújo et al., 2015). Another explanation for these results is that naming speed may involve

additional regions not reflected in the network studied here and associations would only be evident in a more widespread network of brain areas.

Other factors that we were unable to assess may play a role in the relationships studied here. We did not directly assess reading skills in the children and thus cannot be certain that they are all "pre-readers". Moreover, in addition to having high-average scores, most participants had parents with high education and income, which are known to moderate brain-reading associations (Noble et al., 2006, Romeo et al., 2022). Future studies should explore these factors in the context of associations between brain connectivity and pre-reading skills in young children.

2.6 Conclusion

In conclusion, our large longitudinal dataset of young children shows associations between structural network connectivity and pre-reading skills that emerge before and during early formal reading instruction. This is important given that most reading disorders go undiagnosed until children have been struggling in school for years, which negatively impacts their academic performance and mental health. Thus, focus on early diagnosis and interventions for reading difficulties is necessary.

Chapter 3: The brain's structural connectivity and pre-reading abilities in young children with prenatal alcohol exposure

3.1 Abstract

Children with prenatal alcohol exposure (PAE) may develop a range of neurological and behavioral deficits, including reading and language disorders. Studying the brain's structural connectivity and its relationship to pre-reading/reading skills in young children with PAE can help understand the roots of reading deficits associated with PAE. 363 diffusion MRI scans from 135 children (114 scans from 53 children with PAE) were collected between ages 3–7 years. Children completed NEPSY-II Phonological Processing and Speeded Naming to assess pre-reading skills at each scan. Structural brain network properties were assessed in 16 regions from both hemispheres using graph theory. Linear mixed models were used to account for repeated measures within participants. Children with PAE had significantly lower pre-reading scores than unexposed children, and significantly lower graph theory metrics across bilateral reading networks. Moreover, PAE significantly moderated the associations between Phonological Processing and global efficiency and nodal degree in the bilateral and left hemisphere reading networks, such that children with PAE had stronger associations than unexposed controls. No significant associations were found for Speeded Naming. Our results suggest that brain alterations may underlie early pre-reading difficulties in children with PAE.

3.2 Background

Approximately 10 % of children are exposed to alcohol during pregnancy (Popova et al., 2023), which can cause aberrant brain development through a variety of biological mechanisms that impact neurodevelopmental and cognitive outcomes. Alcohol can cross the placenta and hinder the development of fetal glial and neural stem cells and impair regular cellular mechanisms such as cell proliferation and differentiation that are essential for neurodevelopment (Goodlett and Horn, 2001, Caputo et al., 2016, Veazey et al., 2013).

Evidence from animal studies shows that prenatal alcohol exposure (PAE) interferes with neural tube formation and causes craniofacial dysmorphologies in the first trimester. It also causes abnormal synapse formation, neuronal cell migration, angiogenesis, myelination, and growth restrictions in the second trimester, and affects neurogenesis, gliogenesis, and myelination in the third trimester (Godin et al., 2011, Almeida et al., 2020, Veazey et al., 2013). Furthermore, whole brain network organization is disrupted in rats prenatally exposed to ethanol (Tang et al., 2020).

In humans, PAE is associated with a range of neurological deficits revealed by brain imaging, including volume reductions and atypical connectivity (Fan et al., 2016, Gautam et al., 2015, Lebel et al., 2011, Nardelli et al., 2011). Alterations have been observed across different stages of development (Donald et al., 2015, Stuempflen et al., 2023), and even at low levels of PAE (Long and Lebel, 2022).

Individuals with PAE can develop cognitive, motor, and behavioral deficits that may impact their day-to-day activities (Mattson et al., 2019, Popova et al., 2017, Subramoney et al., 2018). The literature on language and reading disabilities in individuals with PAE is mixed. Several studies

have shown that children with PAE perform worse on measures of phonological awareness (Glass et al., 2015, Adnams et al., 2007), spelling (Glass et al., 2017), reading comprehension (Lindinger et al., 2022), and expressive and receptive language compared to controls (Hendricks et al., 2019, McGee et al., 2009, Wyper and Rasmussen, 2011). However, other studies show no impairments in phonological awareness (Lindinger et al., 2022) or expressive and receptive language (Hendricks et al., 2020). These discrepancies may reflect the heterogeneity of PAE, its variable effects on individual children, other social and environmental factors (Flannigan et al., 2022, Mantha et al., 2013, McLachlan et al., 2017), or characteristics of the control group. Nevertheless, further research is necessary to better understand early language skills and impairments in young children with PAE.

Studying the brain's structural connectivity in children with PAE and how that connectivity is associated with pre-reading and reading skills from an early age can provide insight into the neurological roots of reading disabilities in children with PAE. Graph theory analysis is a mathematical technique used to examine brain networks by representing the network components as nodes (brain regions) and edges (connections between regions) (Fornito, 2016, Bullmore and Sporns, 2009). Structural connectomes can be assessed using diffusion MRI techniques to measure connectivity. This is done by virtually reconstructing white matter pathways microstructure (i.e., edges) connecting the gray matter regions (i.e., nodes), and sometimes weighting them by connection strength (e.g., using fractional anisotropy (FA)) (Fornito, 2016).

Previous studies examining structural network connectivity have reported positive associations between reading/pre-reading performance and global efficiency in children and adults (Lou et al., 2021, Sihvonen et al., 2021). We recently reported that stronger structural reading network

connectivity was associated with phonological awareness in unexposed young children (Ghasoub et al., 2024). However, the extent to which these relationships are present in children at higher risk of reading difficulties, including children with PAE is not fully understood.

A handful of studies have investigated the functional brain connectomes of children with PAE. One study found abnormal functional clustering coefficient and global network efficiency in adolescents with fetal alcohol spectrum disorder (FASD; the neurodevelopmental disorder associated with PAE), who also scored lower on vocabulary assessments compared to typically developing adolescents (Rodriguez et al., 2021). Abnormally low functional global efficiency in school-aged children with FASD was observed in another study (Wozniak et al., 2013). A study examining the functional connectome of young children with PAE found no significant differences in graph theory measures; however, children with PAE had increasing intra-participant stability with age, while controls had increased inter-participant stability with age, suggesting altered development of brain networks in children with PAE (Long et al., 2019).

To our knowledge, only two studies have examined the structural connectome in children with PAE. A study in neonates found no significant differences at the global level, but neonates with PAE had lower connectivity in parietal regions and higher connectivity in frontal, occipital, and temporal regions compared to unexposed neonates (Roos et al., 2021). Another study found decreased structural connectivity overall, as well as in the attention, somatomotor, and default-mode networks in children and adolescents with PAE compared to an unexposed group (Long et al., 2020).

The extent to which these structural connectivity alterations may underlie pre-reading abilities and early language skills is not fully understood. Here, we aimed to characterize the structural

connectivity properties of the reading network in children with PAE, and determine how PAE moderates these associations, in young children (3–7 years).

3.3. Methods

3.3.1. Participants and pre-reading assessments

3.3.1.1. Children with PAE

114 datasets collected from 53 children with PAE (26 males, mean age 5.6 years) were included in this study (table 3.1). Of the 53 children, 16 had one scan only, 18 had two scans, and 19 had ≥3 scans. Children were recruited through Alberta Children's Services, caregiver support groups, and early intervention services. Children were born after 34 weeks gestation, spoke English as their primary language, and had no history of head injury, epilepsy, autism spectrum disorder (ASD), or other genetic or medical conditions associated with cognitive disabilities. Children with conditions such as attention deficit hyperactivity disorder (ADHD), learning disabilities, and other mental health diagnoses were included, as these are frequently observed in children with PAE. None of the children had an official FASD diagnosis given their age (FASD diagnoses in Alberta are typically given at age 7 years or older). PAE was confirmed through the child's welfare file and/or through interviews with caregivers, caseworkers, and family members. All children were in adoptive, foster, or kinship care. Further details about the sample can be accessed in Kar et al. (2021).

Table 3.1 Descriptive statistics of participants with and without PAE (total and matched). Chi-square tests were used for sex and household income, while linear mixed models were used to examine group differences for the remaining variables.

	PAE (n= 53; 114 datasets)	**Unexposed full sample (n= 82; 249 datasets)**	**Age-matched unexposed controls *(n= 60; 114 datasets)***	***P (PAE vs unexposed full sample)***	***P (PAE vs age-matched unexposed)***
Age across all scans (years; mean ± SD)	5.6 ± 1.0	4.6 ± 1.0	5.35 ± 0.908	**< 0.001***	0.112
Age range (years)	2.94–7.39	2.95–7.01	2.95, 7.01	-	-
Sex (males/females)	26/27	41/41	29/31	0.1236	0.2893
Household income (Median annual, CDN$)	$75,000-$99,999	≥ $150,000	≥ $150,000	**< 0.001***	**< 0.001***
Phonological Processing scaled scores (mean ± SD)	9.8 ± 3.0 (n= 98)	11.5 ± 2.9	11.7 ± 2.9	**0.002***	**0.001***
Speeded Naming scaled scores (mean ± SD)	10.6 ± 3.3 (n= 96)	11.8 ± 2.8	12.1± 2.7	**0.006***	**0.001***

3.3.1.2. Unexposed children

Control data consisted of 249 datasets collected from 82 children unexposed to alcohol (41 males, mean age 4.6 years) from Calgary, Alberta, Canada (table 3.1). Of the 82 control children, 30 had one scan only, 8 had two scans only, and 44 had ≥3 scans. Unexposed children were recruited from the Alberta Pregnancy Outcomes and Nutrition (APrON) study and from the Calgary community. Children were born ≥35 weeks gestation, spoke English as their primary language, and had no diagnosed learning disabilities, brain injury, or genetic or motor disorders.

3.3.1.2.1 Matched sample

There was a significant age difference between groups (~1 year different; $p < 0.001$), so we conducted an additional analysis where we matched a subgroup of 114 unexposed children with

the PAE group based on age and sex using the MatchIt package in R (Ho et al., 2011). The package matches each scan from the PAE group to the nearest age- and sex-matched unexposed control scan using the propensity scores difference. Additional information about how the package works can be found here (https://cran.r-project.org/web/packages/MatchIt/index.html).

3.3.1.3 Pre-reading assessment measures

Children from both groups underwent pre-reading assessments, generally on the same day as their MRI scan and always within one week, using the Phonological Processing (PP) and Speeded Naming (SN) subtests from the Developmental Neuropsychological Assessment (NEPSY-II; Korkman et al., 2007). PP assesses the segmentation of phonemes and words while SN assesses the ability to rapidly identify pictures of shapes and colors. Both measures took approximately 10 minutes to complete and were administered at each visit.

3.3.2 Image acquisition and preprocessing

All children underwent a diffusion MRI scan on the same General Electric 3 T MR750w system with a 32-channel head coil at the Alberta Children's Hospital in Calgary, Canada. Diffusion tensor imaging (DTI) data were acquired in 4:03 minutes using single-shot spin- echo, echo planar imaging (EPI) sequence of 1.6 × 1.6 × 2.2 mm resolution (resampled to 0.78 × 0.78 × 2.2 mm on scanner), TR = 6750 ms; TE = 79 ms, 30 gradient encoding directions at b = 750 s/mm2, and 5 images at b = 0 s/mm2.

The preprocessing protocol included flipping/permuting volumes, and correction for signal drift, Gibbs ringing, head motion, and eddy current distortions using ExploreDTI (Leemans et al., 2009). Diffusion tensors were calculated and then used to compute FA values. Whole brain

diffusion tractography was performed using seedpoint resolution = 2 × 2 × 2 mm3, with FA threshold = 0.15, fiber length range = 50–500 mm, angle threshold = 30°, and step size = 1.

3.3.3 Connectome reconstruction

DTI-based connectivity matrices were generated to construct structural connectomes using calculated whole brain tractography, FA maps, as well as the Automated Anatomical Labeling Atlas (AAL 90; Tzourio-Mazoyer et al., 2002). AAL 90 was used to parcellate the cerebrum FA map into 90 grey matter regions excluding the cerebellum and create individualized atlases for each scan. These were manually inspected to ensure accuracy of region labels The whole brain tractography and AAL atlas were then used to generate a weighted 90×90 matrix consisting of the 90 parcellated brain regions and the FA values of the streamlines connecting them (figure 3.1). The connectivity matrices were manually inspected to ensure the connectomes were fully connected. For analysis, we defined a reading network consisting of bilateral brain regions associated with language and reading based on previous studies and were also shown to be associated with phonological awareness in unexposed preschool aged children (Ghasoub et al., 2024, Hertrich et al., 2020, Martin et al., 2015, Turker et al., 2019, Wilcox et al., 2022). The selected regions were: the opercular and triangular parts of the inferior frontal gyrus (phonological and semantic processing, respectively), the lingual, fusiform, and inferior temporal gyri (visual components of reading), the angular gyrus (integration and decoding of audiovisual components of reading), as well as Heschl's and the superior temporal gyri (phonological retrieval and semantic processing), (figure 3.2). Regions were dilated by 3 mm using FSL to include the adjacent white matter (Jenkinson et al., 2012).

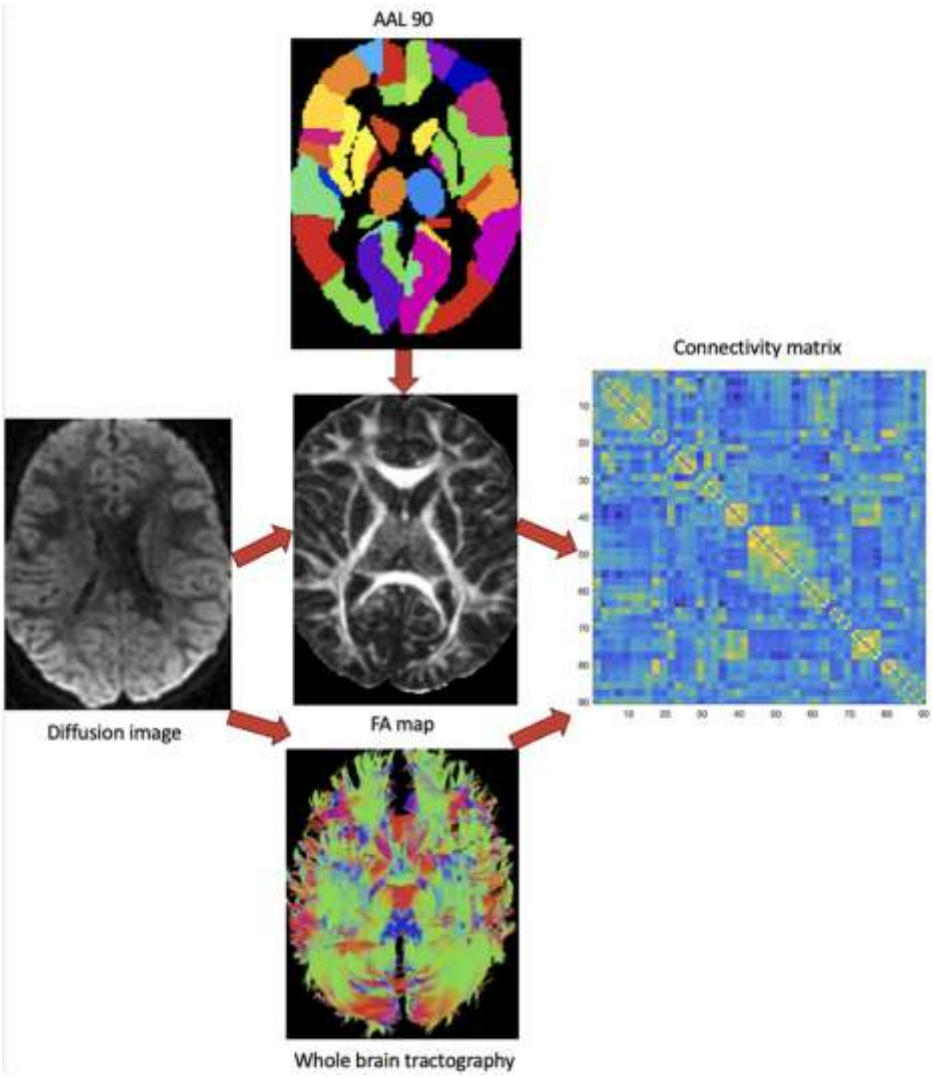

Figure 3.1 Preprocessing protocol for DTI-connectome construction. Diffusion weighted images were preprocessed to calculate the diffusion tensor and to generate whole brain tractography and FA maps. The AAL90 atlas was then used to parcellate the brain into 90 regions excluding the cerebellum and create individualized atlases from FA maps. Individualized atlases were then used with whole brain tractography to generate 90 ×90 connectivity matrices weighted by average FA and composed of the atlas parcellated regions and the FA values of the streamlines generated from FA maps and whole brain tractography connecting them.

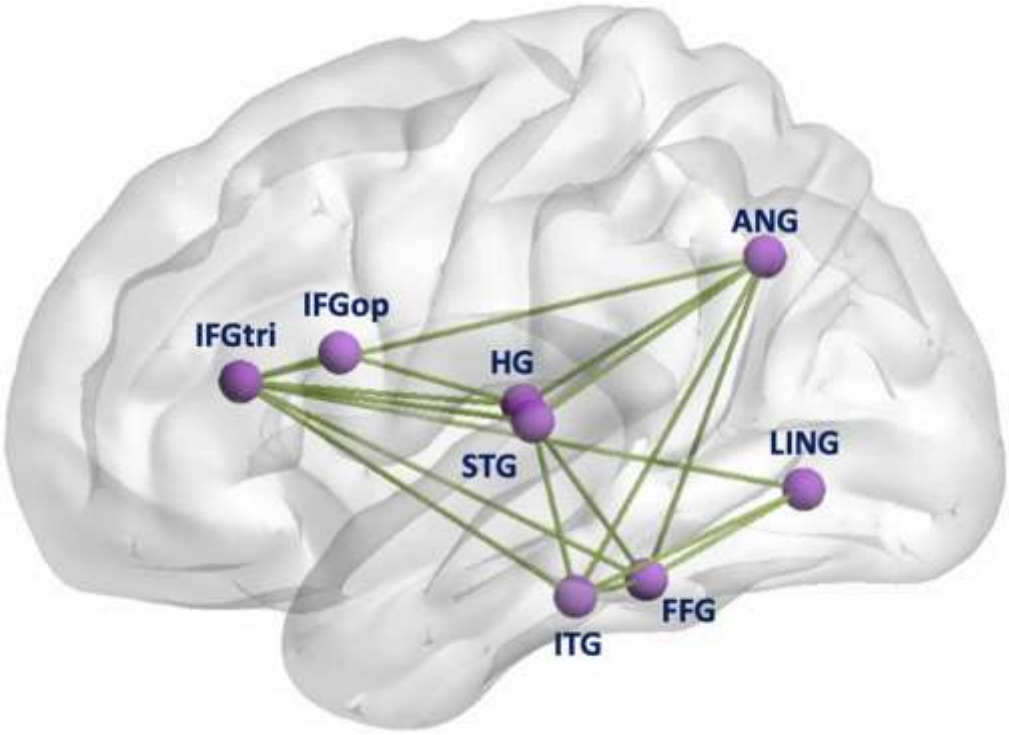

Figure 3.2 16 Regions of interest (8 from each hemisphere) included in the network of interest: opercular part of the inferior frontal gyrus (IFGop), the triangular part of the inferior frontal gyrus (IFGtri), the lingual gyrus (LING), the fusiform gyrus (FFG), the angular gyrus (AG), Heschl's gyrus (HG), the superior temporal gyrus (STG), and the inferior temporal gyrus (ITG). Figure was constructed using BrainNet Viewer (Xia et al., 2013).

A 16×16 connectivity matrix of regions from both hemispheres and 8×8 connectivity matrices from each hemisphere were extracted separately for analysis. The connectivity matrices were weighted by the average FA values of the connected fiber tracts. Graph theory measures (global efficiency, local efficiency, clustering coefficient, nodal degree) were calculated from each network (left, right, and bilateral) using the Brain Connectivity Toolbox (Rubinov and Sporns, 2010).

3.3.4. Statistical analysis

We used linear mixed effect models to test associations between graph theory measures and age-normed scaled pre-reading scores, and the moderating effect of PAE on these associations in both the full sample of unexposed controls and the age and sex matched sample. We ran two different models for each graph theory metric. The first model tested associations between PAE and graph theory measures with the equation: graph theory measure ~ age + sex + PAE + PAE*age + [1|Participant], where age, sex, PAE, and the interaction between age and PAE were fixed effects in the model, and participant was a random effect to account for varying scans per participant.

The second model tested the association between pre-reading assessments and graph theory measures, and how PAE moderates these associations with the equation: pre-reading assessment score ~ age + sex + PAE + graph theory measures + PAE* graph theory measures + [1|Participant], with participant as a random effect and the remaining covariates as fixed effects. Median household income and other diagnoses were initially included in the models to account for their effects on brain-reading relationships, but they were not significant and did not improve the model fit and therefore were removed from the models.

Linear mixed effect models were run in R (R Core Team, 2021) using the lme4 and lmer packages (Bates et al., 2015). False discovery rate correction (FDR) at $q < 0.05$ was used to correct for multiple comparisons for each pre-reading measure.

3.4 Results

3.4.1. Group differences in pre-reading skills

Compared to unexposed children, children with PAE had lower scores on the Phonological Processing ($p = 0.002$) and Speeded Naming ($p= 0.006$) measures (table 3.1). Scores for the PAE group were still within the normal range of scores based on the population mean (10 +/- 3).

3.4.2. Associations between PAE and graph theory metrics

There were significant group differences in all graph theory metrics across all three networks. In all cases, children with PAE had significantly lower metrics than controls (figure 3.3). Age was significantly correlated with global and local efficiency across all networks. The age*PAE interaction was positive and significant for global efficiency, local efficiency, and clustering coefficient in the bilateral network, as well as local efficiency and clustering coefficient in the right hemisphere network (table 3.2), indicating the age changes are stronger in the PAE group compared to controls. Sex was not significant in any of the models. In the age- and sex- matched subset, children with PAE had significantly lower graph theory metrics than unexposed children across all networks similar to the full sample (Supplementary Table 1).

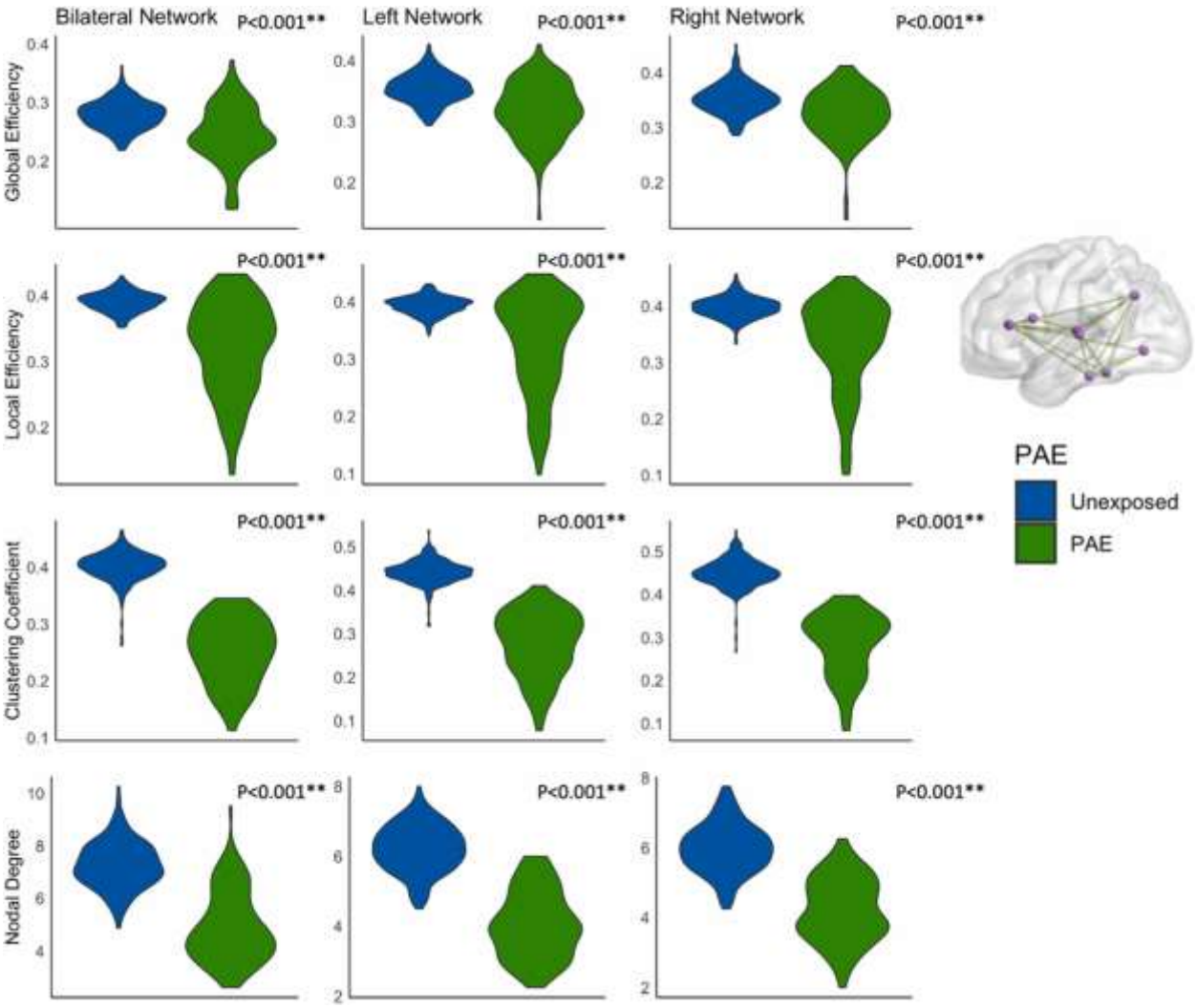

Figure 3.3 Violin plots displaying mean scores for graph theory metrics in PAE and unexposed control groups in bilateral brain network and each hemisphere network. The violin plots are color-coded to represent the two groups, with the PAE group in green and the control group in blue. Linear mixed models showed unexposed children had significantly higher graph theory metrics than children with PAE across all networks and measures ($p < 0.001$). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 3.2 Graph theory metrics linear mixed model parameters for the PAE group and the full unexposed control sample. Estimate: Unstandardized Beta Coefficient, Cl: Confidence Interval, p: p-value.

Predictors	***Beta***	***Cl***	***p***	***Beta***	***Cl***	***p***	***Beta***	***Cl***	***p***
Global Efficiency	Bilateral Network			Left Network			Right Network		
(Intercept)	0.25	0.24 – 0.27	**<0.001**	0.31	0.30 – 0.33	**<0.001**	0.31	0.30 – 0.33	**<0.001**
PAE	−0.18	−0.21 – −0.14	**<0.001**	−0.13	−0.17 – −0.10	**<0.001**	−0.11	−0.15 – −0.07	**<0.001**
Sex	−0.00	−0.01 – 0.01	0.460	−0.00	−0.01 – 0.01	0.729	0.00	−0.01 – 0.01	0.583
Age	0.01	0.00 – 0.01	**<0.001**	0.01	0.01 – 0.01	**<0.001**	0.01	0.01 – 0.01	**<0.001**
PAE × Age	0.02	0.02 – 0.03	**<0.001**	0.02	0.01 – 0.02	**<0.001**	0.01	0.01 – 0.02	**<0.001**
Local Efficiency	Bilateral Network			Left Network			Right Network		
Intercept	0.36	0.34 – 0.38	**<0.001**	0.35	0.33 – 0.38	**<0.001**	0.36	0.34 – 0.39	**<0.001**
PAE	−0.29	−0.33 – −0.24	**<0.001**	−0.28	−0.33 – −0.22	**<0.001**	−0.21	−0.26 – −0.15	**<0.001**
Sex	0.00	−0.01 – 0.02	0.555	0.00	−0.01 – 0.02	0.894	0.01	−0.00 – 0.02	0.167
Age	0.01	0.00 – 0.01	**<0.001**	0.01	0.00 – 0.01	**<0.001**	0.01	0.00 – 0.01	**0.010**
PAE × Age	0.04	0.03 – 0.05	**<0.001**	0.04	0.03 – 0.05	**<0.001**	0.02	0.01 – 0.03	**<0.001**
Clustering Coefficient	Bilateral Network			Left Network			Right Network		
Intercept	0.39	0.37 – 0.41	**<0.001**	0.42	0.40 – 0.45	**<0.001**	0.44	0.41 – 0.47	**<0.001**
PAE	−0.28	−0.33 – −0.24	**<0.001**	−0.36	−0.41 – −0.30	**<0.001**	−0.31	−0.37 – −0.25	**<0.001**

Sex	0.00	−0.01 – 0.01	0.805	−0.00	−0.02 – 0.01	0.933	0.00	−0.01 – 0.02	0.545
Age	0.00	−0.00 – 0.01	0.347	0.00	−0.00 – 0.01	0.059	0.00	−0.00 – 0.01	0.540
PAE × Age	0.02	0.02 – 0.03	**<0.001**	0.03	0.02 – 0.04	**<0.001**	0.02	0.01 – 0.04	**<0.001**
Nodal Degree	Bilateral Network			Left Network			Right Network		
Intercept	7.27	6.72 – 7.81	**<0.001**	6.20	5.80 – 6.61	**<0.001**	5.82	5.41 – 6.22	**<0.001**
PAE	−5.88	−7.12 – −4.64	**<0.001**	−4.17	−5.10 – −3.25	**<0.001**	−3.48	−4.41 – −2.56	**<0.001**
Sex	−0.08	−0.40 – 0.24	0.623	−0.00	−0.24 – 0.23	0.988	0.11	−0.13 – 0.35	0.363
Age	0.00	−0.10 – 0.11	0.957	−0.01	−0.08 – 0.07	0.888	0.02	−0.06 – 0.09	0.687
PAE × Age	0.62	0.40 – 0.85	**<0.001**	0.36	0.20 – 0.53	**<0.001**	0.30	0.14 – 0.47	**<0.001**

3.4.3 Pre-reading assessments

PAE significantly moderated associations between Phonological Processing and global efficiency in both the bilateral (p= 0.010) and left hemisphere (p=0.011) networks, as well as nodal degree in the bilateral (p= 0.009) and left hemisphere (p=0.048) networks (table 3.3). In all cases, there was a more positive relationship between brain measures and phonological processing in the PAE group than in controls (figure 3.4). Age was also significant in most models. All associations remained significant after FDR corrections for multiple (12) comparisons except for nodal degree in the left hemisphere network. No significant associations were noted with Speeded Naming (table 3.4).

Table 3.3 Linear mixed effect models for phonological processing for the PAE group and the full unexposed control sample. Beta: Unstandardized Beta Coefficient, CI: Confidence Interval, p: p-value.

PP	**Bilateral**			**Left**			**Right**		
Predictors	***Beta***	***CI***	***p***	***Beta***	***CI***	***p***	***Beta***	***CI***	***p***
Intercept	9.85	5.50 – 14.20	**<0.001**	10.34	4.83 – 15.84	**<0.001**	5.05	0.31 – 9.78	**0.037**
PAE	−7.85	−13.16 – −2.53	**0.004**	−10.10	−17.13 – −3.07	**0.005**	−3.96	−10.33 – 2.41	0.222
Sex	0.08	−0.73 – 0.89	0.848	0.06	−0.75 – 0.86	0.892	−0.03	−0.83 – 0.77	0.945
Age	0.32	0.03 – 0.60	**0.033**	0.36	0.06 – 0.66	**0.020**	0.26	−0.04 – 0.55	0.085
Global Efficiency	−0.51	−16.50 – 15.48	0.950	−2.29	−18.87 – 14.29	0.786	14.18	0.11 – 28.25	**0.048**
PAE × Global Efficiency	25.60	6.05 – 45.16	**0.010**	26.52	6.17 – 46.86	**0.011**	8.68	−9.83 – 27.20	0.357
Intercept	5.17	−5.83 – 16.16	0.356	11.75	0.65 – 22.85	**0.038**	4.13	−4.43 – 12.68	0.343
PAE	−2.43	−14.31 – 9.44	0.687	−7.65	−19.80 – 4.50	0.217	−0.40	−9.68 – 8.89	0.933
Sex	−0.04	−0.84 – 0.75	0.912	−0.01	−0.82 – 0.81	0.990	−0.12	−0.92 – 0.67	0.765
Age	0.26	−0.06 – 0.58	0.112	0.39	0.05 – 0.74	**0.027**	0.29	−0.01 – 0.59	0.056

Local Efficiency	12.46	−17.28 – 42.21	0.410	−5.99	−36.34 – 24.35	0.698	14.60	−7.86 – 37.07	0.202
PAE × Local Efficiency	5.64	−24.59 – 35.86	0.714	17.02	−13.39 – 47.43	0.272	−0.67	−23.98 – 22.64	0.955
Intercept	6.86	1.24 – 12.49	**0.017**	10.28	4.29 – 16.26	**0.001**	7.65	2.77 – 12.53	**0.002**
PAE	−4.07	−10.21 – 2.06	0.192	−5.91	−12.36 – 0.54	0.072	−4.36	−9.63 – 0.91	0.104
Sex	−0.03	−0.84 – 0.77	0.933	0.04	−0.78 – 0.85	0.925	−0.11	−0.91 – 0.68	0.784
Age	0.34	0.06 – 0.61	**0.017**	0.36	0.08 – 0.64	**0.013**	0.34	0.07 – 0.62	**0.015**
Clustering Coefficient	6.99	−6.78 – 20.76	0.319	−1.70	−15.31 – 11.91	0.806	4.51	−5.96 – 14.98	0.397
PAE × Clustering Coefficient	14.13	−3.09 – 31.36	0.107	14.42	−1.22 – 30.07	0.071	12.36	−0.83 – 25.55	0.066
Intercept	9.33	6.02 – 12.64	**<0.001**	9.40	5.66 – 13.14	**<0.001**	6.17	2.82 – 9.52	**<0.001**
PAE	−5.54	−9.30 – −1.77	**0.004**	−5.08	−9.40 – −0.76	**0.021**	−3.28	−7.44 – 0.87	0.121
Sex	0.05	−0.77 – 0.86	0.913	−0.02	−0.84 – 0.80	0.962	−0.10	−0.90 – 0.71	0.810
Age	0.35	0.08 – 0.63	**0.013**	0.39	0.11 – 0.67	**0.007**	0.37	0.09 – 0.64	**0.009**

Nodal Degree	0.03	−0.38 – 0.44	0.886	0.00	−0.55 – 0.56	0.988	0.57	0.05 – 1.09	**0.032**
PAE × Nodal Degree	0.82	0.21 – 1.43	**0.009**	0.84	0.01 – 1.68	**0.048**	0.63	−0.20 – 1.46	0.137

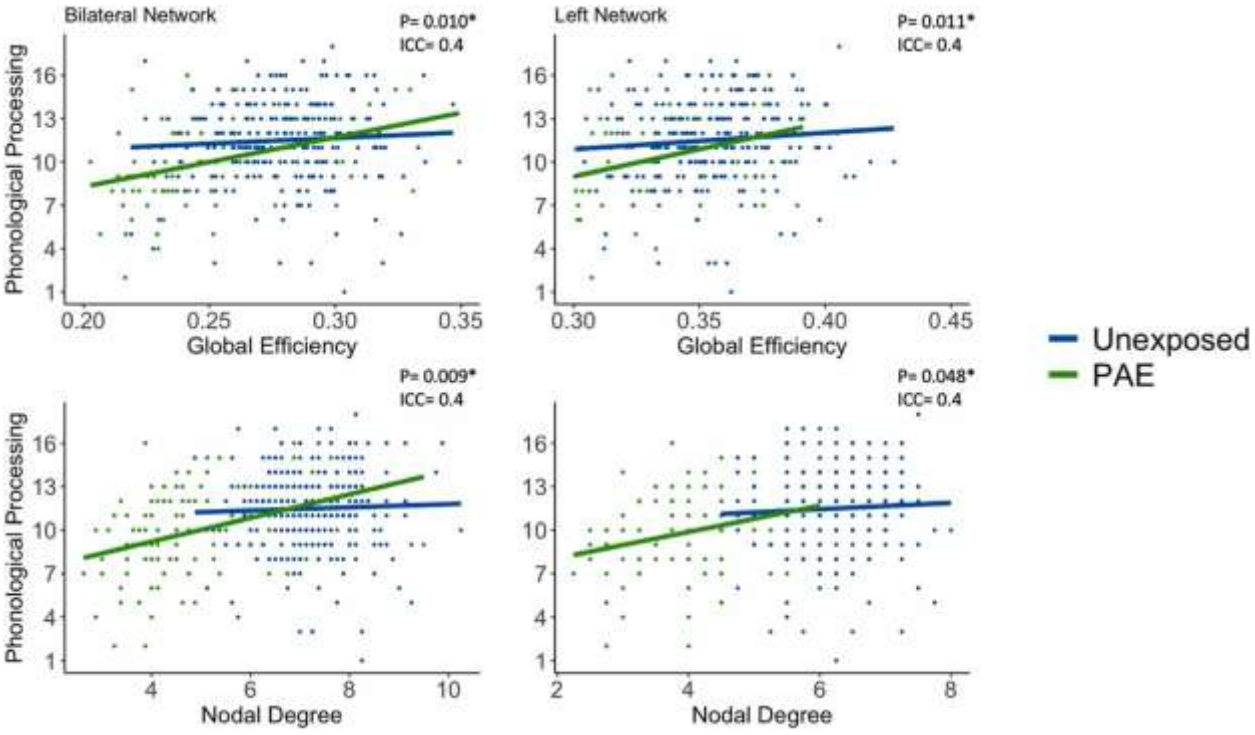

Figure 3.4 Associations between Phonological Processing scores and global efficiency in the left hemisphere, as well as global efficiency and nodal degree in the bilateral network, are shown by group. The PAE group is displayed in green and unexposed controls in blue. The PAE group had steeper positive relationships. P= p-values, ICC= interclass correlation coefficient.

Table 3.4 Linear mixed effect models of speeded naming for the PAE group and the full unexposed control sample. Estimate: Unstandardized Beta Coefficient, CI: Confidence Interval, p: p-value.

SN	**Bilateral**			**Left**			**Right**		
Predictors	***Beta***	***CI***	***p***	***Beta***	***CI***	***p***	***Beta***	***CI***	***p***
Intercept	9.75	5.30 – 14.20	**<0.001**	6.40	0.79 – 12.01	**0.025**	11.28	6.44 – 16.12	**<0.001**
PAE	−3.53	−8.98 – 1.92	0.204	1.52	−5.65 – 8.69	0.677	−5.63	−12.16 – 0.89	0.090
Sex	0.57	−0.29 – 1.43	0.192	0.55	−0.30 – 1.40	0.206	0.54	−0.32 – 1.40	0.217
Age	0.30	0.01 – 0.60	**0.043**	0.26	−0.05 – 0.57	0.095	0.35	0.05 – 0.65	**0.021**
Global Efficiency	0.54	−15.84 – 16.93	0.948	10.48	−6.42 – 27.39	0.223	−4.48	−18.88 – 9.93	0.541
PAE × Global Efficiency	8.14	−11.90 – 28.17	0.425	−8.46	−29.21 – 12.30	0.423	12.02	−6.93 – 30.97	0.213
Intercept	7.15	−4.23 – 18.52	0.217	2.99	−8.25 – 14.24	0.601	13.23	4.42 – 22.04	**0.003**
PAE	−1.50	−13.78 – 10.79	0.811	3.77	−8.55 – 16.09	0.548	−7.00	−16.58 – 2.59	0.152
Sex	0.52	−0.33 – 1.37	0.234	0.53	−0.32 – 1.38	0.219	0.51	−0.35 – 1.36	0.245
Age	0.25	−0.07 – 0.58	0.126	0.17	−0.18 – 0.52	0.336	0.37	0.06 – 0.67	**0.018**
Local Efficiency	7.69	−23.13 – 38.51	0.624	19.12	−11.66 – 49.90	0.223	−9.00	−32.16 – 14.16	0.445

PAE × Local Efficiency	1.74	−29.50 – 32.97	0.913	−11.92	−42.73 – 18.90	0.447	14.36	−9.67 – 38.39	0.241
Intercept	6.28	0.59 – 11.96	**0.031**	4.73	−1.27 – 10.73	0.122	8.48	3.54 – 13.43	**0.001**
PAE	−0.30	−6.52 – 5.93	0.925	1.84	−4.64 – 8.32	0.577	−1.82	−7.20 – 3.57	0.508
Sex	0.54	−0.32 – 1.40	0.216	0.54	−0.31 – 1.40	0.211	0.51	−0.34 – 1.37	0.238
Age	0.30	0.02 – 0.58	**0.037**	0.27	−0.02 – 0.55	0.064	0.32	0.04 – 0.60	**0.027**
Clustering Coefficient	9.13	−4.78 – 23.04	0.197	12.08	−1.58 – 25.74	0.083	3.07	−7.53 – 13.68	0.569
PAE × Clustering Coefficient	0.53	−16.99 – 18.05	0.953	−4.84	−20.56 – 10.89	0.546	2.62	−10.92 – 16.17	0.704
Intercept	9.79	6.43 – 13.15	**<0.001**	7.49	3.72 – 11.26	**<0.001**	9.73	6.30 – 13.16	**<0.001**
PAE	−3.62	−7.46 – 0.22	0.065	−0.52	−4.87 – 3.84	0.816	−3.75	−8.05 – 0.54	0.087
Sex	0.57	−0.29 – 1.42	0.191	0.54	−0.31 – 1.39	0.208	0.50	−0.36 – 1.36	0.251
Age	0.31	0.03 – 0.59	**0.030**	0.33	0.05 – 0.61	**0.020**	0.32	0.05 – 0.60	**0.023**
Nodal Degree	0.01	−0.41 – 0.43	0.958	0.37	−0.19 – 0.93	0.194	0.02	−0.51 – 0.55	0.944

PAE × Nodal Degree	0.43	−0.19 – 1.05	0.176	−0.07	−0.92 – 0.77	0.868	0.53	−0.33 – 1.38	0.229

In the matched sample, PAE still significantly moderated the associations between Phonological Processing and global efficiency in the bilateral and left hemisphere networks as well as nodal degree in the bilateral network, consistent with the full sample analysis (table 3.5). Moreover, we found significant moderation effects of PAE for the associations between Phonological Processing and clustering coefficient in all three networks and nodal degree in the right network, which was not observed in the full sample. No significant associations with local efficiency or Speeded Naming were found. Results remained significant after multiple comparison corrections.

Table 3.5 Linear mixed effect models of phonological processing for the PAE group and the age- and sex-matched control sample. Beta: Unstandardized Beta Coefficient, CI: Confidence Interval, p: p-value.

Predictors	***Beta***	***CI***	***p***	***Beta***	***CI***	***p***	***Beta***	***CI***	***p***
PP	**Bilateral**			**Left**			**Right**		
Intercept	13.60	6.89 – 20.31	**<0.001**	11.36	2.94 – 19.78	**0.008**	9.41	2.16 – 16.66	**0.011**
PAE	−12.43	−19.42 – −5.44	**0.001**	−11.88	−21.29 – −2.46	**0.014**	−9.03	−17.26 – −0.79	**0.032**
Sex	0.34	−0.60 – 1.29	0.474	0.34	−0.61 – 1.29	0.485	0.25	−0.70 – 1.19	0.607

Age	0.37	−0.02 – 0.76	0.061	0.44	0.03 – 0.85	**0.034**	0.42	0.03 – 0.82	**0.036**
Global Efficiency	−16.25	−38.83 – 6.33	0.158	−7.62	−31.96 – 16.72	0.538	−1.57	−21.99 – 18.85	0.880
PAE × Global Efficiency	41.45	16.39 – 66.51	**0.001**	31.16	4.67 – 57.66	**0.021**	22.47	−0.90 – 45.84	0.059
	Bilateral			**Left**			**Right**		
Intercept	16.04	0.88 – 31.21	**0.038**	19.59	3.86 – 35.31	**0.015**	12.40	1.38 – 23.42	**0.028**
PAE	−14.16	−30.02 – 1.70	0.080	−16.75	−33.40 – −0.10	**0.049**	−9.46	−20.98 – 2.06	0.107
Sex	0.24	−0.70 – 1.17	0.617	0.30	−0.67 – 1.28	0.539	0.15	−0.78 – 1.09	0.746
Age	0.42	0.02 – 0.83	**0.042**	0.57	0.13 – 1.00	**0.011**	0.46	0.07 – 0.85	**0.022**
Local Efficiency	−18.14	−58.13 – 21.86	0.372	−29.03	−70.80 – 12.73	0.172	−8.96	−37.15 – 19.22	0.531
PAE × Local Efficiency	34.79	−5.33 – 74.92	0.089	39.49	−2.01 – 81.00	0.062	21.48	−7.25 – 50.20	0.142
	Bilateral			**Left**			**Right**		
Intercept	11.11	3.91 – 18.30	**0.003**	13.94	6.29 – 21.59	**<0.001**	11.19	4.81 – 17.56	**0.001**
PAE	−8.83	−16.12 – −1.55	**0.018**	−10.45	−18.12 – −2.79	**0.008**	−8.24	−14.53 – −1.96	**0.010**

Sex	0.21	−0.73 – 1.15	0.663	0.34	−0.62 – 1.30	0.484	0.10	−0.83 – 1.03	0.838
Age	0.40	0.02 – 0.79	**0.039**	0.43	0.05 – 0.82	**0.029**	0.41	0.03 – 0.79	**0.035**
Clustering Coefficient	−5.21	−22.13 – 11.71	0.545	−11.91	−28.40 – 4.57	0.156	−4.54	−17.50 – 8.41	0.490
PAE × Clustering Coefficient	25.55	5.84 – 45.25	**0.011**	24.50	6.33 – 42.66	**0.008**	20.55	5.42 – 35.68	**0.008**
	Bilateral			**Left**			**Right**		
Intercept	12.09	6.91 – 17.26	**<0.001**	8.88	3.14 – 14.62	**0.003**	8.53	3.33 – 13.73	**0.001**
PAE	−8.97	−13.85 – −4.09	**<0.001**	−5.47	−11.17 – 0.23	0.060	−6.27	−11.53 – −1.02	**0.020**
Sex	0.29	−0.66 – 1.24	0.552	0.23	−0.74 – 1.20	0.642	0.13	−0.82 – 1.08	0.793
Age	0.40	0.01 – 0.78	**0.042**	0.49	0.10 – 0.88	**0.013**	0.47	0.09 – 0.85	**0.017**
Nodal Degree	−0.43	−1.02 – 0.16	0.150	−0.06	−0.88 – 0.76	0.885	0.04	−0.70 – 0.79	0.910
PAE × Nodal Degree	1.29	0.55 – 2.03	**0.001**	0.90	−0.12 – 1.91	0.083	1.11	0.13 – 2.09	**0.026**

3.4.4 Post hoc mediation analysis

Following our main analysis in Section 3.4, we conducted a post-hoc supplementary mediation analysis cross-sectionally by selecting the first scan and last reading time points for each participant in R using the mediation package (Tingley et al., 2014) with the four graph theory measures that were significant in our main dataset to further examine the effects of PAE on the brain-pre-reading associations and determine whether they mediate the linkage between PAE and PP. This was done in 129 datasets (82 controls; mean age 4.6 years, 47 PAE; mean age 5.6 years). We found a significant indirect mediation effect of PAE on Phonological Processing scores through the bilateral and left hemisphere network global efficiency ($p= 0.002$, $p= 0.01$, respectively). There were no direct effects of PAE on Phonological Processing scores independent of graph theory measures (Supplementary Table 2).

3.5 Discussion

Here, we show reduced structural connectivity within the reading network in young children with PAE compared to unexposed controls. This weaker connectivity, for both bilateral and left hemisphere networks, appears to underlie lower pre-reading scores (Phonological Processing) in children with PAE, suggesting that white matter alterations in the reading network may explain some of the later reading difficulties associated with PAE.

Children with PAE performed significantly worse on both pre-reading tasks (Phonological Processing, Speeded Naming) than unexposed children. However, children with PAE still scored at the expected population level (i.e., means scores of 10 +/-3). Findings from previous studies examining reading and language in children with PAE are mixed, with some studies showing poor reading ability in older children and adolescents (Lindinger et al., 2022, Wyper and

Rasmussen, 2011), and others showing no differences in younger children and toddlers (Hendricks et al., 2020, Subramoney et al., 2018). However, it is unclear in previous studies whether scores were lower than population means, or just lower than the control sample as in our study. Participant differences among studies, such as different alcohol exposure patterns may influence outcomes. In addition, socioeconomic and environmental factors that may go unreported (Hendricks et al., 2019) can influence reading performance (Noble et al., 2006, Romeo et al., 2022). Children with PAE had lower household incomes than controls in this study, though both groups were within or above the average median household income in Canada (Government of Canada, 2023).

Children with PAE had significantly weaker reading network connectivity than unexposed children across both hemispheres. This is in line with previous findings in older children and adolescents with PAE showing reduced whole brain structural connectivity as well as reduced connectivity in the attention, somatomotor, and default mode networks (Long et al., 2020). In a small sample, Roos et al., (2021) found higher connectivity in regions associated with reading and language including the fusiform, superior middle and temporal gyri in neonates with PAE compared to unexposed neonates. However, they found no group differences in the overall global structural connectivity. Together, these studies suggest that structural network differences become increasingly global in nature with age, underlining the increasingly widening gaps in cognitive and behavioral outcomes between unexposed and exposed individuals.

In addition to the main effects, the children with PAE in our study had a wider distribution of graph theory metrics than controls (figure 3.3). Graph theory metrics in the PAE group also had a more negatively skewed distribution. Findings from neuroimaging and cognitive studies on PAE are heterogeneous (Donald et al., 2015, McLachlan et al., 2017). This heterogeneity may be

attributed to factors such as the severity and timing of alcohol exposure during pregnancy as well as postnatal adversity, all of which have been shown to influence fetal development (Popova et al., 2023). Moreover, recent evidence from functional neuroimaging studies shows the development of language regions in typically developing children occurs sequentially (Tang et al., 2024). This variation in regional development, along with evidence of early brain maturation in children with PAE (Kar et al., 2022), could potentially explain the wider distribution of graph theory metrics observed in our study. Future research is needed to investigate how the structural connectivity of different individual regions of the reading network is associated with pre-reading skills in young children with and without PAE.

Weaker structural connectivity likely stems from altered white matter microstructural properties in children with PAE (Donald et al., 2015, Kar et al., 2022, Treit et al., 2013), due to alcohol's effects on gliogenesis and myelination resulting in disruptions to white matter development (Almeida et al., 2020). Interestingly, the overall weaker connectivity observed here differs from findings in an overlapping sample showing stronger connectivity in individual white matter tracts in young children (Kar et al., 2021). The discrepancy could be explained by methodological differences when looking at individual tracts' connectivity (i.e., microstructure) compared to examining network connectivity (i.e., macrostructure); for example, although individual large white matter connections may show stronger microstructure, it could be that smaller connections are weaker and drive the graph theory network results. Graph theory analysis can provide a more comprehensive picture by looking at the overall connectivity between these regions rather than examining individual pathways/tracts, which in turn may provide additional insight into the potential basis for poorer performance on early reading and pre-reading assessments.

Studies examining white matter pathways in children with PAE show alterations in white matter developmental trajectories, particularly, altered white matter microstructure (Fan et al., 2016, Roos et al., 2021, Treit et al., 2013) and slower white matter development (Kar et al., 2022, Ostertag et al., 2023). Moreover, these slow developmental trajectories in the arcuate fasciculus are associated with pre-reading skills (Ostertag et al., 2023). Here, we show global efficiency and nodal degree in the reading network are associated with Phonological Processing scores, thereby suggesting damage in the structural connectivity of the reading network may explain the lower Phonological Processing scores in children with PAE. The relationship between graph theory metrics and pre-reading scores was stronger in children with PAE compared to unexposed children. A supplementary mediation analysis showed that PAE mediates the poorer phonological processing abilities indirectly through the global efficiency of the reading networks, further suggesting that PAE drives pre-reading abilities via altered brain connectivity. Together, this significantly reduced network connectivity and the post hoc mediation analysis, suggest that structural alterations in the reading network drive poorer pre-reading performance in children with PAE, and possibly lead to later reading difficulties. Importantly, when groups were matched by age, these significant moderations remained, and significant interactions with clustering coefficients emerged across all networks, suggesting this is a robust finding.

We did not find any significant brain-reading relationships between graph theory metrics and Speeded Naming scores, despite the significant differences in performance between the groups. This may be due to rapid naming skills possibly engaging regions distinct from those involved in phonological awareness. Our findings are similar to prior studies showing no significant associations of Speeded Naming with white matter connectome in typical children (Ghasoub et al., 2024, Lou et al., 2021).

Our study had limitations that may have influenced the results. The DTI model does not account for crossing fibers; other more advanced methods can overcome these limitations and provide more information about structural connectivity and should be considered in future studies with appropriate data. Additionally, we had a generally high-performing sample of unexposed controls that scored above the expected mean population norm in pre-reading assessments, potentially influencing our results. We also did not directly assess the children's reading abilities to confirm they were all pre-readers. Like many studies of individuals with PAE, it is difficult to obtain accurate information on the amount and timing of alcohol exposure; these factors may influence outcomes.

3.6 Conclusion

To conclude, in a large longitudinal sample, we showed that young children with PAE had weaker connectivity in the reading network compared to unexposed children and that PAE moderated the associations between structural network connectivity and pre-reading skills, suggesting the weaker connectivity underlies pre-reading deficits in children with PAE. These moderation effects at young ages imply that the roots of reading deficits in young children with PAE might begin early, suggesting the need for early diagnosis and interventions to support appropriate reading development. Furthermore, alcohol exposure during pregnancy should be considered a potential risk factor for reading disabilities. This is important given that childhood reading deficits are associated with later academic achievement and mental health (Livingston et al., 2018). Future research should examine how the early structural neural correlates of pre-reading ability are associated with reading skills later in children with and without PAE.

Chapter 4: The Effects of Prenatal Alcohol Exposure on Structural Brain Connectivity and Early Language Skills in a South African Birth Cohort

4.1 Abstract

Prenatal alcohol exposure (PAE) is associated with various neurological, behavioral and cognitive deficits, including reading and language. Previous studies have demonstrated altered white matter in children and adolescents with PAE and associations with reading and language performance in children aged 3 years and older. However, little research has focused on the toddler years, despite this being a critical period for behavioral and neural development. We aimed to determine associations between structural brain connectivity and early language skills in toddlers, in the context of PAE. Eighty-eight toddlers (2–3 yr, 56 males), 23 of whom had PAE, underwent a diffusion MRI scan in Cape Town, South Africa, with language skills assessed using the Expressive and Receptive Communication subtests from the Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III). Diffusion scans were preprocessed to create a structural network of regions associated with language skills using graph theory analysis. Linear regression models were used to examine moderation effects of PAE on structural network properties and language skills. Toddlers with PAE had higher structural connectivity in language networks than unexposed children. PAE moderated the relationship between structural network properties and Expressive Communication scores. None of the effects survived correction for multiple comparisons. Our findings show weak moderation effects of PAE on structural language network properties and language skills. Our study sheds light on the

structural connectivity correlates of early language skills in an understudied population during a critical neurodevelopmental period, laying the foundation for future research.

4.2 Background

Prenatal alcohol exposure (PAE) can negatively impact brain development, causing a range of neurological and physiological deficits (Popova et al., 2023). Alcohol consumption in pregnancy is prevalent worldwide, with approximately 10% of children exposed to alcohol in utero (Popova et al., 2023). Evidence of the teratogenic effects of alcohol on fetal brain development are present throughout neurodevelopment, with alterations to brain structure and function, and their growth over time (Almeida et al., 2020; Lebel et al., 2011; Moore & Xia, 2022). PAE can lead to a wide range of long-term neurobehavioral deficits, and in some cases, a diagnosis of fetal alcohol spectrum disorders (FASD), the neurodevelopmental disorder associated with PAE (Flannigan et al., 2022).

Language deficits are one of the neurobehavioral impairments observed in individuals with PAE (Hendricks et al., 2019; Popova et al., 2016). Several studies have noted phonological awareness and spelling impairments in individuals with PAE (Adnams et al., 2007; Glass et al., 2015). On the other hand, Lindinger et al. (2022) found adolescents with PAE perform poorly on reading comprehension, but not on phonological awareness tasks compared to unexposed adolescents. Several studies found children with PAE have lower expressive and/or receptive language skills compared to unexposed children (Davies et al., 2011; Poth et al., 2023; Proven et al., 2014; Wyper & Rasmussen, 2011), though not all studies show difficulties (Hendricks et al., 2020; Lindinger et al., 2022). Language impairments seem to become more apparent with age, with deficits more commonly reported in older children (Kippin et al., 2021; Proven et al., 2014). Conflicting findings in the literature may also be partly attributed to socioeconomic factors, amount and duration of alcohol exposure, as well as prenatal exposures to other substances that could influence language skills (Flannigan et al., 2022; McLachlan et al., 2020).

Studying the brain's structural properties can provide a better understanding of the neural basis underlying early language skills in children with and without PAE. Diffusion weighted imaging (DWI) is a neuroimaging technique commonly used to study the brain's white matter properties due to its sensitivity to white matter microstructure (Beaulieu, 2002). DWI studies consistently show differences in white matter microstructure between typical readers and individuals with reading disabilities, where typical readers tend to have higher fractional anisotropy (FA) and/or lower mean diffusivity (MD) in white matter pathways related to reading and language processing compared to poorer readers (Carter et al., 2009; Lebel et al., 2013; Nikki Arrington et al., 2017; Niogi & McCandliss, 2006; Wang et al., 2021). Recent studies provide evidence for similar relationships between white matter microstructure and early language skills, including receptive and expressive communication, in young children (Feng et al., 2019; Girault et al., 2019; Sket et al., 2019). Travis et al. (2017) found that the FA in the left arcuate fasciculus and superior longitudinal fasciculus were positively associated with phonological awareness in 6-year-old readers and pre-readers. They also found that FA in the right uncinate fasciculus and left superior longitudinal fasciculus were positively associated with receptive and expressive language skills.

In the context of PAE, widespread microstructural brain alterations have been found in pathways associated with language and reading processing in children with PAE (Fan et al., 2016; Gómez et al., 2022; Kar et al., 2021; Lebel et al., 2008; Roos et al., 2021b), but few studies have directly examined associations between brain structure and reading or language performance. One study found that changes over time in MD of the superior fronto-occipital fasciculus were related to changes in reading and receptive vocabulary scores in school-aged children with FASD (Treit et al., 2013). A study by Yu et al. (2022) found significant differences in reading performance and

associations with FA of both the superior and inferior longitudinal fasciculi between adolescents with and without PAE. They also found significant differences in the association between lateralization of the inferior longitudinal fasciculus and phonemic decoding performance (Yu et al., 2022). On the other hand, one study found no significant associations between white matter language pathways and reading ability in individuals with FASD (Sowell et al., 2008). Thus, further work is needed to clarify the nature of these associations. Further, there remains a significant gap in the brain–language relationship during the toddler years—when language acquisition is at its peak as most published neuroimaging studies of PAE were conducted in older children. Another significant gap is across diverse socioeconomic and cultural contexts, as most studies have been conducted in high-income countries.

In addition to studying individual white matter pathways, DWI can be utilized to study brain networks associated with language using graph theory, a technique that represents brain regions and the functional and/or structural connectivity between them as a network of nodes connected by edges. This comprehensive map is also known as a connectome (Bullmore & Sporns, 2009; Fornito, 2016). Graph theory has been used to map neural networks from the cellular levels of neurons and synapses to the brain systems levels.

Studies examining structural network connectivity in children reported positive associations between reading performance and global efficiency, a measure of information integration across the network (Lou et al., 2021). Bathelt et al. (2018) found academic performance, measured by reading and math abilities, to be associated with better organization of the white matter connectome, measured by higher global efficiency as well as clustering coefficient, a measure of connection density. Recently, stronger structural network properties were found to be associated with higher phonological processing skills in typically developing preschool-aged children,

suggesting that the neural correlates of early reading skills emerge from a young age (Ghasoub et al., 2024a).

Few studies have investigated the structural brain connectomes of children with PAE. One study found no global connectivity differences between neonates with PAE and unexposed infants, though at the regional level, neonates with PAE had lower connectivity in parietal regions and higher connectivity in frontal, occipital, and temporal regions compared to unexposed neonates (Roos et al., 2021a). Another study found overall decreased structural connectivity in the attention, somatomotor, and default-mode networks in children and adolescents with PAE compared to unexposed children and adolescents (Long et al., 2020). Moreover, decreased structural connectivity and network organization in the reading network, measured by global efficiency, nodal degree, and clustering coefficient are associated with poorer phonological awareness skills in preschool-aged children with PAE (Ghasoub et al., 2024b). Nonetheless, most prior studies were conducted on children living with non-birth families with high socioeconomic status. Furthermore, the extent to which these structural connectivity alterations in PAE play a role in early expressive and communication language skills, as well as the presence of these associations in the toddler years, remain to be fully understood.

This study aimed to investigate the structural network connectivity in language networks, how it is associated with early receptive and expressive language skills in a cohort of South African toddlers (age 2–3 yr), and the extent to which PAE moderates these associations.

4.3 Methods

4.3.1 Participants

Eighty-eight children aged 2–3 years (2.75 ± 0.14 years, 56 males) from the Drakenstein Child Health Study (DCHS), a population-based longitudinal birth cohort study conducted in the Western Cape region of South Africa (Donald et al., 2018; Stein et al., 2015), were included in this study. A total of 121 children from the DCHS were initially recruited for magnetic resonance imaging (MRI) scans at ages 2–3 years. Thirty-three datasets were excluded from the analysis for poor quality (28 for motion artifacts and 5 for connectomes that were not fully connected), resulting in the final sample size of 88 participants. Twenty-three children had PAE) confirmed via the Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST). None of the children with PAE in our sample had an FASD diagnosis, as assessments for FASD are typically conducted at older ages in South Africa (>6 yr). Prenatal tobacco exposure (PTE) was reported in 14 of the 23 PAE participants and 11 of the 55 controls. Children with confirmed exposures to other drugs (e.g., cannabis, cocaine, opiates, methamphetamine, or barbiturates) were excluded from the study. Infants with congenital malformations, born prematurely, and twins or triplets were also excluded. The Western Cape region is culturally and linguistically heterogeneous. The children spoke primarily Afrikaans or isiXhosa as their native language. Informed parental/guardian consent was obtained from all participants.

4.3.2 Language Assessments

Child development was assessed objectively by trained assessors using the Bayley Scale of Infant Development, third edition (BSID-III; Bayley, 2012). The BSID-III is validated and

standardized using a representative sample of the United States population and has demonstrated its reliability for use in the South African population (Rademeyer & Jacklin, 2013). The Expressive Communication and Receptive Communication subsets of the BSID-III were used to assess early language skills. Expressive Communication describes the child's ability to communicate their thoughts and feelings, which includes gesturing and naming objects. Receptive Communication describes the process of receiving and understanding language, which includes the child's ability to recognize words and objects. Assessments were translated from English (forward and back translation) and conducted in the child's native language with the assessors blinded to the child's exposure status. For both Expressive and Receptive Communication, scales scores were used; these have a range of 1–19 and a mean score of 10 ± 3.

4.3.3 Image Acquisition and Processing

All MRI data was acquired on a 32-channel head coil Siemens Skyra 3T MRI scanner (Siemens, Erlangen, Germany) at Groote Schuur Hospital in Cape Town, South Africa. DWI data acquisition was done using voxel size 1.8 × 1.8 × 2.0 mm, TR = 7,800 ms; TE = 92 ms, slice thickness of 2 mm, with 30 gradient diffusion directions at b = 1,000 s/mm2, and one b = 0 s/mm2. One full diffusion imaging protocol was acquired in each of the anterior-posterior and posterior-anterior phase encoding directions. Participants were not sedated and were sleeping naturally during the scans. DWI data were preprocessed using ExploreDTI (Leemans et al., 2009) to flip/permute images, and correct for Gibbs ringing, head motion, and eddy current distortions. The diffusion tensor was calculated, and FA values were extracted. Whole brain tractography was performed with seedpoint resolution 2 × 2 × 2 mm3, FA threshold = 0.15, fiber length = 50–500 mm, angle threshold = 30°, step size = 1. DWI data of each participant were

manually inspected for quality control and to ensure their usability for the following analyses. This step resulted in the exclusion of 28 scans from the initial 121 datasets.

4.3.4 Connectome Construction and Graph Theory Analysis

The brain was parcellated into 90 regions, excluding the cerebellum, using the Automated Anatomical Labeling atlas (AAL; Tzourio-Mazoyer et al., 2002). AAL gray matter regions were dilated by 3 mm to ensure white matter tracts could reach AAL regions using FSL (Jenkinson et al., 2012). Binarized connectivity matrices of the brain regions of interest were generated using the 90 regions from the AAL and whole brain tractography with ExploreDTI (Leemans et al., 2009), where the parcellated regions represented the nodes of the graph. If the average FA of streamlines between nodes was above 0.15, the edge between these nodes was included in the resultant (binarized) connectome. The connectivity matrices were manually inspected for quality control to ensure that the regions of the network were fully connected, and five scans were found to not have a fully connected network and were thus excluded. This resulted in our final sample size of 88 datasets.

Brain regions that have well-established associations with language skills (Hertrich et al., 2020; Martin et al., 2015; Turker et al., 2019) were selected to form a network for analysis: the opercular part of the inferior frontal gyrus, the triangular part of the inferior frontal gyrus, the lingual gyrus, the fusiform gyrus, the angular gyrus, Heschl's gyrus, the superior temporal gyrus, and the inferior temporal gyrus (figure 4.1). Moreover, PAE has been recently reported to moderate the associations between this network and other language skills (Ghasoub et al.,

2024b), further supporting their selection for analysis. The connectivity matrix of this network was extracted from the whole brain matrix.

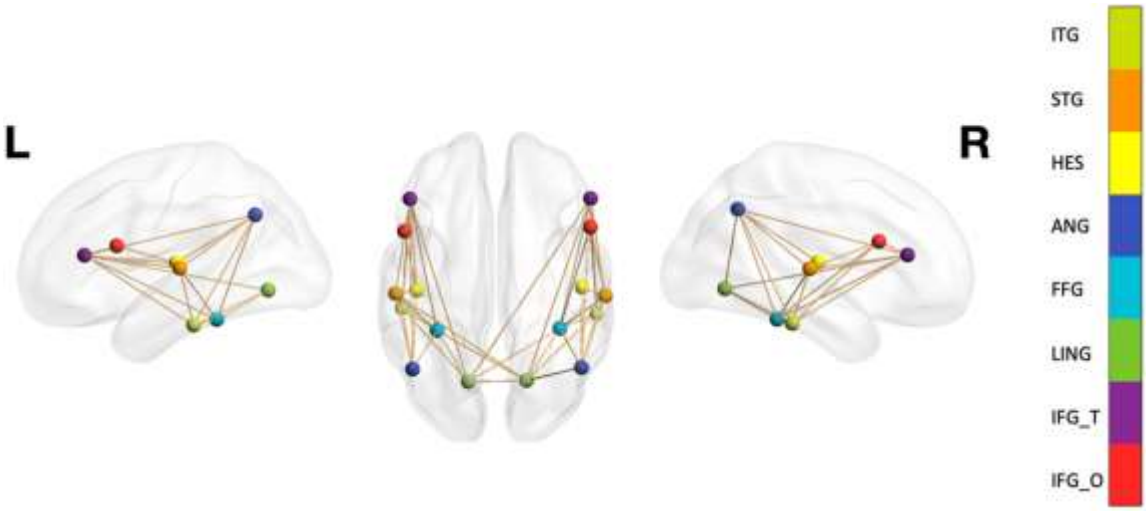

Figure 4.1 Left, bilateral, and right hemisphere language networks were defined as including the inferior temporal gyrus (light green; ITG), superior temporal gyrus (orange; STG), Heschl's gyrus (yellow; HES), angular gyrus (navy blue; ANG), fusiform gyrus (sky blue; FFG), lingual gyrus (green; LING), triangular part of the inferior frontal gyrus (purple; IFG_T), and opercular part of the inferior frontal gyrus (red; IFG_O). Figure was generated using BrainNet Viewer (Xia et al., 2013).

Graph theory measures of network connectivity (clustering coefficient, global efficiency, local efficiency, nodal degree, and betweenness centrality) were calculated at the selected language network level using the Brain Connectivity Toolbox (Rubinov & Sporns, 2010). These measures have been previously related to reading skills in older children (Mao et al., 2021; Vourkas et al., 2011). Clustering coefficient, a measure of functional specialization, describes the average

density of connections between regions. Global efficiency measures the efficiency of information transfer across the whole network, and local efficiency measures average information transfer efficiency between local neighboring nodes. Nodal degree is the average number of connections (edges) projecting to/from each region. Betweenness centrality measures the average node's role in acting as a bridge between separate clusters across the network. All five metrics were calculated for the bilateral network (16 × 16 matrix), as well as the left and right networks separately (8 × 8 matrices).

4.3.5 Statistical Analysis

Statistical analysis was conducted using R studio (Version 4.2.1; R Core Team, 2021). T tests were used to test group differences in age, Expressive Communication scaled scores, and Receptive Communication scaled scores. Differences in sex and household income distributions between groups were tested using chi-squared tests. Two linear regression models were used to examine PAE's effects on graph theory metrics and language scores. The first regression model examined differences in graph theory metrics between children with PAE and controls while controlling for age, sex, and household income with the following equation: Graph Theory Metric ~ Sex + Age + Household Income + PAE. We then used a second model to determine how PAE moderated the association between language skills and graph theory metrics using the following equation: language ~ Sex + Age + Household Income + PAE + Graph Metric + Graph Metric * PAE. Initially, native language was included as a covariate in the regression models but was removed as it did not have significant effects and did not contribute to the fit of the model. Household income had significant effects and contributed to the model fit, therefore was included as a covariate. Given its prevalence in this dataset, we also ran the same models with

PTE included to examine its effects. Separate models were used to test each graph theory metric (clustering coefficient, global efficiency, local efficiency, nodal degree, betweenness centrality) from each network (bilateral, left, right), with each language measure (Expressive Communication, Receptive Communication). Results are reported both uncorrected and corrected for multiple comparisons using false discovery rate (FDR) at $q < 0.05$.

4.3.6 Supplementary Analysis

In addition to the network selected for the main analysis, we examined the PAE moderation effects on the brain–language associations in an extended network that included the same regions of interest with the addition of the middle temporal gyrus and supramarginal gyrus. The results of this analysis are reported under the supplementary materials (appendices in thesis), available in the Supporting Information at https://doi.org/10.1162/nol_a_00161.

4.4 Results

4.4.1 Group Differences in Demographics and Language Performance

Children in the PAE group were younger than the control group by just under 1 month ($p = 0.02$). There were no significant differences in sex or household income distribution between groups. Expressive Communication and Receptive Communication scores did not differ significantly between the PAE and unexposed groups (table 4.1). Given that age was significantly different, we re-ran the language models to control for age as a covariate only and then added a group-age interaction. In these models, there were still no significant group differences in Expressive or Receptive Communication scores.

Table 4.1 Participant demographics and language scores

	PAE (n = 23)	**Control (n = 65)**	**p value**
Age (months)	32.57	33.52	0.02*
Sex	Male = 13 (56.5%)	Male = 43 (66.2%)	0.57
Household income	<R1,000/month = 8	<R1,000/month = 13	0.29
	R1,000–5,000/month = 13	R1,000–5,000/ month = 41	
	>R5,000/month = 2	>R5,000/month = 11	
Expressive Communication scaled score (n = 76)	6.86	7.38	0.45
Receptive Communication scaled score (n = 78)	6.71	6.93	0.68

4.4.2 Group Differences in Graph Theory Metrics

Children with PAE had higher average local efficiency (beta = 0.04, 95% CI [0.01, 0.07], t = 2.71, p = 0.008, q = 0.060) and clustering coefficient (beta = 0.05, 95% CI [0.01, 0.08], t = 2.73, p = 0.008, q = 0.060) in the bilateral language network compared to unexposed children (figure 4.2). These differences did not survive multiple comparison correction.

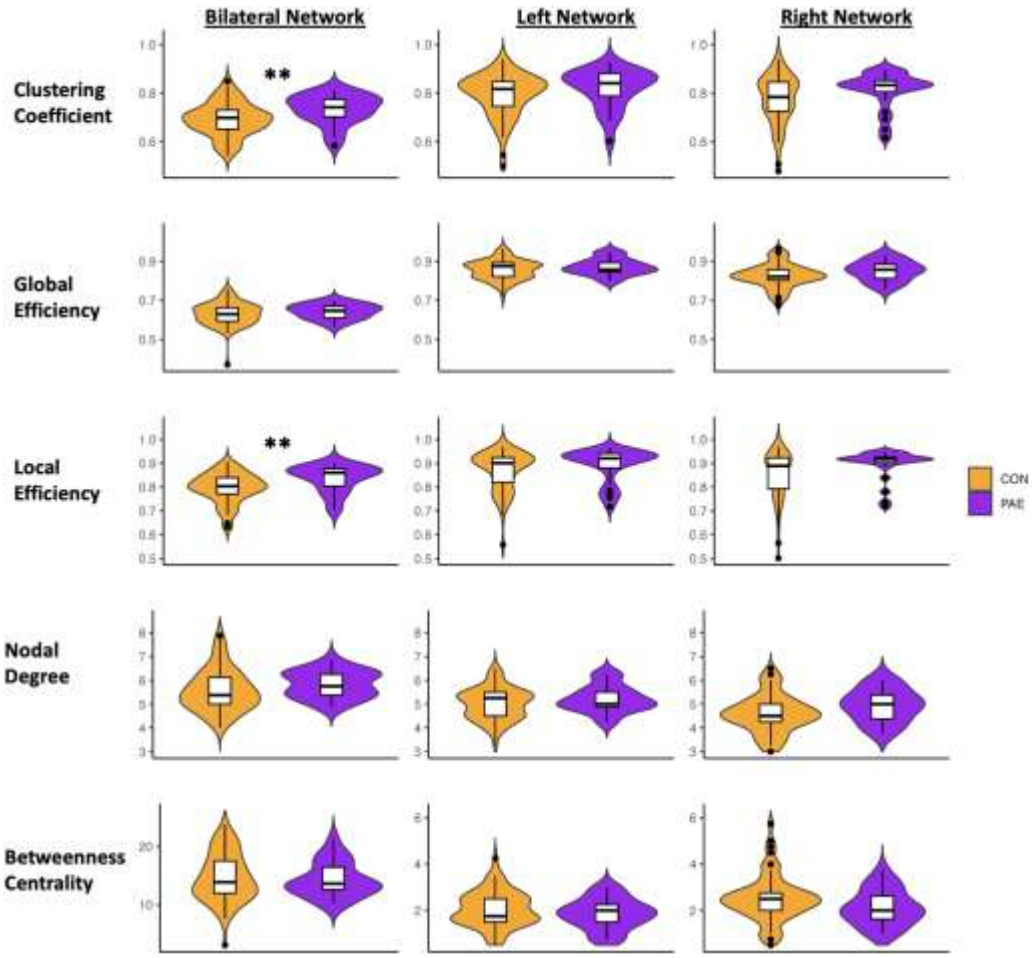

Figure 4.2 Differences in graph theory metrics between prenatal alcohol exposure (PAE) and control (CON) groups. Clustering coefficient (top row), global efficiency (second row), local efficiency (third row), nodal degree (fourth row), and betweenness centrality (fifth row) in the bilateral network (16 × 16 matrix, first column), left network (8 × 8 matrix, second column), and right network (8 × 8 matrix, third column). The PAE group had higher clustering coefficient ($p = 0.008$) and local efficiency ($p = 0.008$) in the bilateral network compared to controls. ** indicates significant differences ($p < 0.01$); however, these differences did not survive multiple comparison correction ($q < 0.05$).

4.4.3 Language Assessments

Regression models for Expressive Communication revealed significant moderation effects of PAE on communication–graph theory metric associations for right hemisphere network global efficiency (beta = 22.70, 95% CI [1.57, 43.83], t = 2.14, p = 0.036, q = 0.205), nodal degree (beta = 1.70, 95% CI [0.13, 3.27], t = 2.15, p = 0.035, q = 0.205), and betweenness centrality (beta = −1.44, 95% CI [−2.83, −0.06], t = −2.08, p = 0.041, q = 0.205; table 4.2). In these models, children with PAE had a positive relationship between Expressive Communication and global efficiency and nodal degree and a negative relationship between Expressive Communication and betweenness centrality, while the opposite relationship was found in the unexposed children (figure 4.3). None of the significant moderations survived FDR corrections. Additionally, there were main effects of global efficiency (beta = −11.72, 95% CI [−21.82, −1.63], t(69) = −2.32, p = 0.023, q = 0.125), nodal degree (beta = −0.88, 95% CI [−1.64, −0.11], t(69) = −2.29, p = 0.025, q = 0.125), and betweenness centrality (beta = 0.73, 95% CI [0.10, 1.37], t(69) = 2.32, p = 0.023, q = 0.125) on Expressive Communication scores; these did not survive FDR correction. Children with PAE had lower Expressive Communication scores in these models (table 4.2). There were no significant sex or household income effects in any of the models. No significant moderation effects were found in the rest of the regression models or Receptive Communication scores (table 4.3).

Table 4.2 Associations between graph theory metrics and Expressive Communication scores

Predictors	**Bilateral**			**Left**			**Right**		
	β	**CI**	***p***	***β***	**CI**	***p***	***β***	**CI**	***P* (*q*)**
Clustering coefficient									
Age	0.30	[−0.03, 0.63]	0.073	0.28	[−0.04, 0.61]	0.089	0.37	[0.03, 0.70]	0.031 (0.105)

PAE status	−9.19	[−22.68, 4.30]	0.179	−4.03	[−15.67, 7.60]	0.492	−4.83	[−16.69, 7.03]	0.419
Clustering coefficient	−0.37	[−9.42, 8.68]	0.935	3.68	[−2.86, 10.23]	0.265	−5.39	[−12.09, 1.32]	0.113
PAE status × Clustering coefficient	12.39	[−6.11, 30.88]	0.186	4.70	[−9.54, 18.93]	0.512	6.06	[−8.61, 20.73]	0.413
Global efficiency									
Age	0.31	[−0.01, 0.64]	0.057	0.27	[−0.06, 0.60]	0.108	0.38	[0.06–0.70]	0.019 (0.105)
PAE status	−14.37	[−33.43, 4.68]	0.137	−13.77	[−36.81, 9.27]	0.237	−19.15	[−37.06, −1.23]	0.037 (0.260)
Global efficiency	−9.02	[−20.39, 2.35]	0.118	3.71	[−8.02, 15.44]	0.531	−11.72	[−21.82, −1.63]	0.023 (0.125)
PAE status × Global efficiency	22.33	[−7.30, 51.95]	0.137	15.63	[−10.82, 42.08]	0.243	22.70	[1.57, 43.83]	0.036 (0.205)
Local efficiency									
Age	0.31	[−0.02, 0.63]	0.065	0.28	[−0.05, 0.61]	0.090	0.36	[0.03–0.69]	0.035 (0.105)
PAE status	−12.71	[−29.55, 4.13]	0.137	−6.60	[−20.55, 7.34]	0.348	−6.22	[−21.31, 8.87]	0.414
Local efficiency	−1.79	[−11.30, 7.71]	0.708	3.83	[−3.21, 10.88]	0.282	−4.21	[−11.14, 2.72]	0.230
PAE status × Local efficiency	15.18	[−5.10, 35.46]	0.140	7.19	[−8.50, 22.88]	0.364	7.03	[−9.93, 24.00]	0.411
Nodal degree									
Age	0.31	[−0.02, 0.63]	0.063	0.27	[−0.06, 0.60]	0.110	0.37	[0.06, 0.69]	0.022 (0.105)
PAE status	−9.68	[−20.83, 1.47]	0.088	−6.57	[−16.95, 3.81]	0.211	−8.19	[−15.92, −0.46]	0.038 (0.260)
Nodal degree	−0.50	[−1.18, 0.18]	0.149	0.24	[−0.63, 1.12]	0.579	−0.88	[−1.64, −0.11]	0.025 (0.125)
PAE status × Nodal degree	1.66	[−0.25, 3.57]	0.087	1.23	[−0.75, 3.21]	0.220	1.70	[0.13, 3.27]	0.035 (0.205)
Betweenness centrality									

Age	0.32	[−0.01, 0.64]	0.054	0.27	[−0.06, 0.60]	0.104	0.40	[0.08, 0.72]	0.016 (0.105)
PAE status	3.87	[−1.76, 9.50]	0.175	1.54	[−1.89, 4.96]	0.373	3.24	[−0.02, 6.50]	0.052
Betweenness centrality	0.12	[−0.03, 0.27]	0.119	−0.29	[−1.06, 0.48]	0.454	0.73	[0.10, 1.37]	0.023 (0.125)
PAE status × Betweenness centrality	−0.27	[−0.66, 0.11]	0.162	−0.91	[−2.62, 0.80]	0.292	−1.44	[−2.83, −0.06]	0.041 (0.205)

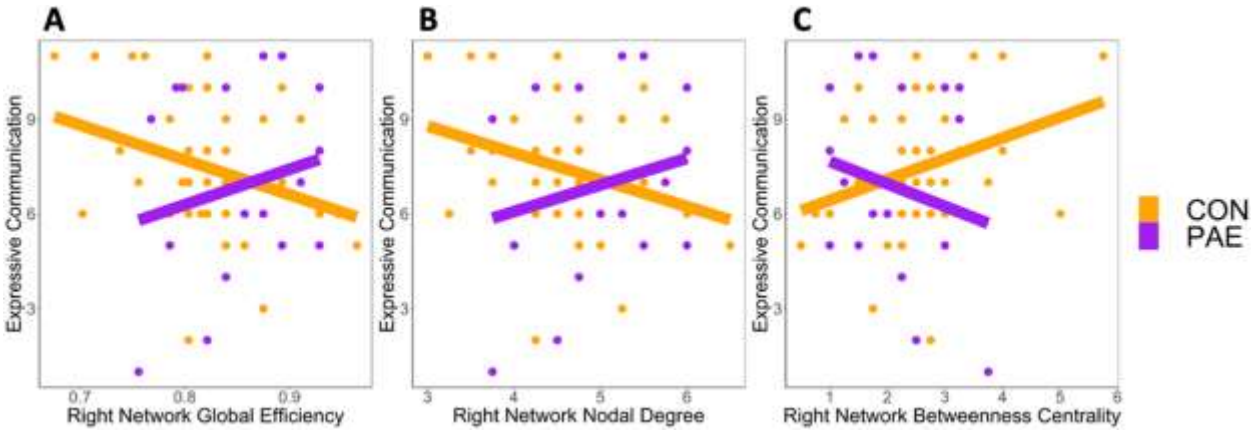

Figure 4.3 PAE moderated the Expressive Communication–graph theory metric associations for (A) global efficiency, (B) nodal degree, and (C) betweenness centrality in the right hemisphere network.

Table 4.3 Associations between graph theory metrics and Receptive Communication scores

Predictors	**Bilateral**			**Left**			**Right**		
	β	**CI**	***p***	***β***	**CI**	***p***	***β***	**CI**	***P* (*q*)**
Clustering coefficient									
Age	0.24	[−0.01, 0.48]	0.061	0.23	[−0.02, 0.48]	0.065	0.25	[0.00, 0.49]	0.050 (0.081)
PAE status	−3.92	[−14.36, 6.52]	0.457	0.29	[−8.64, 9.21]	0.949	10.12	[−7.74, 9.97]	0.802

Clustering coefficient	−0.83	[−7.74, 6.08]	0.811	20.02	[−2.97, 7.01]	0.422	−3.31	[−8.15, 1.53]	0.177
PAE status × Clustering coefficient	50.35	[−8.92, 19.63]	0.457	−0.42	[−11.30, 10.46]	0.939	−1.24	[−12.20, 9.72]	0.822
Global efficiency									
Age	0.24	[−0.01, 0.49]	0.056	0.22	[−0.03, 0.46]	0.085	0.26	[0.02, 0.50]	0.037 (0.081)
PAE status	10.68	[−12.65, 16.00]	0.816	−4.69	[−22.20, 12.82]	0.595	20.57	[−11.13, 16.26]	0.710
Global efficiency	−2.40	[−9.67, 4.86]	0.512	40.99	[−3.91, 13.89]	0.267	−6.15	[−13.69, 1.39]	0.108
PAE status × Global efficiency	−2.57	[−24.87, 19.72]	0.819	50.29	[−14.81, 25.39]	0.601	−2.84	[−18.99, 13.31]	0.727
Local efficiency									
Age	0.24	[−0.01, 0.49]	0.055	0.23	[−0.01, 0.48]	0.065	0.25	[0.00, 0.50]	0.047 (0.081)
PAE status	−6.07	[−19.16, 7.02]	0.358	−0.90	[−11.91, 10.10]	0.871	−0.43	[−11.71, 10.85]	0.940
Local efficiency	−2.24	[−9.49, 5.01]	0.540	10.82	[−3.57, 7.21]	0.503	−2.75	[−7.62, 2.11]	0.263
PAE status × Local efficiency	70.34	[−8.38, 23.05]	0.355	0.94	[−11.39, 13.28]	0.879	0.60	[−12.08, 13.28]	0.925
Nodal degree									
Age	0.24	[−0.00, 0.49]	0.053	0.22	[−0.03, 0.47]	0.083	0.25	[0.01, 0.50]	0.040 (0.081)
PAE status	10.51	[−7.11, 10.13]	0.728	−2.06	[−9.95, 5.84]	0.605	10.29	[−4.63, 7.21]	0.666
Nodal degree	−0.18	[−0.69, 0.34]	0.495	0.37	[−0.29, 1.04]	0.266	−0.44	[−1.02, 0.13]	0.127
PAE status × Nodal degree	−0.25	[−1.73, 1.22]	0.734	0.38	[−1.13, 1.89]	0.619	−0.23	[−1.44, 0.97]	0.701
Betweenness centrality									
Age	0.25	[0.01, 0.50]	0.044	0.21	[−0.03, 0.46]	0.087	0.26	[0.02, 0.51]	0.033 (0.081)
PAE status	0.46	[−3.76, 4.67]	0.829	0.61	[−1.99, 3.20]	0.642	−0.20	[−2.68, 2.28]	0.871
Betweenness centrality	0.07	[−0.04, 0.18]	0.194	−0.32	[−0.90, 0.26]	0.274	0.41	[−0.06, 0.87]	0.088
PAE status × Betweenness centrality	−0.03	[−0.32, 0.26]	0.831	−0.37	[−1.67, 0.93]	0.576	0.17	[−0.89, 1.22]	0.753

4.4.4 PTE Effects on Language Assessments

There were no significant main effects of PTE in any of the regression models. When controlling for PTE, nominally significant moderation effects for PAE on the Expressive Communication-graph theory metric associations remained similar to the models without PTE (table 4.4).

Table 4.4 Associations between graph theory metrics and Expressive Communication scores with PTE as a covariate

Predictors	**Global efficiency**			**Nodal degree**			**Betweenness centrality**		
	β	**CI**	***p***	***β***	**CI**	***p***	***β***	**CI**	***p***
Age	0.36	[0.03, 0.69]	0.032	0.35	[0.02, 0.67]	0.036	0.38	[0.05, 0.70]	0.026
PTE status	0.28	[−1.40, 1.97]	0.739	0.28	[−1.40, 1.97]	0.737	0.29	[−1.40, 1.98]	0.734
PAE status	−20.06	[−38.19, −1.92]	0.031	−8.81	[−16.68, −0.94]	0.029	2.90	[−0.46, 6.25]	0.089
Graph theory metric	−12.19	[−22.50, −1.88]	0.021	−0.91	[−1.69, −0.14]	0.022	0.76	[0.11, 1.41]	0.022
PAE status × Graph theory metric	23.25	[1.93, 44.57]	0.033	1.73	[0.15, 3.31]	0.033	−1.49	[−2.89, −0.09]	0.037

4.4.5 Supplementary Network Analysis

The extended network analysis in the Expressive Communication models revealed similar weak PAE moderation effects on the right hemisphere global efficiency, nodal degree, and betweenness centrality that were insignificant. The complete results are reported in the Supporting Information (Supplementary Tables 1 and 2).

4.5 Discussion

In this study, we found nominally higher clustering coefficient and local efficiency in a language network in the PAE group compared to unexposed toddlers. PAE also moderated the associations between expressive language skills and graph theory metrics such that toddlers with PAE had positive associations between language scores and structural connectivity while the opposite relationship was found in controls. To our knowledge, this is the first study examining structural network connectivity in toddlers with PAE and only the fourth study looking at the structural connectome in individuals with PAE (Ghasoub et al., 2024b; Long et al., 2020; Roos et al., 2021a). Our findings shed light on the neural correlates of early language skills in toddlers with PAE and suggest the early emergence of small differentiations in brain–language relationships. These findings also demonstrate the need for further research investigating the effects of PAE on structural brain connectivity and language development longitudinally to determine how these associations change with age as children get older and language skills develop.

Toddlers with PAE had higher local efficiency and clustering coefficient in the bilateral network compared to unexposed controls, though these differences did not survive FDR correction. Clustering coefficient measures the density of connection between nodes, while local efficiency measures how well information is transferred between neighboring regions (Bullmore & Sporns, 2009; Fornito, 2016). Thus, higher local efficiency and clustering coefficient in the network indicate higher efficient information transfer and specialized processing at the local level. Our study shows that toddlers with PAE may have denser connections and better and more mature processing between language regions at the local level, possibly indicating more specialized processing of cognitive functions. These findings align with a prior study that found no significant differences in white matter connectome measures at the global level in neonates with

PAE, but higher regional connectivity (Roos et al., 2021a). However, our findings contrast studies in older children (3+ yr) and adolescents with PAE that found overall weaker structural connectivity compared to unexposed controls (Ghasoub et al., 2024b; Long et al., 2020). Our results, along with those from previous connectome studies, suggest that children with PAE may have slightly higher and/or similar connectivity and specialized processing in the structural language network during the early stages of development, and then display weaker connectivity compared to controls as they get older. This is also supported by findings from tract-based analyses that show stronger white matter connectivity (higher FA and/or lower diffusivity) in young children with PAE (Donald et al., 2024; Kar et al., 2021, 2022; Roos et al., 2021b), and weaker white matter connectivity in older children and adolescents (Ghazi Sherbaf et al., 2019; Lebel et al., 2008). Future longitudinal studies will be essential to better understanding how the structural connectome changes over time in children with PAE.

PAE had weak moderation effects on the associations between Expressive Communication scores and global efficiency, nodal degree, and betweenness centrality in the right hemisphere network. Higher global efficiency, nodal degree, and lower betweenness centrality were associated with better expressive communication skills in children with PAE, while the opposite relationship was found in unexposed children. The connectome–language relationship exhibited by the PAE children in our sample is what has been previously observed in slightly older unexposed children (3+ yr; Ghasoub et al., 2024b; Lou et al., 2021) and suggests that stronger patterns of connectivity, network integration, and decentralized communication underlie better language skills in these toddlers. Interestingly, however, the controls showed opposite relationships to those observed in older cohorts of unexposed children. These effects were in the right hemisphere, while language is typically left-lateralized. Prior work has shown more right

hemisphere involvement in younger children and in individuals with reading or language difficulties (Waldie et al., 2013; Zhao et al., 2016), suggesting that more connectivity in the right hemisphere may reflect a compensatory mechanism or lack of specialization. Furthermore, these findings could also reflect, at least in part, the influence of external factors such as socioeconomic status (SES), and/or the timing and duration of exposure. All participants in this study lived with their biological parents and came from low-income families. This contrasts much prior work that has examined PAE in the context of higher-income families in North America, often in children no longer living with their biological parents. While the influence of SES on brain changes is attenuated/absent in youth with PAE (Uban et al., 2020), our findings may not be generalizable to higher SES populations. Our findings instead may be more relevant to children with PAE from low-income contexts and living with their biological parents, a population that has been vastly understudied. This is especially important as participants from low SES contexts are more likely to have more severe FASD diagnoses, making them one of the most impacted populations by PAE (May & Gossage, 2011). Nonetheless, future longitudinal studies along with replication in other cohorts are needed to investigate this further.

Children with and without PAE performed similarly on Expressive and Receptive Communication assessments. This contrasts with studies showing receptive and expressive language deficits in older children and adolescents with PAE (Poth et al., 2023; Proven et al., 2014; Wyper & Rasmussen, 2011). Language and communication deficits tend to worsen with age in individuals with PAE (Kippin et al., 2021; Proven et al., 2014), and thus may become apparent later. It is also possible that language deficits in individuals with PAE are influenced by other prenatal (e.g., amount and timing of exposure) and postnatal (e.g., socioeconomic) factors that may not be fully captured in these studies.

The findings of our study are limited by the small sample size, especially of children with PAE. We were also unable to test the interaction effects of prenatal alcohol and tobacco exposure due to low power, but this is important to investigate in future studies. Further research is needed to mitigate these limitations by examining the effects of PAE on structural network connectivity and language development longitudinally. The diffusion tensor model is limited by its inability to capture crossing white matter fibers (Soares et al., 2013), which could be addressed in future studies using improved diffusion modeling methods such as constrained spherical deconvolution (CSD) and neurite orientation dispersion and density imaging (NODDI) models as well as multimodal approaches. However, it is worth noting that these models have been difficult to implement in pediatric populations (especially toddlers) due to factors such as longer image acquisition time.

4.6 Conclusion

In summary, our study unveils novel findings into the effects of PAE on structural connectivity and language development during the toddler years, a critical neurodevelopmental period that has been understudied. We show that PAE moderates the relationships between structural brain connectivity and early language skills in toddlers, complementing studies in older children and suggesting that brain alterations are present during the toddler years. However, it is important to note that these findings did not remain significant following corrections, potentially because of the limitations discussed earlier. While we did not find group differences in language performance, the small differences in brain–language relationship between exposed and unexposed children could suggest the emergence of different trajectories from a young age that may underlie and possibly lead to later language deficits. Our findings also support the need for further longitudinal research to fully capture the differences in these associations and potentially

lay the groundwork for earlier identification of reading and language deficits associated with PAE.

Chapter 5: Discussion

5.1 Summary

Language and reading development begin early in childhood and occur at the same time as rapid brain development. The overall goal of this thesis was to provide a better understanding of how structural neural network properties are associated with early language and reading development in young children, and to examine the effect of PAE on these associations. To accomplish this, two cohorts of children from Canada and South Africa were studied separately.

In chapter 2, we examined the structural neural correlates of pre-reading skills in typically developing preschool aged children in an accelerated longitudinal design. We found significant associations between pre-reading skills and structural network properties, suggesting the neural foundations that support reading skills are established early on. In chapter 3, we expanded on the second chapter and looked at the extent to which PAE moderates the associations found between structural network properties and pre-reading skills. We found that children with PAE had significantly lower structural connectivity compared to unexposed children. We also found significant moderation effects of PAE on these neural correlates of pre-reading skills, highlighting that structural connectivity appears to underlie emerging reading deficits in children with PAE. In chapter 4, we examined an even younger cohort of toddlers with PAE, investigating similar moderation effects on the structural network properties and their associations with early language skills. We initially hypothesized that we would find a relationship similar to that found in chapter 3; however, we found weak moderation effects of PAE on these associations. These weak moderation effects could suggest the emergence of brain-language alterations that are found in older children and adults, or they may be related to

differences in study design or population, such as imaging acquisition, assessments used, and/or the child's primary language. Together, these findings suggest an effect of PAE on structural network properties that may underlie the language and reading challenges seen in children with PAE. Having a better understanding of these structural network correlations with early language skills at an early age in children with and without PAE can lay the groundwork for earlier and more effective interventions for learning disabilities broadly and reading disabilities in particular.

5.2 Integrating results across studies

The findings in this thesis contribute additional insight into the broader field of brain and language development and specifically to the early correlates of brain and language development in young children with PAE. Several emerging themes are noted from the findings of this thesis.

First, the findings from all studies suggest that the structural neural correlates of reading and language abilities are apparent from a very young age. In study 1, structural network properties of the reading network were significantly associated with pre-reading skills in typically developing preschool aged children. In study 2, similar associations were found in preschool aged children with PAE. The results from both studies indicate that the structural connectivity properties of the reading network underlie early reading skills from a young age, before formal reading instruction begins in school. Moreover, in study 3, structural network properties were associated with expressive communication skills in toddlers with PAE, showing the presence of similar associations to pre-reading skills from even a younger age during an early sensitive period of language development. These findings complement those from previous studies that examined the presence of these associations in individual white matter tracts and in smaller

sample sizes (Myers et al., 2014; Saygin et al., 2013; Walton et al., 2018). Expanding on this, our findings provide novel insights by showing how the overall network organization and properties of the reading network are also present early and are associated with early reading and language skills. This is important since reading and language develop early, around the same time as rapid brain developing is happening, and most reading and language difficulties don't get diagnosed until children are older and struggling in school, impacting their academic achievement and mental health. The presence of these associations from an early age can be potentially explored as early markers of reading and language challenges and in turn, early interventions.

Second, the effects of PAE on language and reading skills as well as how they relate to structural connectivity differ across age groups. In study 3, the toddlers with PAE did not have significantly different language scores compared to unexposed controls. Whereas in study 2, preschool aged children with PAE had significantly lower pre-reading scores than unexposed controls albeit within the population norm. These findings, combined with previous ones that found older children and adolescents with PAE perform worse with age on reading and language assessments, highlights the fact that reading and language challenges in children with PAE seem to become more evident with age. Similar trends are found at the brain level as well. The structural connectivity properties in toddlers with PAE from study 3 were not significantly different compared to unexposed controls while they were significantly lower in the preschoolers with PAE from study 2. These findings are also in alignment with both previous connectome studies of PAE (Long et al., 2020; Roos et al., 2021) as well as previous studies showing earlier maturation of white matter pathways in children with PAE that later declines with age (Donald et al., 2024; Kar et al., 2022). Together, these findings underscore the age-specific effects of PAE

on development, suggesting the need for caution when interpreting PAE studies depending on the age groups examined. Moreover, they underscore the need for longitudinal PAE cohort studies to fully capture the teratogenic effects of PAE on brain and behavior development. Nonetheless, these differences may also be unique to early language and pre-reading skills respectfully.

Third, socioeconomic status had a significant effect in study 3 in our South Africa cohort with PAE but not in the Calgary cohort. In contrast with the South Africa cohort, the findings from the Calgary cohort are in line with previous studies done on PAE which showed that PAE attenuated socioeconomic status effects (McLachlan et al., 2020; Uban et al., 2020). Interestingly, all children from Calgary with PAE lived in foster or adoptive care, similar to these previous studies that did not find socioeconomic status effects in PAE, while all children with PAE from the South Africa cohort were living with their biological parents. Looking at the results from both studies, an interesting theme emerges. It is possible that socioeconomic factors such as household income play a more significant role during the children's earliest environment including in the prenatal and early postnatal periods. Consistent with this, the children in the Calgary cohort were older than those in the South Africa cohort. It is possible that the reason why household income was not significant in study 2 could have been because the children were placed in foster or adoptive care with parents from a higher socioeconomic status and, therefore, more time was spent away from their early pre/postnatal environment with their biological parents. These effects have not been directly examined in the literature. The findings from this thesis lay the foundation for future studies to investigate this further using other socioeconomic

factors such as household environment and parental interactions that may provide additional insight beyond household income.

Furthermore, another emerging theme and novel contribution of this thesis is the use of graph theory analysis to further understand brain and behavior development and particularly in the context of language and PAE. Graph theory analysis offers an interesting approach to study brain development from a network perspective and has been used extensively over the last two decades to better understand neural networks in typically developing children as well as children with neurodevelopmental disorders (Fornito, 2016). Graph theory analysis also provides insight into white matter development at a more comprehensive macrostructural level compared to most structural and DTI studies examining the microstructure of individual white matter pathways (Yu et al., 2018). For instance, one key advantage of graph theory analysis is its ability to identify key regions that are highly interconnected and serve as a communication mediator between regions (i.e., hubs) (Fornito, 2016). Graph theory analysis can also be utilized to better understand some aspects of pathology and atypical development that conventional DWI methods does not capture such as hypo/hyper connectivity network properties and how they relate to behavior such as in cases of ADHD and ASD. In children with PAE, the use of graph theory analysis can shed light on how PAE influences brain network development and in turn, cognition and behavior, thus providing more information to understand the teratogenic effects of alcohol on brain development during pregnancy. In the context of reading and language, although previous DTI studies highlight the importance of the microstructural integrity of the white matter pathways connecting Broca's and Wernicke's regions (i.e., arcuate fasciculus) in reading processing and comprehension, graph theory analysis can provide a more complete picture of

how the connectivity between all regions and pathways associated with reading influence performance. In this thesis, we found associations between graph theory measures and reading/language abilities with various significance levels across all studies, suggesting that structural properties of the reading and language network such as organization, connectivity density, as well as efficiency of transferring information between regions play a role in an individual's reading and language abilities from a young age. This was seen in both typically developing children as well as children with reading and language deficits such as PAE. Having a better understanding of how these network measures are related to behavioral outcomes can lead us closer to understanding the behavioral challenges seen in PAE from a neurological viewpoint and integrating this knowledge for earlier and better intervention outcomes.

Finally, as is the case for most behavioral brain research, the end goal of understanding the neurobiological underpinnings of language and reading processes is to further drive progress of diagnosis and interventions of reading and language challenges. Neuroimaging research can be utilized for this in several ways, such as understanding the biological mechanisms of these challenges, as well as identifying early markers of neurological deficits in the reading network. This is essential since language develops early and has been shown to have a critical period of development. Therefore, identifying language difficulties is crucial to be able to intervene early and ensure proper development. As for reading, although it does not necessarily have a critical period of development, children develop reading skills early, and most children with reading difficulties get diagnosed years after already having been in the school system, consequently impacting their mental health and academic achievement. More notably, reading disabilities account for almost 80% of known learning disabilities, further underlining the significance of the

need for achieving this (Kohli et al., 2018). In this thesis, we investigated the structural neural correlates of early language and early reading skills in children spanning the age range of 2-7 years and found the presence of these correlates from an early age during a crucial brain and language developmental period. The findings of this thesis addressed the gaps in the literature, particularly in this age group, and supports the case for the importance of early diagnosis and interventions. Furthermore, PAE has been shown to disproportionately affect marginalized communities. These populations, including the ones included in this thesis, often tend to have negligible resources and a history of both trauma and neglect. (Eisenstat et al., 2023). By considering these factors, along with the fact that PAE can affect brain and language development, this thesis shed light on the importance of this issue. Studying populations that have been historically neglected in the literature reinforces the need for further research to provide a better understanding and more comprehensive support for these populations.

5.3 Limitations

Several limitations may confound the findings of this thesis and should be considered in its interpretation and/or addressed in future research. First, all studies used DTI to calculate white matter microstructural and connectivity measures. The tensor model best represents white matter fibers in single fiber populations that corresponds to a single fiber orientation; it is however limited in representing complex multiple fiber populations in which fibers are crossing and/or bending (Qiu et al., 2015). Moreover, it is estimated that 63-90% of white matter voxels in the brain have multiple fiber populations (Jeurissen et al., 2013). Given that the DTI model is limited as it cannot account for crossing fiber, our findings are potentially influenced by this limitation. In addition, children with PAE from study 2 were all in adoptive or foster care. Consequently,

information about their early environment as well as polysubstance exposure are limited. Early environmental factors are significantly associated with children's brain and behavior development, thus, not being able to account for these factors can influence the results of this thesis. Additionally, information about the amount, frequency, and duration of alcohol exposure are limited in this cohort and thus may further influence the results. Moreover, children with PAE from cohorts in studies 2 and 3 were from different age groups, had different native languages, underwent different assessments, as well as had different scanning acquisition protocol. For these reasons, it was not feasible to directly compare the results from the two cohorts to gain a more comprehensive and universal understanding on the effects of PAE on brain and language development. Furthermore, another major difference between the studies is the range of socioeconomic factors. In studies 1 and 2, the children came from a relatively high-income families compared to the national median; thus, the findings may not be generalizable to the population. In study 3, the children's families were on the other end of the socioeconomic spectrum, coming from low-income backgrounds. Reading and language development have been shown to be influenced by socioeconomic status (Noble et al., 2006). While having children from opposing ends of the spectrum is a strength of this thesis, it can also be considered a limitation. Given that neither cohort was representative of the average population income, the results of this thesis may not be generalizable to the general population. Equally important, socioeconomic status was measured by median household income only, without taking other familiar factors such as household environment, parent interaction, and home literacy that also influence language and reading outcomes.

5.4 Future directions

The findings of this thesis lay the groundwork for several future research projects to provide a more comprehensive understanding of the neural underpinnings of early language development as well as the teratogenic effects of alcohol on these mechanisms. Made possible by recent advances in diffusion imaging techniques, the application of advanced modalities and techniques such as CSD could help to address the limitations of DTI and would provide a more precise representation of white matter pathways in the brain. Expanding on the findings of chapter 2, longitudinal research examining the relationship between pre-reading skills, reading skills, and changes in structural connectivity will shed light on the trajectories of brain and reading development as children transition to formal reading instruction. This would aid the identification of risk factors for reading disabilities from an earlier age and lead to more effective interventions. In order to better uncover the underlying teratogenic effects of PAE on brain development, similar longitudinal research that examines the age-specific effects of PAE on brain and language development, particularly white matter development and structural connectivity, is also needed. Having a better understanding of these effects is crucial to further bring attention to the topic, raises awareness on the effects of PAE on child's development, as well as inform government policies. The studies in chapters 3 and 4 were also the first to examine PAE moderation effects on early reading and language skills and brain connectivity in toddlers and preschool aged children. Examining these moderation effects in older children with PAE provides a natural extension to see how these relationships change with age, specifically whether structural connectivity worsens as children with PAE get older and their reading skills develop/worsen. Putting it all together, the findings from all studies lay the groundwork for intervention studies investigating treatment outcomes for children with language and reading

disabilities and those with PAE particularly. Future studies could examine structural network properties along with treatments to explore potential intervention strategies for this understudied population. In addition, even though structural connectivity provides the anatomical basis for functional connectivity, the findings in the literature are somewhat mixed and young children are understudied. Future research could be done to investigate the structural-functional connectivity coupling in these young children and how it relates to their language and reading skills. Moreover, the findings of these studies motivate the need for conducting further research in this area by recruiting more representative samples of various socioeconomic backgrounds to increase the generalizability of the findings as well as examining the effects of other social factors on the brain-language relationships. Having a sample encompassing the full range of socioeconomic status can better uncover its effects. Furthermore, investigating genetic risk along environmental factors and how they in turn influence brain development and subsequent reading and language outcomes can provide a more comprehensive picture of the underlying roots of said outcomes and consequently, a more comprehensive framework for early diagnosis and interventions. Building on the overall findings of this thesis, these longitudinal, representative studies should collect additional information from the perinatal period to examine the prenatal and postnatal environmental effects on brain development and consequently, predict future reading skills in order to identify early risk factors as well as critical and sensitive period for diagnosis and interventions. Finally, international collaborations are further needed to better understand the effects of PAE on brain and language development, and this can be done by conducting studies with similar acquisition protocols and behavioral assessments in order to bridge the gap in the literature and increase the validity and reliability of the findings.

5.6 Conclusion

Reading and language skills develop early, along with ongoing rapid brain development. Despite this, limited research has been done on this age group particularly with regards to structural network properties. Additionally, research studies are more limited in children that are at risk for reading and language challenges such as children with PAE. This thesis aimed to investigate the structural properties of the reading network and how they are associated with early reading and language skills, as well as the effects of PAE on these associations. Using graph theory analysis, we found significant associations between pre-reading skills and structural network properties of the reading network, highlighting the presence of these associations from an early age and before reading acquisition. We also found that PAE moderates these associations and alters network properties albeit being age specific, underscoring the teratogenic effects of PAE on structural brain development, and suggesting that language and reading difficulties in these children may be attributed to alterations to structural brain networks. These novel findings address the current gaps in the literature and provide additional insight to better understand the neural and behavioral challenges faced by this understudied population. The findings of this thesis also lay the groundwork for future work investigating early diagnosis and intervention in young children, an important area of research given the role of language and reading skills in our everyday lives and their impact on other behavioral skills, mental health, and academic achievement.

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Appendices

Supplementary Materials for chapter 3

Supplementary Table 1. Graph theory metrics group differences for the matched sample.

Estimate: Unstandardized Beta Coefficient, Cl: Confidence Interval, p: p-value.

Global Efficiency	**Bilateral Network**			**Left Network**			**Right Network**		
Predictors	*Beta*	*Cl*	*p*	*Beta*	*Cl*	*p*	*Beta*	*Cl*	*p*
Intercept	0.27	0.23 – 0.31	**<0.001**	0.31	0.27 – 0.35	**<0.001**	0.31	0.27 – 0.35	**<0.001**
PAE	-0.18	-0.23 – -0.13	**<0.001**	-0.12	-0.17 – -0.07	**<0.001**	-0.11	-0.16 – -0.06	**<0.001**
Sex	-0.00	-0.02 – 0.01	0.484	-0.00	-0.01 – 0.01	0.852	0.01	-0.01 – 0.02	0.375
Age	0.00	-0.00 – 0.01	0.266	0.01	0.00 – 0.02	**0.003**	0.01	0.00 – 0.01	**0.034**
PAE × Age	0.02	0.02 – 0.03	**<0.001**	0.01	0.00 – 0.02	**0.005**	0.01	0.00 – 0.02	**0.008**

Local Efficiency	**Bilateral Network**			**Left Network**			**Right Network**		
Predictors	*Beta*	*Cl*	*p*	*Beta*	*Cl*	*p*	*Beta*	*Cl*	*p*

Intercept	0.36	0.30 – 0.41	**<0.001**	0.35	0.29 – 0.42	**<0.001**	0.35	0.29 – 0.42	**<0.001**
PAE	-0.21	-0.28 – -0.14	**<0.001**	-0.21	-0.29 – -0.12	**<0.001**	-0.17	-0.26 – -0.09	**<0.001**
Sex	0.01	-0.01 – 0.02	0.457	0.00	-0.02 – 0.02	0.898	0.02	-0.00 – 0.03	0.091
Age	0.01	-0.00 – 0.01	0.226	0.01	-0.00 – 0.02	0.140	0.01	-0.01 – 0.02	0.340
PAE × Age	0.02	0.01 – 0.04	**<0.001**	0.02	0.01 – 0.04	**0.003**	0.02	0.00 – 0.03	**0.020**

Clustering Coefficient	**Bilateral Network**			**Left Network**			**Right Network**		
Predictors	*Beta*	*Cl*	*p*	*Beta*	*Cl*	*p*	*Beta*	*Cl*	*p*
Intercept	0.40	0.35 – 0.45	**<0.001**	0.44	0.38 – 0.50	**<0.001**	0.44	0.38 – 0.50	**<0.001**
PAE	-0.27	-0.33 – -0.20	**<0.001**	-0.33	-0.42 – -0.25	**<0.001**	-0.31	-0.39 – -0.22	**<0.001**
Sex	0.01	-0.01 – 0.02	0.394	-0.00	-0.02 – 0.02	0.904	0.01	-0.01 – 0.03	0.173
Age	-0.00	-0.01 – 0.01	0.876	0.00	-0.01 – 0.01	0.885	-0.00	-0.01 – 0.01	0.800
PAE × Age	0.02	0.01 – 0.03	**0.001**	0.03	0.02 – 0.04	**<0.001**	0.03	0.01 – 0.04	**0.001**

Nodal Degree	**Bilateral Network**			**Left Network**			**Right Network**		
Predictors	*Beta*	Cl	*p*	*Beta*	Cl	*p*	*Beta*	Cl	*p*
Intercept	7.88	6.66 – 9.10	**<0.001**	6.25	5.34 – 7.15	**<0.001**	6.02	5.14 – 6.90	**<0.001**
PAE	-6.29	-7.91 – -4.66	**<0.001**	-4.08	-5.28 – -2.87	**<0.001**	-3.85	-5.01 – -2.68	**<0.001**
Sex	-0.10	-0.48 – 0.28	0.595	0.02	-0.25 – 0.30	0.863	0.17	-0.10 – 0.45	0.212
Age	-0.08	-0.28 – 0.12	0.435	-0.01	-0.16 – 0.14	0.906	-0.05	-0.19 – 0.09	0.489
PAE × Age	0.69	0.40 – 0.98	**<0.001**	0.34	0.12 – 0.55	**0.002**	0.36	0.16 – 0.57	**0.001**

Supplementary Table 2. Post hoc mediation analysis to determine whether graph theory measures mediate the linkage between PAE and reduced Phonological Processing scores. Estimate: Unstandardized Beta Coefficient, Cl: Confidence Interval, p: p-value, ACME: Average Causal Mediation Effect, ADE: Average Direct Effect, Prop: Proportion Mediated.

Bilateral Global Efficiency					
	Estimate	CI Lower	CL Upper	p-value	
ACME	-0.92	-1.595	-0.3	0.002	**

ADE	-0.585	-1.789	0.66	0.348	
Total Effect	-1.505	-2.519	-0.38	0.002	**
Prop.	0.609	0.182	2.33	0.004	**
Left Global Efficiency					
	Estimate	CI Lower	Upper	p-value	
ACME	-0.865	-1.616	-0.22	0.01	**
ADE	-0.625	-1.855	0.62	0.32	
Total Effect	-1.49	-2.562	-0.47	0.01	**
Prop.	0.572	0.144	1.96	0.02	*
Bilateral Nodal Degree					
	Estimate	CI Lower	Upper	p-value	
ACME	-1.3549	-2.6698	0.04	0.058	.
ADE	-0.1502	-1.8216	1.54	0.888	
Total Effect	-1.5052	-2.588	-0.35	0.006	**
Prop.	0.901	-0.0481	3.68	0.064	.
Left Nodal Degree					
	Estimate	CI Lower	Upper	p-value	
ACME	-0.989	-2.536	0.56	0.17	
ADE	-0.511	-2.324	1.36	0.62	
Total Effect	-1.5	-2.663	-0.33	0.01	**
Prop.	0.623	-0.599	2.95	0.18	

Supplementary materials for chapter 4

Supplementary Table 1: Associations between graph theory metrics and Expressive Communication scores (β = Beta, p = p-value)

	Bilateral		**Left**		**Right**	
Predictors	β	*p*	β	*p*	β	*p*
(Intercept)	-6.69	0.368	-8.08	0.248	-2.74	0.704
sex	0.31	0.575	0.31	0.584	0.22	0.693
Age	0.31	0.065	0.30	0.070	0.33	0.053
household income	0.77	0.081	0.87	**0.048**	0.88	**0.049**
PAE	-8.90	0.318	-2.48	0.733	-5.39	0.589
Clustering Coefficient	3.81	0.553	5.22	0.337	-2.22	0.694
Clustering Coefficient × PAE	11.46	0.328	2.99	0.734	6.38	0.593

	Bilateral		**Left**		**Right**	
Predictors	β	*p*	β	*p*	β	*p*
(Intercept)	0.37	0.958	-7.99	0.362	5.48	0.466
sex	0.27	0.630	0.42	0.445	0.26	0.629
Age	0.31	0.065	0.26	0.111	0.37	**0.026**
household income	0.83	0.061	0.87	**0.044**	0.74	0.088
PAE	-11.84	0.259	-16.79	0.176	-21.78	0.056
Global Efficiency	-6.75	0.307	6.32	0.416	-13.34	0.063

Global Efficiency × PAE	18.54	0.262	19.20	0.179	25.47	0.056

	Bilateral		**Left**		**Right**	
Predictors	β	*p*	β	*p*	β	*p*
(Intercept)	-4.88	0.581	-7.89	0.314	-3.52	0.661
sex	0.40	0.480	0.35	0.527	0.23	0.680
Age	0.31	0.065	0.30	0.068	0.33	**0.049**
household income	0.72	0.103	0.80	0.069	0.83	0.060
PAE	-16.12	0.160	-6.65	0.470	-16.19	0.237
Local Efficiency	1.21	0.871	4.57	0.470	-1.24	0.842
Local Efficiency × PAE	18.58	0.164	7.37	0.471	17.64	0.240

	Bilateral		**Left**		**Right**	
Predictors	β	*p*	β	*p*	β	*p*
(Intercept)	-1.21	0.842	-4.97	0.426	-1.02	0.858
sex	0.31	0.577	0.41	0.459	0.25	0.645
Age	0.30	0.071	0.26	0.112	0.36	**0.028**
household income	0.79	0.075	0.88	**0.042**	0.76	0.082
PAE	-9.32	0.149	-7.20	0.188	-8.96	0.071
Nodal Degree	-0.34	0.323	0.37	0.402	-0.75	0.069

Nodal Degree × PAE	1.28	0.150	1.06	0.192	1.40	0.070
	Bilateral		**Left**		**Right**	
Predictors	β	*p*	β	*p*	β	*p*
(Intercept)	-5.18	0.356	-1.81	0.739	-7.90	0.162
sex	0.25	0.649	0.44	0.423	0.28	0.601
Age	0.31	0.064	0.26	0.108	0.37	**0.024**
household income	0.87	**0.049**	0.85	**0.049**	0.71	0.101
PAE	2.96	0.332	2.41	0.198	3.69	0.052
Betweenness Centrality	0.06	0.343	-0.31	0.445	0.70	0.057
Betweenness Centrality × PAE	-0.16	0.309	-1.05	0.158	-1.40	**0.040**

Supplementary Table 2: Associations between graph theory metrics and Receptive Communication scores (β = Beta, p = p-value)

	Bilateral		**Left**		**Right**	
Predictors	β	*p*	β	*p*	β	*p*
(Intercept)	-1.59	0.773	-4.09	0.443	0.67	0.900
sex	-0.17	0.689	-0.19	0.648	-0.21	0.619
Age	0.22	0.074	0.23	0.070	0.24	0.057
household income	0.35	0.285	0.42	0.205	0.42	0.198
PAE	-7.05	0.297	-0.73	0.897	-1.68	0.819
Clustering Coefficient	1.10	0.815	3.82	0.352	-2.47	0.561

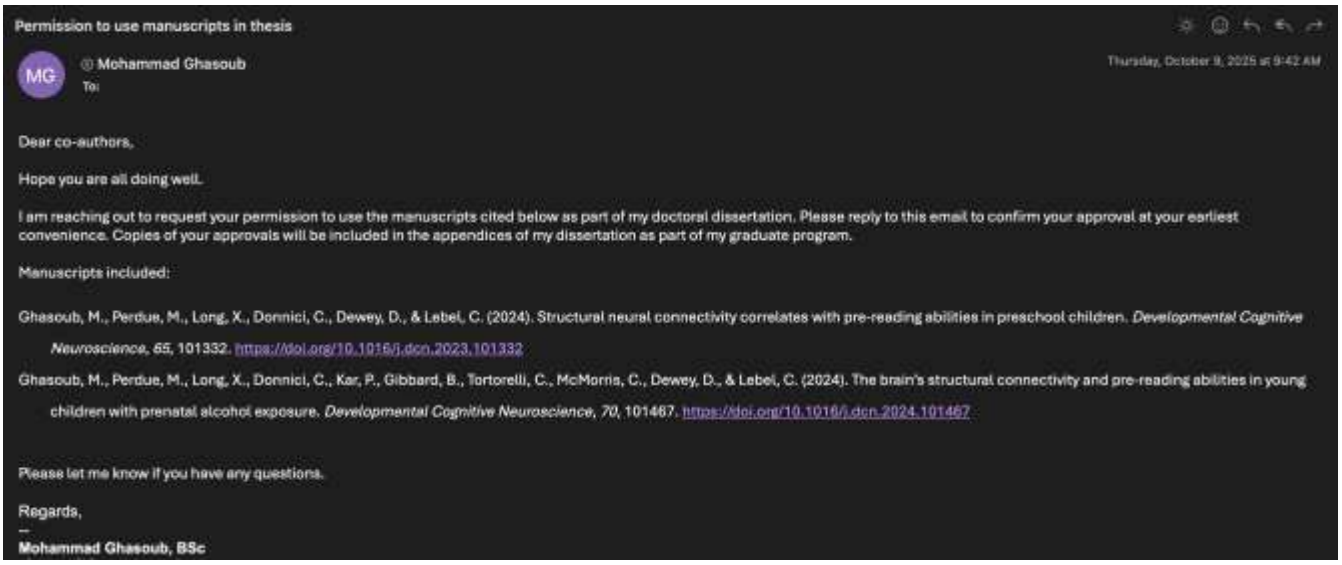
Clustering Coefficient × PAE	9.23	0.299	0.94	0.890	2.05	0.817

	Bilateral		**Left**		**Right**	
Predictors	*B*	*p*	*B*	*p*	*B*	*p*
(Intercept)	-0.06	0.990	-5.84	0.383	5.21	0.364
sex	-0.24	0.566	-0.11	0.793	-0.25	0.541
Age	0.24	0.062	0.20	0.100	0.26	**0.034**
household income	0.43	0.190	0.42	0.186	0.38	0.236
PAE	0.17	0.982	-9.05	0.338	-1.49	0.862
Global Efficiency	-1.87	0.652	6.51	0.271	-8.62	0.108
Global Efficiency × PAE	-0.28	0.982	10.40	0.338	1.84	0.854
	Bilateral		**Left**		**Right**	
Predictors	β	*p*	β	*p*	β	*p*
(Intercept)	0.17	0.980	-4.39	0.463	0.00	1.000
sex	-0.09	0.823	-0.16	0.697	-0.23	0.588
Age	0.22	0.072	0.23	0.069	0.24	0.055
household income	0.32	0.328	0.37	0.257	0.40	0.224
PAE	-12.16	0.162	-2.94	0.678	-7.88	0.443
Local Efficiency	-1.17	0.833	3.86	0.421	-1.52	0.744
Local Efficiency × PAE	14.12	0.162	3.31	0.673	8.65	0.443

	Bilateral		**Left**		**Right**	
Predictors	β	*p*	β	*p*	β	*p*
(Intercept)	-0.25	0.957	-2.67	0.574	0.97	0.821
sex	-0.24	0.569	-0.12	0.775	-0.26	0.531
Age	0.24	0.059	0.20	0.101	0.26	**0.034**
household income	0.40	0.219	0.43	0.179	0.39	0.228
PAE	0.04	0.993	-3.85	0.355	-0.14	0.971
Nodal Degree	-0.14	0.575	0.37	0.270	-0.49	0.115
Nodal Degree × PAE	-0.01	0.992	0.58	0.354	0.03	0.952
	Bilateral		**Left**		**Right**	
Predictors	β	*p*	β	*p*	β	*p*
(Intercept)	-2.29	0.587	0.60	0.884	-3.39	0.425
sex	-0.22	0.602	-0.09	0.823	-0.24	0.560
Age	0.24	0.054	0.20	0.098	0.26	**0.034**
household income	0.38	0.248	0.41	0.200	0.37	0.250
PAE	0.81	0.713	1.36	0.340	0.61	0.673
Betweenness Centrality	0.05	0.294	-0.34	0.275	0.45	0.099
Betweenness Centrality × PAE	-0.04	0.698	-0.57	0.312	-0.20	0.694

Supplementary materials for co-authors approval

Chapters 2 & 3



Permission to use manuscripts in thesis

MG Mohammad Ghasoub
To:

Thursday, October 9, 2025 at 9:42 AM

Dear co-authors,

Hope you are all doing well.

I am reaching out to request your permission to use the manuscripts cited below as part of my doctoral dissertation. Please reply to this email to confirm your approval at your earliest convenience. Copies of your approvals will be included in the appendices of my dissertation as part of my graduate program.

Manuscripts included:

Ghasoub, M., Perdue, M., Long, X., Donnici, C., Dewey, D., & Lebel, C. (2024). Structural neural connectivity correlates with pre-reading abilities in preschool children. *Developmental Cognitive Neuroscience, 65*, 101332. https://doi.org/10.1016/j.dcn.2023.101332

Ghasoub, M., Perdue, M., Long, X., Donnici, C., Kar, P., Gibbard, B., Tortorelli, C., McMorris, C., Dewey, D., & Lebel, C. (2024). The brain's structural connectivity and pre-reading abilities in young children with prenatal alcohol exposure. *Developmental Cognitive Neuroscience, 70*, 101467. https://doi.org/10.1016/j.dcn.2024.101467

Please let me know if you have any questions.

Regards,
--
Mohammad Ghasoub, BSc

Re: Permission to use manuscripts in thesis

CL Catherine Lebel
To: Mohammad Ghasoub

Thursday, October 9, 2025 at 9:49 AM

Yes, you have my permission to include them.

Re: Permission to use manuscripts in thesis

CD Claire Donnici
To: Catherine Lebel, Mohammad Ghasoub

Thursday, October 9, 2025 at 9:57 AM

You have my permission to include these manuscripts!

Claire Donnici

Re: Permission to use manuscripts in thesis

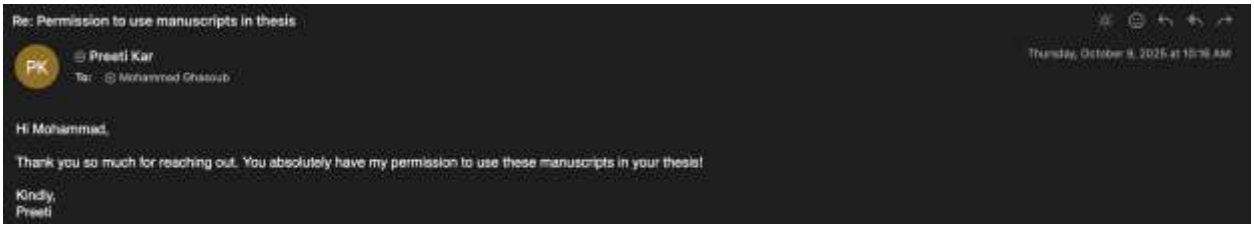
XL Xiangyu Long
To: Mohammad Ghasoub

Thursday, October 9, 2025 at 10:12 AM

Hi Mo,

Sure you have my permission to include them and good luck on the thesis!

Best,
Xiangyu



Re: Permission to use manuscripts in thesis

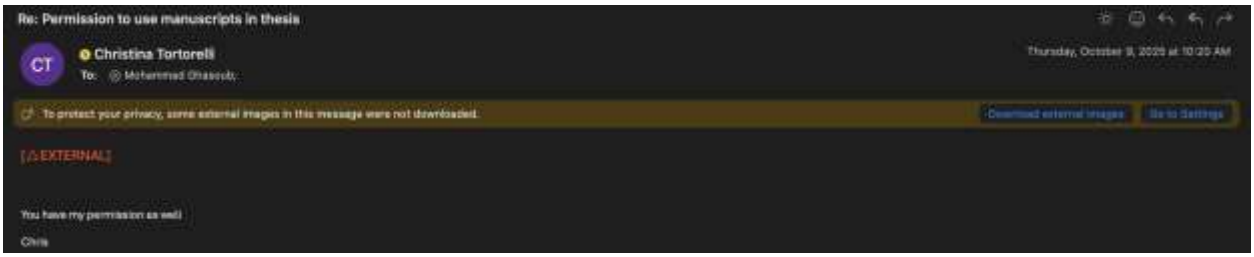
PK Preeti Kar
To: Mohammad Ghasoub

Thursday, October 9, 2025 at 10:16 AM

Hi Mohammad,

Thank you so much for reaching out. You absolutely have my permission to use these manuscripts in your thesis!

Kindly,
Preeti


Re: Permission to use manuscripts in thesis
CT
Christina Tortorelli
To: Mohammad Ghasoub;
To protect your privacy, some external images in this message were not downloaded.
[△EXTERNAL]
You have my permission as well.
Chris

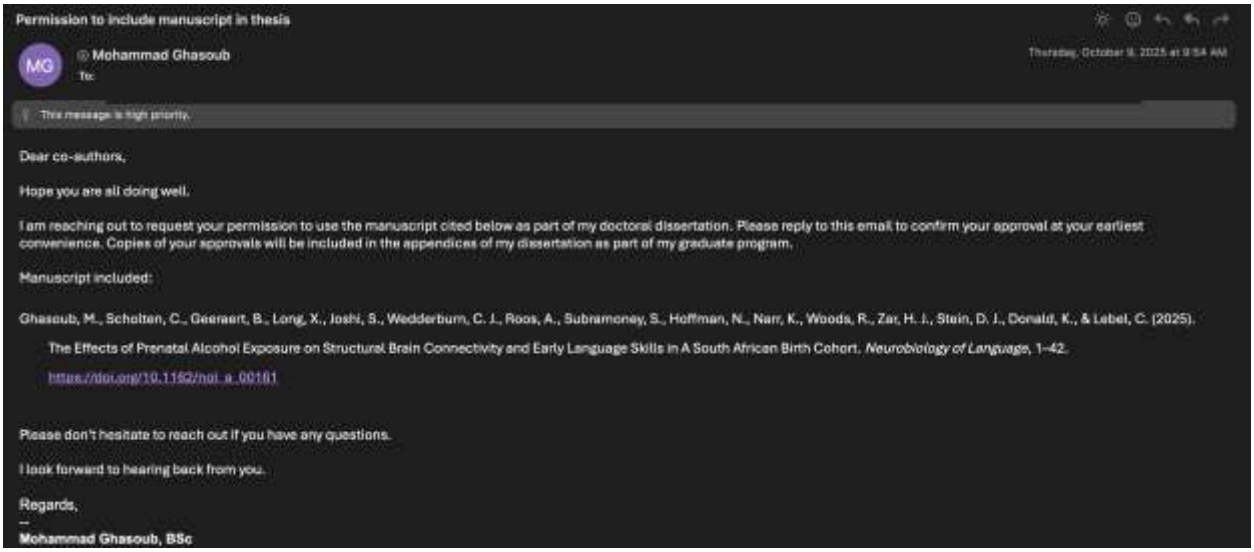

Re: Permission to use manuscripts in thesis
Carly McMorris -
To: Mohammad Ghasoub;
Yes you have my permission.
Warmly,
Carly


Re: Permission to use manuscripts in thesis
BG
Ben Gibbard
To: Mohammad Ghasoub;
Yes, you have my permission to include them.
Ben


Re: Permission to use manuscripts in thesis
DM
Deborah M. Dewey
To: Mohammad Ghasoub;
Yes, you have my permission to include these manuscripts in your thesis.


Re: Permission to use manuscripts in thesis
PM
Perdue, Meaghan V
To:
[△EXTERNAL]
Yes, you have my permission to include these manuscripts in your thesis.
Best regards,

Chapter 4



Permission to include manuscript in thesis

MG — Mohammad Ghasoub
To:
Thursday, October 9, 2025 at 9:54 AM

This message is high priority.

Dear co-authors,

Hope you are all doing well.

I am reaching out to request your permission to use the manuscript cited below as part of my doctoral dissertation. Please reply to this email to confirm your approval at your earliest convenience. Copies of your approvals will be included in the appendices of my dissertation as part of my graduate program.

Manuscript included:

Ghasoub, M., Scholten, C., Geeraert, B., Long, X., Joshi, S., Wedderburn, C. J., Roos, A., Subramoney, S., Hoffman, N., Narr, K., Woods, R., Zar, H. J., Stein, D. J., Donald, K., & Lebel, C. (2025).

The Effects of Prenatal Alcohol Exposure on Structural Brain Connectivity and Early Language Skills in A South African Birth Cohort. *Neurobiology of Language*, 1–42.

https://doi.org/10.1162/nol_a_00161

Please don't hesitate to reach out if you have any questions.

I look forward to hearing back from you.

Regards,
--
Mohammad Ghasoub, BSc

Re: Permission to include manuscript in thesis

SJ — Shantanu Joshi
To: Mohammad Ghasoub
Thursday, October 9, 2025 at 9:58 AM

[△EXTERNAL]

Hi Mo,

Absolutely. And great that you are defending your dissertation. All the best!

Shantanu

Re: Permission to include manuscript in thesis

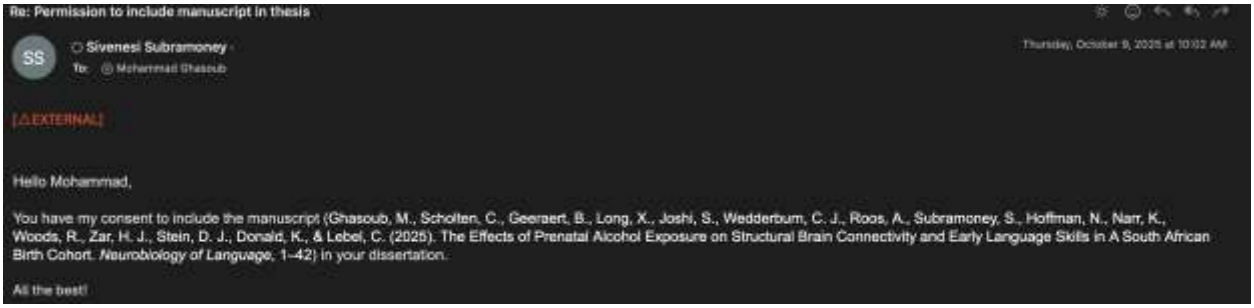
CL — Catherine Lebel
To: Mohammad Ghasoub
Thursday, October 9, 2025 at 9:59 AM

You have my permission to include.

Re: Permission to include manuscript in thesis

Bryce Landon Geeraert
To: Mohammad Ghasoub
Thursday, October 9, 2025 at 10:01 AM

Congratulations Mo, you have my permission to include this material.



Re: Permission to include manuscript in thesis

SS — Sivenesi Subramoney
To: Mohammad Ghasoub
Thursday, October 9, 2025 at 10:02 AM

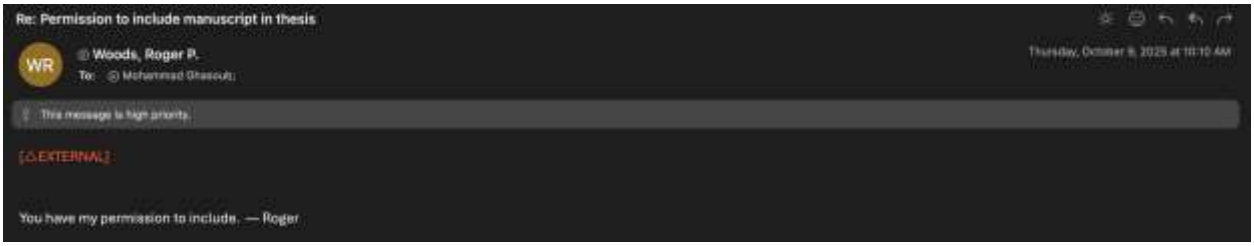
[△EXTERNAL]

Hello Mohammad,

You have my consent to include the manuscript (Ghasoub, M., Scholten, C., Geeraert, B., Long, X., Joshi, S., Wedderburn, C. J., Roos, A., Subramoney, S., Hoffman, N., Narr, K., Woods, R., Zar, H. J., Stein, D. J., Donald, K., & Lebel, C. (2025). The Effects of Prenatal Alcohol Exposure on Structural Brain Connectivity and Early Language Skills in A South African Birth Cohort. *Neurobiology of Language*, 1–42) in your dissertation.

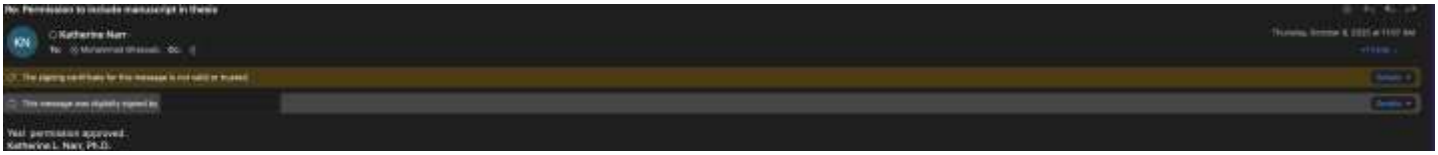
All the best!

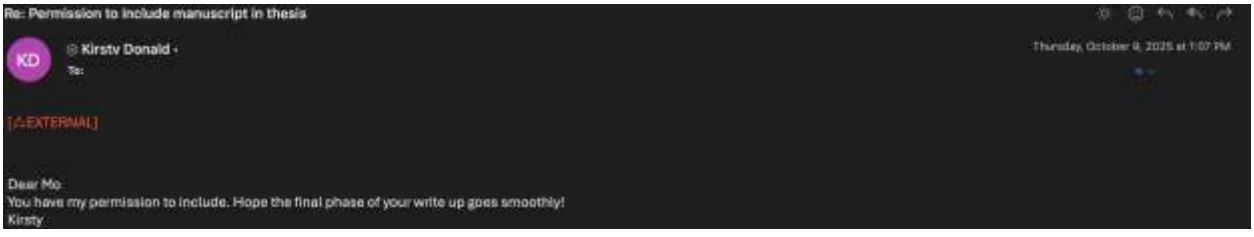

Re: Permission to include manuscript in thesis
DS
Dan Stein
To: Catherine Label, Mohammad Ghasoub;
Thursday, October 9, 2025 at 10:04 AM
[△EXTERNAL]
You have my permission to include.


Re: Permission to include manuscript in thesis
WR
Woods, Roger P.
To: Mohammad Ghasoub;
Thursday, October 9, 2025 at 10:10 AM
This message is high priority.
[△EXTERNAL]
You have my permission to include. — Roger


Re: Permission to include manuscript in thesis
XL
Xiangyu Long
To: Mohammad Ghasoub
Thursday, October 9, 2025 at 10:14 AM
Hi Mo,
You have my permission for this paper as well!
Best,
Xiangyu


Re: Permission to include manuscript in thesis
CS
Chloe Scholten
To:
Thursday, October 9, 2025 at 10:21 AM
You have my permission to include.
Chloe


KN
Katherine Narr
To: Mohammad Ghasoub, Cc:
Yes, permission approved.
Katherine L. Narr, Ph.D.


Re: Permission to include manuscript in thesis
KD
Kirsty Donald
To:
Thursday, October 9, 2025 at 1:07 PM
[△EXTERNAL]
Dear Mo
You have my permission to include. Hope the final phase of your write up goes smoothly!
Kirsty


Re: Permission to include manuscript in thesis
CW
Catherine Wedderburn
To: Mohammad Ghasoub;
Thursday, October 9, 2025 at 1:35 PM
[△EXTERNAL]
You have my permission to include.
Kind regards,
Catherine


Re: Permission to include manuscript in thesis
HZ
Heather Zar
To:
Thursday, October 9, 2025 at 1:49 PM
[△EXTERNAL]
Thanks I give permission for this paper to be included in your thesis
Heather


Re: Permission to include manuscript in thesis
NH
Nadia Hoffman
To:
Monday, October 13, 2025 at 12:45 AM
[△EXTERNAL]
You have my permission to include.
Kind regards,
Nadia