Associations between Frontoparietal and Temporal White Matter, Neurocognitive Abilities and Age in Children and Youth with Prenatal Alcohol Exposure

by

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Abstract

Prenatal alcohol exposure (PAE) has been linked to neurological, behavioural, cognitive, and emotional problems. The neurocognitive impairments identified in individuals with PAE are prevalent and have a major impact on the quality of life of individuals living with the effects of PAE. Understanding the structural connectivity that underpins these neurocognitive deficits is crucial for furthering our understanding of PAE. This thesis aims to examine the relationships between frontoparietal and temporal white matter as assessed by diffusion tensor imaging (DTI) tractography, neurocognitive abilities, and age-related changes in children and youth with PAE.

DTI was obtained from 31 participants with PAE and 31 unexposed controls aged 7-15 years. Mean diffusivity (MD) and fractional anisotropy (FA) were derived from tractography of the genu, body, and splenium of the corpus callosum (CC), bilateral cingulum, inferior longitudinal fasciculus (ILF), and superior longitudinal fasciculus (SLF). All participants completed three language subtests from the NEPSY-II. Executive functioning was measured using the Behavior Rating Inventory of Executive Functioning-Parental Report (BRIEF-PR), and verbal learning was assessed using the California Verbal Learning Test-Children's Version (CVLT-C) in the children with PAE only.

The data presented in this thesis showed lower mean diffusivity values in the right superior longitudinal fasciculus in children and youth with PAE compared to unexposed peers. This cross-sectional analysis revealed positive linear correlations of fractional anisotropy versus age in white matter tracts except the genu of the corpus callosum, the right and left inferior longitudinal fasciculus, and negative linear correlations of mean diffusivity versus age in all white matter tracts. However, there were no significant age-group interactions. In addition, there were no significant associations between MD or FA of the tracts with age-standardized cognitive scores in either

unexposed controls or children with PAE who scored lower than unexposed peers in language subtests and below population norms in tests that assess executive functioning and verbal learning.

This thesis provides evidence of group differences in mean diffusivity of only one frontoparietal tract, the SLF, in children and youth with PAE, although these changes were not correlated to cognitive disability. Steeper decreases in mean diffusivity values with age have been observed in the SLF in children with PAE in previous research. This project also contributes to the existing limited literature that has identified similar age-related changes of diffusion metrics in white matter tracts in participants with PAE and typically developing peers, suggesting normative neurodevelopment in individuals with PAE.

Preface

This thesis is an original work by María José Castro Gómez. The research project, of which this thesis is part, received ethics approval from the University of Calgary Conjoint Health Research Ethics Board, Project Name "Brain Development in Childhood and Adolescence," No. REB13-1346, April 24, 2014, and Project Name "Cumulative Risk Project," No. REB17-0663, June 8th, 2017.

A portion of Chapter 3 was presented at the 2021 Organization for Human Brain Mapping (OHBM) Annual Meeting, and a version of Chapter 3 has been submitted to a journal: Gomez, MJ., Beaulieu, C., McMorris, C., Gibbard, B., Tortorelli, C., Lebel, C. Diffusion tensor tractography of frontoparietal and temporal white matter in children and youth with prenatal alcohol exposure on April 1, 2022. I conducted all image and statistical analysis, created all figures, and wrote the manuscript with the feedback and guidance of my co-authors.

To my family and friends

To all the children and youth with PAE and their families who participated in this research

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List of abbreviations

ARND- Alcohol-related neurodevelopmental disorder

ARBD- Alcohol-related birth defects

BRIEF-PR- Behavior Rating Inventory of Executive Function-Parental Report

BRAVO- Brain Volume imaging Pulse Sequence

CC- Corpus Callosum

CVLT-C- California Verbal Learning Test Children's Version

DTI-Diffusion Tensor Imaging

EPI- Echo Planar Imaging

FA- Fractional Anisotropy

FASD- Fetal Alcohol Spectrum Disorder

FAS-Fetal Alcohol Syndrome

FDR- False Discovery Rate

ILF- Inferior Longitudinal Fasciculus

MRI- Magnetic Resonance Imaging

MD- Mean Diffusivity

NEPSY-II- A Developmental NEuroPSYchological Assessment

ND-PAE- Neurobehavioral disorder associated with prenatal alcohol exposure

PAE- Prenatal Alcohol Exposure

SLF- Superior Longitudinal Fasciculus

SNR- Signal to Noise Ratio

TE- Echo Time

TI- Inversion Time

TR- Repetition Time

Chapter 1

1. Introduction

Prenatal alcohol exposure (PAE) is defined as maternal alcohol consumption at any stage of pregnancy. Fetal alcohol spectrum disorder (FASD) is the neurodevelopmental disorder related to heavy PAE (Cook et al., 2016), and its estimated prevalence ranges from 2 to 21% around the world (Lange et al., 2017; Popova et al., 2019). The dosage, timing and frequency of prenatal alcohol exposure contribute to the heterogeneity observed in FASD (Mattson et al., 2019). However, determining and confirming the dosage, timing, and frequency of PAE is challenging.

PAE has been linked to several neurological, behavioural, mental, and emotional problems. Notably, the neurocognitive impairments identified in PAE have a significant influence on the quality of life, especially neurocognitive deficits related to self-regulation, executive functioning, verbal learning, and language. Understanding the anatomical connectivity underlying these neurocognitive domains is critical for furthering our knowledge of PAE and its effects.

Neurocognitive development has been linked to a range of critical life outcomes, including academic and career accomplishment, socioemotional development, and mental and physical health. Therefore, disruption in development can increase the probability of long-term disability.

Different magnetic resonance imaging (MRI) techniques contribute to study the brain's structural characteristics and properties. Diffusion tensor imaging (DTI) is an advanced MRI technique that has been instrumental for virtually identifying white matter pathways, and quantitative measures sensitive to microstructural properties of white matter. It has been successfully used in PAE research (Fryer et al., 2009; Lebel, Rasmussen, et al., 2008; Paolozza et al., 2014, 2016; Sowell et al., 2008; Treit et al., 2013, 2017; Wozniak et al., 2006, 2009). Usually, participants with PAE are group all together, but some PAE studies have examined the changes in

the diffusion metrics with age (Lebel, Rasmussen, et al., 2008; Paolozza et al., 2016; Treit et al., 2013.

Due to the implication of frontoparietal and temporal white matter in cognitive domains such as language, executive functions, and verbal learning (Treit et al., 2013; Wozniak & Muetzel, 2011; Ghazi Sherbaf et al., 2018; Sowell et al., 2001), the genu, body and splenium of the corpus callosum, the cingulum, inferior longitudinal fasciculus (ILF), and superior longitudinal fasciculus (SLF; without the arcuate fasciculus) were selected as tracts of interest in this project. In addition, little is known about the relationship between diffusion metrics versus age in PAE and the number of studies looking at this relationship is limited (Lebel, Rasmussen, et al., 2008; Paolozza et al., 2016; Treit et al., 2013). Therefore, this study on PAE had two aims: (i) to examine the relationship between frontoparietal and temporal white matter as assessed by diffusion tensor imaging (DTI) tractography and neurocognitive abilities, and (ii) to assess whether white matter diffusion metrics changes in PAE versus age are similar to unexposed participants.

This thesis is organized into four chapters: Chapter 1 provides an overview of the existing literature and key concepts related to the current project, including an introduction to PAE, FASD diagnosis, brain MRI studies and cognition in PAE, basics of DTI and data analysis; Chapter 2 outlines the methods used in this thesis; Chapter 3 will show the research done to address the two aims of this thesis, and Chapter 4 provides concluding remarks on the work presented.

1.1. Prenatal Alcohol Exposure

Many pregnancies in Canada are alcohol-exposed, with estimations that roughly 10% and 15% of women in the general population in Canada and the United States, respectively, use alcohol during pregnancy, and around 3% of women in both countries binge drink during pregnancy (Popova et al., 2017). PAE can result in brain alterations and behavioural problems, leading to

fetal alcohol spectrum disorder (FASD) diagnosis. Fetal alcohol syndrome (FAS), partial FAS, alcohol-related neurodevelopmental disorder (ARND), and alcohol-related birth defects (ARBD) are all included under the FASD umbrella (Mattson et al., 2019) (Table 1.1).

The diagnosis of FASD usually requires a multidisciplinary team composed of a psychologist, speech-language pathologist, occupational therapist, social worker and/or developmental pediatrician, who evaluate information gathered from standardized testing, rating scales, clinical observations, interviews, and information from families, teachers, referring physicians, birth records and medical chart review (Cook et al., 2016). The Canadian Guidelines and the 4-digit code are often used to make an FASD diagnosis (Astley et al., 2009; Chudley, 2005). The 4-digit code uses a Likert scale to classify children into four essential categories: growth delay, facial dysmorphology, brain dysfunction, and alcohol exposure.

In Canada, FASD is a diagnosis itself, therefore, individuals with PAE do not necessarily have one of the diagnoses presented above. The Canadian guidelines (Cook et al., 2016) offer a more detailed description of the criteria and recommendations regarding the FASD diagnosis. According to these guidelines (Cook et al., 2016) FASD is diagnosed when there is evidence of heavy prenatal alcohol use: ≥7 drinks per week or ≥2 binge episodes and the following criteria has been met:

1. The presence of all three facial features (palpebral fissure, philtrum, upper lip) has high specificity to PAE and FASD, therefore, the confirmation of PAE is not required, however the presence of fewer than three facial features require other confirmation.
2. Diagnosis is made only when there is evidence of brain dysfunction which is defined by severe impairment in three or more of the following neurodevelopmental domains: motor skills, neuroanatomy/neurophysiology, cognition, language, academic

achievements, memory, executive functions, affect regulation, adaptive skills, social skills and social communication; severe impairment is defined as a global score or major subdomain score on a standardized neurodevelopmental measure that is > 2 standard deviation below the mean.

3. A diagnosis of FASD is made only when an individual meets either of the two sets of criteria:
    - FASD with sentinel facial features: presentation of the three sentinel facial features; PAE confirmed or unknown; evidence of impairment in three or more of the identified neurodevelopmental domains.
    - FASD without sentinel facial features: evidence of impairment in three or more domains and confirmation of PAE with an estimated dose linked to neurodevelopmental impairment.

It is worth pointing out that these guidelines depend significantly on facial traits and physical features linked with alcohol exposure and less on neurocognitive dysfunction, mainly because neurocognitive impairment is not specific to PAE. Nevertheless, most people with PAE lack physical characteristics, and many children are not diagnosed with FASD until the early school years since they may not show major deficits before starting school. Furthermore, some neurocognitive domains (e.g., executive functioning) may be difficult to measure due to limited psychometric tools for use with preschool children (Flannigan et al., 2019).

Table 1.1: FASD Diagnoses

Name	Abbreviation	Diagnosis Requirements
Fetal Alcohol Syndrome	FAS	• History of prenatal exposure • Characteristic facial anomalies: 1) short palpebral fissures, 2) thin upper lip, and 3) smooth philtrum • Growth delay • Central Nervous System (CNS) abnormalities (e.g., microcephaly, neurobehavioural impairment)
Partial Fetal Alcohol Syndrome	pFAS	• History of prenatal exposure • At least one characteristic facial anomaly • Growth delay and/or Central Nervous System abnormalities and/or behavioural/developmental delay
Alcohol-Related Birth Defects	ARBD	• History of prenatal exposure • Congenital anomalies, including malformations or dysplasia
Alcohol-Related Neurobehavioral Disorder	ARND	• History of prenatal exposure • Evidence of CNS abnormalities and/or behavioural/developmental delay

Individuals with an FASD diagnosis show significant heterogeneity across the cognitive and behavioural traits spectrum. One of the most challenging issues in comprehending FASD profiles is determining the dose and gestational timing of alcohol consumption, which could explain this variation. In addition, it is known from animal studies that the amount of alcohol consumed corresponds with the severity of the outcome, and alcohol exposure throughout different stages of fetal development might influence the pattern and severity of structural and functional brain abnormalities (Mattson et al., 2019). Nonetheless, this degree of detail is difficult to document in humans; thus, most research relies on self-report.

PAE can generally have various effects on brain development, from molecular to gross brain changes. Given that in vitro research cannot be done in humans, animal models of prenatal

alcohol exposure have been instrumental in studying the teratogenic effects of alcohol in the brain. These studies have demonstrated that alcohol can cross the placenta and have an immediate impact on fetal neurodevelopment by: disrupting the neural cell migration and axon pathfinding by blocking cell adhesion and axon outgrowth mediated by neural cell adhesion molecules (Dou et al., 2018), alcohol-induced oxidative stress (Zhang et al., 2018); disrupting the proliferation and migration of cortical neurons, and decreased myelination (Miller, 1996); cerebellum abnormalities (Guerri et al., 2009); neurochemical changes (GABA and Glutamate) (Valenzuela et al., 2012); hippocampal alterations (Savage et al., 2010; Varaschin et al., 2010); apoptotic neurodegeneration (Ikonomidou et al., 1999, 2000); neurogenesis and/or gliogenesis (Miller, 1996); and affecting the action of both mitogenic growth factor and growth-inhibiting factors (Luo & Miller, 1998). This research reflects the complexity and heterogeneity observed in PAE. Alongside these effects, PAE's neurocognitive and behavioural impairment can also be mediated by other prenatal factors such as maternal nutrition, stress, and genetics (Guerri et al., 2009).

MRI studies in humans have verified findings from MRI studies in PAE/FASD animal models. Imaging studies of mouse brains in PAE also revealed reduced myelin in major midline white matter tracts such as the anterior commissure, corpus callosum, and hippocampal commissure (Cao et al., 2014). Furthermore, one brain study found that severe forms of FAS show alterations in the septal nuclei, basal ganglia, and cerebellar vermis in mice (Sulik et al., 1984), and later on, MRI studies reported a reduction in the volume of the basal ganglia, especially the caudate nucleus, and presence of abnormalities in the cerebellar vermis in children with FAS (Donald et al., 2015). In addition, heavy PAE has been found to cause hypoplasia or total absence of the corpus callosum (Livy & Elberger, 2008), a finding that has been reported in studies of children with FAS (Riley et al., 1995).

Even though technology such as MRI is not typically used in a diagnostic setting for FASD diganosis, it can contribute to the understanding of the neurobiology underlying the cognitive and behavioural impairment characteristic of FASD, thus improving the identification and diagnosis, particularly in children and youth that do not display facial dysmorphology characteristics. The following sections describe brain development in PAE through the lens of conventional and advanced MRI techniques.

1.2. Brain MRI Studies and Associations with Cognition in PAE

As mentioned above, advanced MRI techniques have helped enhance our knowledge of the effects of alcohol on the brain and contribute to our understanding of the relationship between brain structures and cognition. Therefore, in the following sections examples from structural and volumetric MRI studies and white matter microstructure as assessed by DTI will be discussed. Given that one of the goals of this thesis is to investigate the interaction between brain and cognition in PAE, studies examining this relationship will be given specific attention. As a result, an overview of these investigations will be provided in Table 1.2.

1.2.1. Volumetric MRI in PAE

Quantitative MRI studies have consistently found reductions in total brain, white matter and gray matter volumes in PAE (for reviews, see Donald, Eastman, et al., 2015; Lebel et al., 2011). In addition, deep gray matter structures such as the hippocampus, amygdala, thalamus, putamen, caudate, and globus pallidus have shown significant volume reductions, with the bilateral caudate, globus pallidus and hippocampus being the most affected (Archibald et al., 2001; Cortese et al., 2006; Fryer et al., 2009; Nardelli et al., 2011), and a small cerebellar volume (Archibald et al., 2001; Astley et al., 2009; Bookstein et al., 2006). In white matter tracts, alterations in the shape and volume of the corpus callosum (CC) are among the most common reported structural MRI

findings (Donald, Eastman, et al., 2015; Wozniak et al., 2009). Even though abnormalities have been reported across the entire CC, the splenium may be the most affected (Lebel et al., 2011; Sowell et al., 2001).

The frontal, parietal and temporal lobes tend to have less white matter, gray matter, and total lobe volume (Astley et al., 2009; Chen et al., 2012; Sowell, 2002). The parietal lobe seems to be one of the most affected cerebral lobes, with a disproportionally reduced volume in children with FAS relative to unexposed children (Archibald et al., 2001). In contrast with other regions, the occipital lobes appear relatively spared in individuals with PAE (Lebel et al., 2011). Structural brain abnormalities in PAE seem to be more widespread and diffuse than focal, contributing to the diverse phenotype observed in this neurodevelopmental disorder that could have an impact in the neurocognitive profile display in PAE.

Table 1.2: Summary of volumetric MRI and cognition studies in PAE

Study	N	Age (years)	Cognitive Domain	Brain Structures	Results
Coles et al., 2011	66 PAE, 26 unexposed	22-23	Verbal memory	Hippocampus	Right hippocampus is a significant predictor of verbal and non-verbal recall
Nardelli et al., 2011	17 PAE, 32 unexposed	6-17	Working memory, reading, receptive and expressive vocabulary	Deep gray matter volumes	No correlations were found between the cognitive scores and deep gray matter volumes
Roussette et al., 2012	56 PAE, 43 unexposed	8-16	Intelligence	Basal ganglia and diencephalic structures	Positive correlation between IQ and right and left putamen volume
Gautam et al., 2014	49 PAE, 54 unexposed	6-17	Verbal working memory Attention Intelligence Executive Functions Verbal learning and memory	Superior frontal, middle frontal, superior frontal, supramarginal, superior parietal, inferior parietal, and corpus callosum white matter, as well as total white matter volume	Age-related increases in callosal, frontal, and parietal white matter volume showed significant associations with cognitive improvements in children with PAE.
Gautam et al., 2015	75 PAE, 64 unexposed	7-16	Intelligence Executive Functions	Subcortical white matter and gray volumes	Temporal and parietal regions correlated with arithmetic scores, and frontal and parietal regions with behavioural measures.

1.2.2. Diffusion Tensor Imaging (DTI) Studies

DTI is a diffusion MRI technique that quantifies and models the main direction of diffusion as a 3-dimensional tensor (Basser et al., 1994). It is a technique that can virtually identify and reconstruct white matter pathways, providing quantitative measures sensitive to microstructural properties of white matter. Several DTI metrics can be derived, two of the most reported metrics are fractional anisotropy (FA) and mean diffusivity (MD). FA describes the directionality of water diffusion and ranges from 0-1, where higher FA represents increased anisotropy. MD represents the amount of diffusion within an area averaged over all directions.

In tissue such as white matter, the diffusion is hindered across cellular membranes and myelin but relatively unrestricted along the axon (Beaulieu, 2002) which results in higher FA in white matter compared to grey matter or cerebrospinal fluid (CSF) where coherent and oriented tissue is less predominant. This thesis will be focused on FA and MD because these metrics are sensitive to microstructural factors such as axonal packing, myelin, and tissue coherence (Beaulieu, 2002). Even though FA and MD are sensitive to microstructural properties, it lacks specificity and cannot distinguish between them.

Cross-sectional DTI studies using different analysis techniques have shown diffusion irregularities in white matter tracts in children and youth with PAE and their association with cognitive domains (Table 1.3). One of the first studies using DTI analyzed the CC with region of interest (ROI) analysis and found increased mean diffusivity (MD) in the isthmus of children with FASD (Wozniak et al., 2006). A Voxel-Based Analysis (VBA) study found lower FA in several regions, including the right and left lateral portions of the splenium of the CC, bilateral posterior cingulum, ILF and inferior frontal-occipital fasciculus (IFOF) (Sowell et al., 2008). In addition, a

significant positive correlation between performance on a visuomotor integration test and the bilateral splenium FA was observed within the FASD group (Sowell et al., 2008).

Lebel et al. (2010) found four significant clusters with correlations between FA and math scores in children with FAS/pFAS, mainly the left parietal lobe, upper left parietal lobe and the left cerebellum. In addition, manual tractography was performed within the significant clusters to identify the white matter tracts that passed through them, mainly in the left superior longitudinal fasciculus (SLF), left corticospinal tract (CST), body of the CC, middle cerebellar peduncle, and the bilateral anterior and posterior limbs of the internal capsule.

Fan et al. (2015) found decreased FA in four white matter regions and increased MD in seven areas in children with FAS/pFAS. Three areas of FA and MD differences (left ILF, splenium, and isthmus) overlapped, and the fourth FA cluster was in the same white matter bundle (right ILF) as an MD cluster. Multiple regression models indicated that these DTI changes partially mediated adverse effects of PAE on information processing speed and eyeblink conditioning (Fan et al., 2015).

Moving on to more advanced techniques such as diffusion-based tractography, studies using this approach have demonstrated widespread microstructural differences between children with FASD and typically developed children (Lebel et al., 2008; Wozniak et al., 2009; Paolozza et al., 2017; Treit et al., 2013). A study using diffusion based tractography analyzed the genu and splenium of the corpus callosum, cingulum, corticospinal tracts, inferior fronto-occipital fasciculus, inferior and superior longitudinal fasciculi, globus pallidus, putamen, and thalamus, and found that individuals with FASD had lower FA in the splenium and lower MD in the genu (Lebel et al., 2008). The right cingulum, bilateral ILF and bilateral SLF had lower FA in children with FASD when compared to unexposed children and larger MD values were observed in the

bilateral IFO, left ILF, and right CST; however, no significant correlations were found between cognitive measures and DTI parameters (Lebel et al., 2008).

Wozniak et al. (2009) used a semi-automated tractography to analyze six regions of the CC in children and youth with FASD and found lower FA in the posterior portion of the CC (posterior midbody, isthmus, and splenium) in the FASD group. In addition, white matter FA and cognition measures were correlated and suggested some regional specificity, in that only FA in the posterior regions of the CC were associated with visual-perceptual skills (Wozniak et al., 2009).

Paolozza et al. (2017) used a semi-automated tractography approach to analyze 15 white matter tracts and correlated the DTI metrics with several cognitive domains such as executive functions and working memory. This study showed that the participants with PAE displayed lower FA compared with unexposed children in multiple tracts, including three CC regions, the right CST, and three left hemisphere tracts connecting to the frontal lobe (cingulum, uncinate fasciculus, and SLF). In contrast, no correlations were found between DTI and any of the psychometric tests used in this study. Another study found that in females with FASD, but not males with FASD nor unexposed controls, there was a positive correlation between the genu, ILF, and SLF FA values and reading scores (Treit et al., 2017).

The only longitudinal DTI study of PAE/FASD to date showed that the change in MD over longitudinal scans 2-4 years apart in the superior fronto-occipital fasciculus and the SLF was negatively correlated with the change in reading and receptive vocabulary in children with FASD, but there were no significant correlations between scores of executive functions as measured by the BRIEF-PR and DTI metrics (FA and MD) (Treit et al., 2013).

Taking all this together, these results show widespread but inconsistent diffusion alterations in PAE. The variety of analysis methods could explain this inconsistency, different age

ranges, selection of brain structures and cognitive domains, different diagnostic subgroups, making it difficult to compare and could influence the mixed findings reported.

Table 1.3: Summary of DTI and cognition studies in PAE

Study	N	Age (years)	MRI Method	Cognitive Domain	Brain Structures	Results
Sowell et al., 2008	19 PAE, 19 unexposed	7-15	Voxel-based morphometry	Visual-motor integration Reading abilities Verbal comprehensio n	Temporal and parietal lobe	Significant correlations between performance on a test of visuomotor integration and FA in bilateral splenium but not temporal regions were observed within the FASD group.
Lebel et al., 2008	24 PAE, 95 unexposed	5-13	Semi-automated tractography	Executive functioning, working memory, math abilities, language	Ten major white matter tracts 4 gray matter structures	No significant correlations were found between cognitive measures and DTI parameters.
Wozniak et al.,2009	33 PAE, 19 unexposed	10-17	Seed regions of interest (ROIs) using a semi-automated approach	Intelligence	Corpus Callosum	Measures of white matter integrity and cognition were correlated and suggested some regional specificity, in that only posterior regions of the corpus callosum were associated with visual-perceptual skills
Lebel et al., 2010	21 PAE	5-13	Voxel-based analysis	Math abilities	Parietal region, cerebellum, and bilateral brainstem	Voxel-based analysis revealed 4 clusters with significant correlations between FA and math scores: 2 positively correlated clusters in the left parietal region, one positively correlated cluster in the left cerebellum, and one negatively correlated cluster in the bilateral brainstem.
Treit et al., 2013	17 PAE, 27 unexposed	5-15	Semi-automated tractography	Working Memory Language Intelligence	11 white matter tracts	MD is shown to correlate with reading and receptive vocabulary in the FASD group, with

				Executive functions		steeper decreases of MD in the superior frontal-occipital fasciculus and superior longitudinal fasciculus between scans correlating with greater improvement in language scores.
Fan et al., 2016	41 PAE, 13 unexposed		Voxel Wise analysis 5	Intelligence Verbal Learning and Memory	Cerebellar Peduncles Inferior Longitudinal Fasciculus Splenium Isthmus	Multiple regression models indicated cortical WM impairment partially mediated adverse effects of PAE on information processing speed and eyeblink conditioning.
Paolozza et al., 2017	69 PAE, 67 unexposed	5-18	Semi-automated Tractography	Executive Functions Working Memory	Corpus callosum, ILF SLF, inferior fronto-occipital fasciculus (IFO), cingulum, uncinate fasciculus, and corticospinal tracts (CST).	No correlations were found between DTI and any of the psychometric tests
Treit et al., 2017	70 PAE, 74 unexposed	5-32	Semi-automated tractography	Intelligence Memory Mathematics Vocabulary	Genu, body, and splenium of the corpus callosum, CST, SLF, ILF, superior frontal-occipital fasciculus (SFO), cingulum, and uncinate fasciculus (UF)	Females with FASD, but not males with FASD nor controls, showed positive correlations between the FA of the genu, ILF, and SLF and reading scores

1.2.2.1. DTI Metrics and Change with Age

One of the advantages of DTI is its sensitivity to the white matter microstructural properties in typical and atypical brain development. Age-related changes in DTI metrics during typical white matter development have been extensively investigated in the last decade (for a review, see Lebel et al., 2019). Typical white matter development is associated with increases in FA and decreases

in MD with age during childhood and adolescence (Lebel & Beaulieu, 2011; Tamnes & Mills, 2020). In addition, compared to normal white matter, atypical brain development or acquired brain damage often results in lower FA and higher MD values in damaged white matter (Alexander et al., 2007)

Brain microstructure shows rapid development in infancy and early childhood, primarily driven by increased myelination, and adulthood sees a reduced rate of brain microstructure development (Figure 1.1). However, the underlying processes remain relatively unknown, with research pointing primarily to increased axonal packing (Lebel & Deoni, 2018). In addition, there is evidence of occipital areas and callosal tracts having an earlier development and frontal-temporal areas with their white matter connections, such as the cingulum and SLF, have a protracted development (Lebel, Walker, et al., 2008) This pattern shows the regional variability of white matter across the brain.

Few DTI studies have examined age-related changes in children and youth with PAE. Some of the studies indicate that individuals with PAE have normative age related changes (Lebel et al., 2008b; Paolozza et al., 2016), while others have shown altered brain development in both cross-sectional (Paolozza et al., 2016; Treit et al., 2017) and longitudinal samples (Treit et al., 2013). The only longitudinal study to date (Treit et al., 2013) reported age-related increases of FA and decreases of MD in FASD, showing changes expected in normative development. However, there are age-by-group interactions in the SLF, superior frontal-occipital fasciculus (SFOF) and IFOF, where children with FASD showed more reductions in MD than typically developed children. More significant reductions of MD could reflect atypical development by signalling delayed compensation or more stepwise progression of cellular events compared to healthy development (Treit et al., 2013).

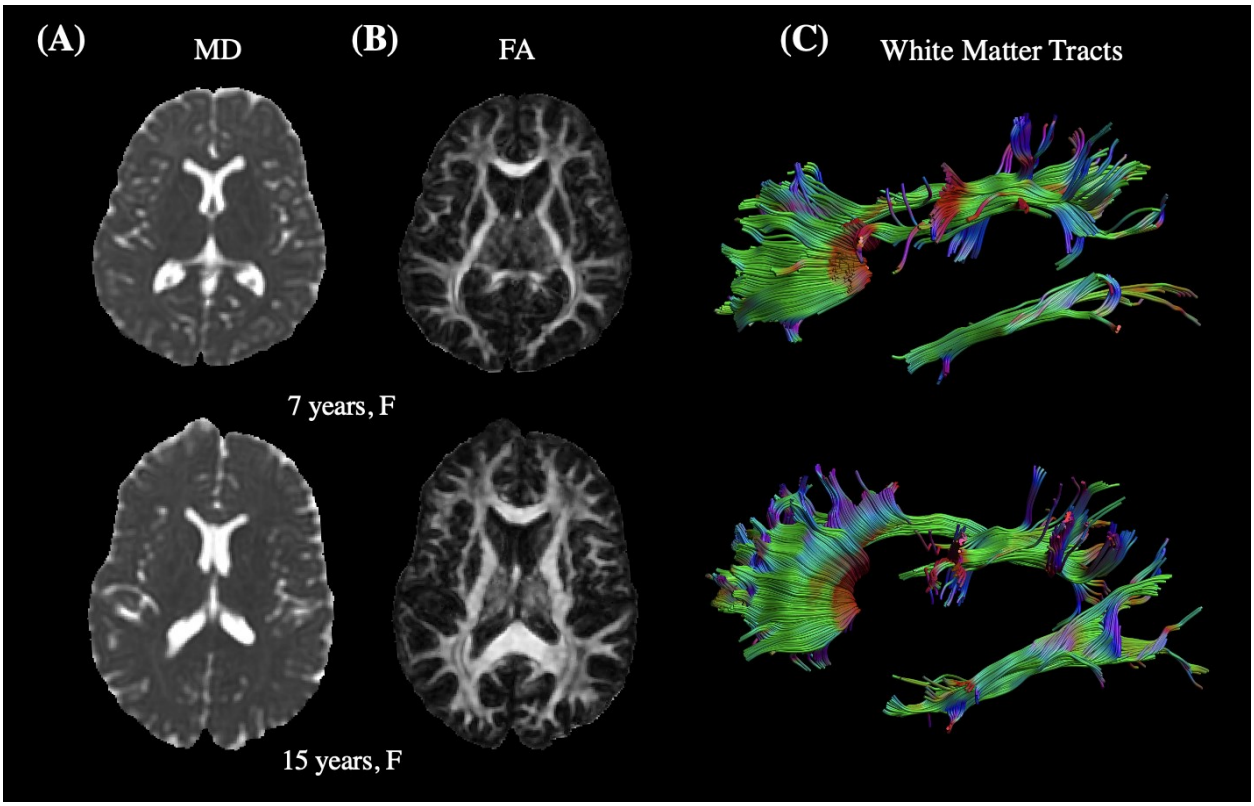


Figure 1.1: Axial view of (A) MD map, (B) FA map and (C) semi-automated deterministic DTI tractography of the genu of the corpus callosum, cingulum and SLF for one of the youngest (7 years, F) and oldest (15 years, F) participants with PAE. The color of the white matter tracts shows the orientation of the diffusion; red indicates left-right, blue is superior-inferior, and green shows anterior-posterior direction. F= female.

1.3. Neurocognitive Outcomes in PAE

Neurocognitive domains in PAE are affected broadly. In utero alcohol exposure has been linked to impairment in various cognitive functions, including overall general intelligence, motor functions, attention, language development and processing, verbal learning and memory, visual perception and construction, and impairment in executive functions (Mattson et al., 2019).

It is important to remember that PAE has significant comorbidity with other clinical diagnoses, complicating the differential diagnosis and its accuracy. For example, the relationship between PAE and Attention Deficit Hyperactivity Disorder (ADHD) has received much attention (Malisza et al., 2012; O'Conaill et al., 2015; Ware et al., 2014). Children exposed to prenatal

alcohol show difficulties with organization, increased impulsive behaviours, poor reaction inhibition, executive dysfunction, and hyperactivity, just like children with ADHD. However, children with FASD display significantly more impairment in executive functions tasks than those with ADHD (Khoury & Milligan, 2019).

Several studies have addressed the need for a neurocognitive profile that can aid in the FASD diagnosis. There is evidence that using a neuropsychological profile for group classification was more accurate than using only IQ scores (Mattson et al., 2019). In addition, executive function and spatial processing measures were more sensitive in identifying prenatal alcohol exposure (Mattson et al., 2019). This thesis will focus on three key neurocognitive domains that are considerably affected in PAE: executive functions/self-regulation, language and verbal learning. These neurocognitive domains are included as one of the criteria to assess and establish an FASD diagnosis (Cook et al., 2016). Even though there is a considerable amount of information regarding the neurocognitive profile in PAE, there is still a gap in our knowledge of its underlying neurobiology.

1.3.1. Executive Functions

Executive functions (also known as executive control or cognitive control) and self-regulation are top-down cognitive processes that are required for concentration and attention when going on autopilot or when relying on instinct or intuition would be inadvisable, insufficient, or impossible (Diamond, 2013). Executive functioning is one of the last cognitive abilities to develop and the first to decline; it has a protracted developmental trajectory that mirrors the maturation and degeneration of the frontal and parietal lobes (Tamnes et al., 2010 Wiebe and Karbach, 2017).

Many distinct models of executive functioning have been proposed, including response inhibition, working memory updating, attention shifting, goal monitoring, and action planning.

However, the most well-known and extensively used model is the one proposed by Miyake, Friedman, and colleagues (Miyake et al., 2000; Miyake & Friedman, 2012), which emphasizes the unity of the executive process alongside its variability (Wiebe and Karbach, 2017). Using a factorial approach, this model focuses on three key features of executive functioning: switching, inhibition, and updating. Switching or shifting refers to the ability to transition or move between other sets of mental functions. The ability to endure input from opposing or prepotent responses or processes is called inhibition. Updating refers to the ability or capability to refresh and keep knowledge in working memory in the face of new information (Lee et al., 2013).

It should be noted that this is a model based on adult literature. This paradigm is assumed to apply to child development; however, recent research has failed to show classification evidence into three subtypes (Espy et al., 2011). According to recent research, the organization of executive functions in childhood appears to evolve from a two-factor structure (switching and working memory) in early childhood to a three-factor structure (switching, working memory, and inhibition) in adolescence (Espy et al., 2011).

Overall, the extended developmental trajectory of executive functions results in more exposure to environmental stimuli and experience, meaning that executive functioning growth is likely to be characterized by increased vulnerability to risk and enhanced chances for intervention (Wiebe and Karbach, 2017). In addition, individual differences have been linked to a range of critical life outcomes, including academic and career accomplishment, socioemotional maturation, and mental and physical health. Children and youth with PAE are notably affected in these areas (Nguyen et al., 2014).

Impairment in executive functioning is one of the most reported deficits in children and youth with PAE (Green et al., 2009; Khoury et al., 2015; Khoury & Milligan, 2019; Pei et al.,

2011; Rasmussen, 2005). They struggle with many domains of executive functioning, displaying a diffuse impairment (Mattson et al., 2019). These abnormalities have been observed in cognitive flexibility, inhibition, planning and strategy use, verbal reasoning, working memory, and emotion-related tests (Rasmussen, 2005; Rasmussen et al., 2013). Even though the impairment appears to be broad, the effects vary between executive functions, with working memory and inhibition showing medium effects and set-shifting showing substantial effects (Khoury et al., 2015). In addition, given that developmental studies have repeatedly demonstrated that executive functioning abilities have a definite course development, age may moderate the strength of the executive functioning-PAE relationship (Khoury et al., 2015).

1.3.1.1. Neural Correlates

Executive functioning is related to frontal-subcortical circuits involving projections from frontal lobes to the basal ganglia and thalamic nuclei, regions vulnerable to PAE (Mattson et al., 2011). Executive functions recruit frontal regions and posterior brain structures in typical neurodevelopment, including parietal, temporal and cerebellar regions (Shen et al., 2020; Treit et al., 2014). Fibre tracts connecting frontoparietal structures, such as the cingulum, genu, body and splenium of the CC, and the SLF, have been associated with measures of executive functioning in participants without disorders (Shen et al., 2020; Treit et al., 2014). Additional temporoparietal white matter, mainly ILF, has also been correlated with performance in classic executive functioning tests like the Stroop test in normative development (Shen et al., 2020).

Children and youth with PAE usually display significant brain alterations related to executive functions. The frontal, parietal and temporal lobes tend to have less white matter, gray matter, and total lobe volume in PAE (Astley et al., 2009; Chen et al., 2012; Sowell, 2002). The parietal lobe seems to be one of the most affected cerebral lobes, with a disproportionally reduced

volume in children with FAS relative to unexposed children (Archibald et al., 2001). Furthermore, there is evidence of an association between DTI metrics in white matter tracts and executive functioning in participants with PAE, where higher FA in the genu of the CC and lower MD in the splenium was associated with better working memory in children with PAE (Wozniak et al., 2009).

1.3.2. Verbal Learning and Memory

During development in childhood, verbal learning and memory are key in school and language acquisition. Moreover, encoding and retaining verbal information remains important throughout the lifespan (Farrer & Drozdick, 2020). Clinical studies have revealed that children with PAE have learning and memory difficulties and these deficits affect specific domains such as verbal and nonverbal skills (Mattson et al., 2011). Learning involves using several cognitive domains, including attention, language, and memory, making it a complex and multifactorial cognitive ability.

Studies have shown that children with histories of heavy prenatal alcohol exposure seem to recall fewer words than unexposed children over five learning trials and after short and long delay intervals of the California Verbal Learning Test- Children's Version (CVLT-C) (Crocker et al., 2011). However, both groups retained similar portions of learned material on the long delay trial. The deficits observed are associated with difficulty learning new information rather than retaining known material (Crocker et al., 2011), which could indicate an attention problem rather than learning or memory deficit.

Even though individuals with PAE tend to perform worse on the CVLT-C than unexposed children, the means sometimes are within the normal range. In addition, there are age differences within the PAE population, showing that younger children perform at a normative level. In

comparison, older children and youth fall short of the expected age-level performance (Gross et al., 2018).

Several studies have suggested that impaired information acquisition-encoding (poor performance in the initial learning trials) is responsible for the impairments in verbal recall-retrieval and that recall per se may be relatively spared in PAE (Mattson & Roebuck, 2002; Roebuck-Spencer & Mattson, 2004).

1.3.2.1. Neural Correlates

Verbal learning and memory involve input from numerous brain regions impaired in children and youth with PAE. One of these is the frontal cortex, which is involved in memory storage and retrieval. Youth with PAE have worse verbal memory scores and decreased volume and surface area of brain regions such as the right frontal, bilateral temporal, and bilateral hippocampi when compared to typically developing unexposed children (Gross et al., 2018).

A thinner cortex and a smaller frontal cortex volume relate to better verbal recall skills in typically developing children (Tamnes et al., 2013). Nonetheless, in children with FASD, the opposite pattern has been observed: a narrower frontal cortex is associated with poor verbal memory skills (Sowell et al., 2007). In addition, they have decreased medial temporal and increased left dorsolateral prefrontal activation during verbal paired-associate tests implying increased demands on frontal executive memory systems because medial temporal mediated encoding is compromised (Lewis et al., 2015; Sowell et al., 2007).

1.3.3. Language

Although language abilities are not as well investigated as other cognitive domains in PAE and the findings are mixed, there is some evidence that children and youth with PAE have

difficulties with articulation, grammatical ability, receptive and expressive language (Aragón et al., 2008; Mattson et al., 2019).

Compared to unexposed children, participants with PAE seem to have a lower performance on measures that assess language functioning (Rasmussen et al., 2013). Recent studies have found that children and youth with PAE had lower scores on measures of oral language comprehension and phonological processing (Davis et al., 2013; Rasmussen et al., 2013).

Individuals with PAE have lower scores than unexposed children in the Speeded naming and Comprehension of Instructions subtest from the Developmental NEuroPSYchological Assessment-Second Edition (NEPSY-II) (Cluver et al., 2019; Rasmussen et al., 2013). In addition, speeded naming significantly demands verbal fluency abilities, which are likely to be affected by FASD's low executive function skills. These significant language deficits have substantial repercussions in school, where verbal expectations may be too high (Rasmussen et al., 2013).

1.3.3.1. Neural Correlates

Structural MRI studies have found that children with PAE have smaller left temporoparietal regions (Sowell, 2002). Given that this area is important in language processing and contains both Wernicke's area and the angular gyrus, abnormally elevated left temporoparietal volume appears to be compatible with the language abnormalities shown in PAE (Lindell, 2019).

DTI studies have also revealed changes in language areas of the left hemisphere. Lebel et al. (2008) investigated 10 canonical white matter tracts in children with PAE and discovered extensive white matter abnormalities in 7/10 white matter pathways compared to unexposed participants. The most significant changes between the PAE and unexposed groups were identified in tracts innervating temporal areas, supporting the hypothesis that atypical left hemisphere anatomy underpins the linguistic deficiencies seen in PAE. Another study discovered a link

between reading and receptive vocabulary and lower MD in the SFOF and SLF in children with PAE (Treit et al., 2013).

1.4. Diffusion Tensor Imaging

1.4.1. White Matter

White matter accounts for ~40% of central nervous system (CNS) tissue. Besides axons, white matter contains glial cells that can be divided into two brain categories: macroglia and microglia. The macroglia are composed of: oligodendrocytes that produce the myelin sheath and support axonal structure and integrity throughout life; the astrocytes that regulate the extracellular ion concentration and provide trophic and possibly metabolic support for neurons and oligodendrocytes; and NG2-positive cells that persist in the adult brain as precursors of mature oligodendrocytes and some astrocytes (Johansen-Berg & Behrens, 2014). Microglia are small phagocytic cells that engulf waste products and dying cells. In addition, white matter contains ependymal cells that line the ventricular system and endothelial cells that form the walls of blood vessels; pericytes and fibroblasts may also be associated with blood vessels (Johansen-Berg & Behrens, 2014).

The axons contain axonal plasma membrane (axolemma), actin microfilaments, microtubules, neurofilaments, microtubules associated proteins (forms cross-bridges between neurofilaments and microtubules), and axonal cytoplasm. Actin filaments provide a scaffold beneath the axonal plasma membrane (axolemma) and may be necessary for membrane integrity and as a substrate for short-distance transport (Johansen-Berg & Behrens, 2014; Letourneau, 2009). Neurofilaments provide structure and are the main axonal diameter determinants. Finally, microtubules provide the tracks upon which proteins transport organelles along the axon in both directions. Both neurofilaments and microtubules, which are readily discerned by electron

microscopy, lie parallel to the direction of the axon and appear as tubes in cross-section (Johansen-Berg & Behrens, 2014).

The main white matter pathways can be classified into association, projection and commissural fibres. The projection pathways are vertically projecting tracts connecting cortical regions and subcortical nuclei or brainstem regions, association pathways constitute the superficial and deep white matter structures, and commissural pathways are connections between the left and right hemispheres (Yeh et al., 2021).

1.4.2. DTI Acquisition

Diffusion is the microscopic movement of molecules without bulk motion. Molecules unrestricted by tissue structure diffuse in an isotropic manner—equally in all planes—via Brownian motion. However, in tissue, diffusion is differentially constrained by barriers such as cell membranes, myelin and can be anisotropic (unequal in all directions faster along the axon direction) in white matter (Moseley et al., 1990; Beaulieu, 2002).

Diffusion-weighted imaging (DWI) is an MRI sequence that uses water diffusion to infer microstructural information about tissue. The most common DWI approach is the pulsed-gradient spin echo pulse sequence with a single-shot, echo-planar imaging (EPI) readout which allows rapid acquisition of multiple volumes of diffusion-weighted images in a reasonable total scan time.

DTI builds upon DWI protocols and uses gradients to encode diffusion in several directions, and the fundamental idea behind it is that water molecules diffuse differentially along tissues based on their type, integrity, architecture, and the presence of barriers, providing information on their orientation and quantitative anisotropy (Soares et al., 2013). DTI protocols involve several practical choices as diffusion tensor estimation requires: high b-values (sensitivity to diffusion) (e.g., 1000 s/mm^2) along at least six non-collinear diffusion encoding directions, but

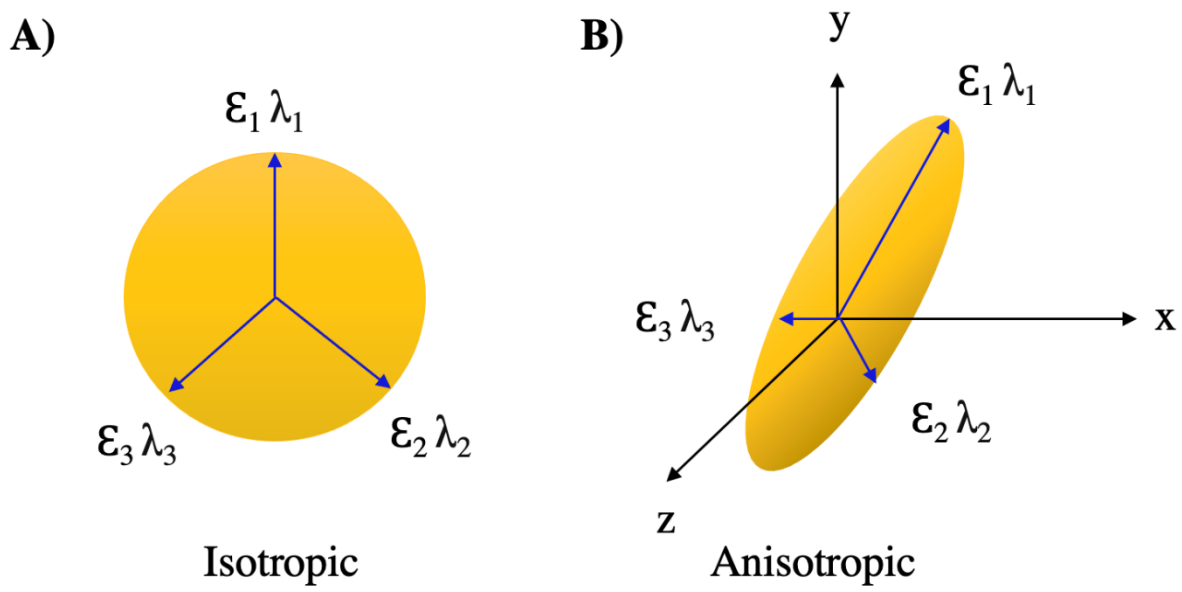
often 30 directions, in addition to a non-diffusion-weighted image (b=0 s/mm^2) with approximately one low-b image for each 5–10 high-b images; a spatial resolution between 2-2.5 mm isotropic (in plane resolution and thickness with equal dimension) or even better if possible; short echo time ideally (TE [time between the delivery of the radio frequency pulse and the receipt centre of the spin echo signal]); and minimum Repetition time (TR[the amount of time between successive excitation radiofrequency pulses to the same slice]) to reduce scan time (Mukherjee, Chung, et al., 2008; Soares et al., 2013).

1.4.3. The Diffusion Tensor Model

DTI measures the orientation and magnitude of water diffusion in three dimensions (Basser & Pierpaoli, 1998). This enables the mapping of white matter structure and voxel-by-voxel evaluation of diffusion metrics that may be related to changes in tissue. Following data acquisition, a diffusion tensor matrix is constructed, and the diagonalization of the tensor is used to calculate the eigenvectors and eigenvalues. Eigenvectors express the diffusion direction and eigenvalues the diffusion magnitude (Basser & Pierpaoli, 1998).

The largest eigenvalue (λ_1) is in the primary diffusion direction, the second largest eigenvalue (λ_2) is in the diffusion direction orthogonal to the first, and the smallest eigenvalue (λ_3) is in the final orthogonal direction. The average of the three eigenvalues is called mean diffusivity (MD) where larger values (in units of 10^{-3} mm^2/s) reflect that molecules diffuse farther on average in a given amount of measurement time. In ordered white matter, the largest eigenvalue, λ_1, represents diffusivity parallel to the axons and is referred to as the axial diffusivity or parallel diffusivity. The second and third eigenvalues λ_2 and λ_3 represent diffusivity in the planes orthogonal to the axons and are usually averaged $(\lambda_2+\lambda_3)/2$, resulting in a measure called radial diffusivity or perpendicular diffusivity. The most commonly reported measure is fractional

anisotropy (FA) which represents the fraction of the tensor's magnitude due to anisotropic diffusion and it ranges from 0 (isotropic diffusion) to 1 (fully anisotropic diffusion) (Pierpaoli & Basser, 1996; Yeh et al., 2021). The eigenvectors of the tensor ellipsoid describe the direction of the diffusion ellipsoid's principal axes (ε_1, ε_2, ε_3) (Figure 1.2). They provide information on fibre orientation, which is necessary for tractography analysis. The primary eigenvector is the



eigenvector with the largest eigenvalue.

Figure 1.2: Isotropic (A) and anisotropic (B) diffusion tensors are shown. The tensor is represented by a diffusion ellipsoid, characterized by six elements: eigenvectors ε_1, ε_2, and ε_3 that represent the principal orientation of the tensor, and the eigenvalues λ_1, λ_2, and λ_3 that denote the size and shape of the ellipsoid.

A color-coded FA map can be created that shows both the directionality of greatest water diffusion and the amount of anisotropy. This calculation involves the multiplication of the FA map with a directionally-encoded color map produced from the first eigenvector of the tensor where red indicates left-right, blue is superior-inferior, and green shows anterior-posterior direction (Alexander et al., 2007) (Figure 1.3).

The local eigenvector orientations can be used to identify and parcellate specific white matter tracts and has the potential to inform applications that require anatomical specificity. The ability to identify specific white matter tracts on the eigenvector color maps has proven useful for mapping white matter anatomy through different techniques such as tractography (Alexander et al., 2007).

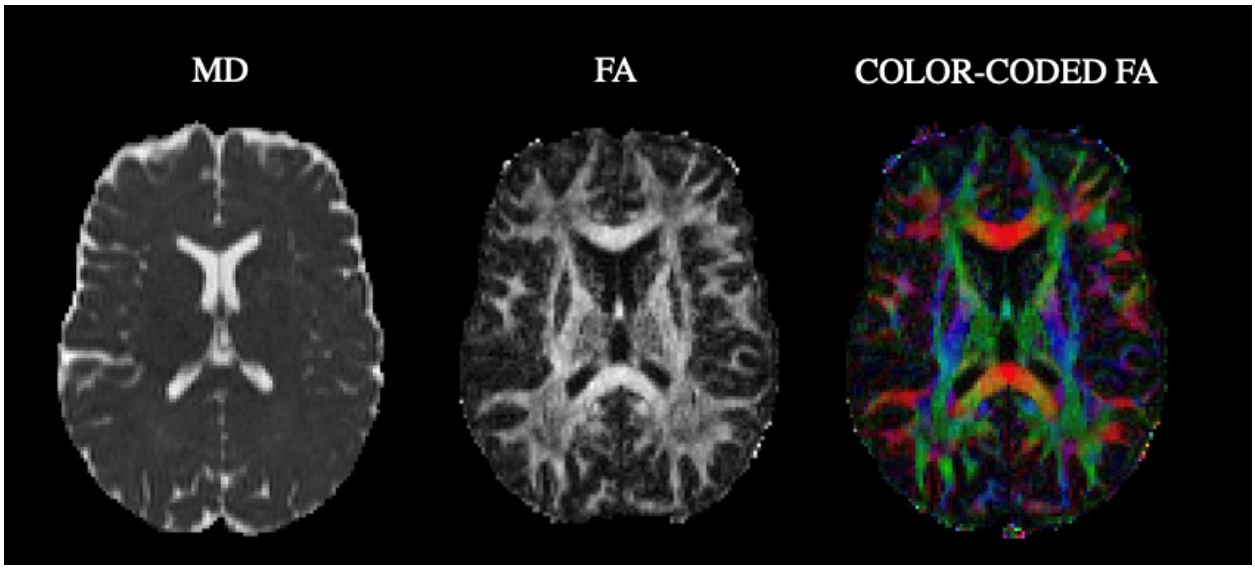


Figure 1.3: Diffusion maps. Standard maps for mean diffusivity (MD), fractional anisotropy (FA) and colour-coded FA maps. The bright signal (i.e., white) in the MD map indicates a high amount of water diffusion, as observed in regions such as the ventricles. The bright areas in the FA map show a high degree of anisotropy, whereas areas of low anisotropy are shown in dark gray. The colour-coded FA map shows the orientation of the white matter tracts; red indicates left-right, blue is superior-inferior, and green shows anterior-posterior direction.

1.4.4. DTI Data Analysis: Tractography

DTI assesses tissue microstructure, particularly in brain tissue (although the number of non-brain applications is increasing). Estimating the primary direction of diffusion by using the tensor has led to the tractography technique, contributing to the study of brain connectivity (for review see Jbabdi & Johansen-Berg, 2011). The use of tractography to virtually segment white matter bundles has been one of the most significant achievements in DTI data analysis.

Fiber tractography assumes that each voxel is characterized by a single main fiber orientation and connects these local orientations to infer global fiber trajectories, where the local

fiber orientations can be considered as a three-dimensional (3D) vector field and the global fiber trajectories as its streamlines (Jeurissen et al., 2019; Mori et al., 1999).

The virtual reconstruction of white matter tracts requires the use of tractography algorithms and can be performed by taking a region of interest (ROI) approach. In summary, a region of interest is drawn around an area, can be white or grey matter, and one algorithm is used to follow the primary diffusion vector voxel-to- voxel, producing a series of streamlines that represent the connections between brain structures. To illustrate this, one can select the cingulum as a region of interest where an ROI called "seed" and a "target" is drawn around the tract, this ROI is usually called "AND", which indicates that the streamlines produced for the cingulum should pass through the selected ROIs. Several ROIs called "NOT" can be drawn to ensure the streamlines that do not belong to the cingulum do not pass through this region. After the reconstruction of the white matter tracts the average of diffusion metrics such as FA and MD can be obtained and analyzed. There are many types of algorithms but most of them can be classified in deterministic and probabilistic.

Deterministic Tractography

Deterministic tractography techniques uses the directional information represented by the diffusion tensor. The most frequent directional assignment corresponds to the diffusion tensor's principal eigenvector. Deterministic tractography is produced by initiating with one or more seed points per voxel within white matter and propagating the trajectories according to the tractography algorithm until the tracts are terminated (Alexander et al., 2007). Tracking is terminated when a voxel is reached that is unlikely to be part of a white matter bundle of interest. A curvature threshold stops a tract from bending sharply and propagating into an adjacent bundle. Thresholding on FA restricts tracking to white matter regions with greater FA and thereby excludes voxels with

gray matter or cerebrospinal fluid that have lower FA. Curvature criteria of 30° to 70° and a threshold of FA>0.2 are commonly used (Caan, 2016).

After that, the algorithm will proceed by taking a fixed user-specified step size out from the starting position along the approximate orientation at that moment. The orientation of the new site is then computed, and the following step in that direction is taken before the track is completed. The original fibre assignment by continuous tracking (FACT) approach is based on fixed step-size tracking and nearest-neighbour interpolation (Mori et al., 1999; Tournier et al., 2011).

In tractography analysis, tract editing techniques introduce prior anatomical knowledge to refine fibre tracking results, which is relevant to neuroscience and the current work (Figure 1.4). It entails identifying regions where the tract of interest is known to pass (Tournier et al., 2011). Even though these procedures effectively remove misleading results, they require a specialized anatomical understanding of the tracts of interest.

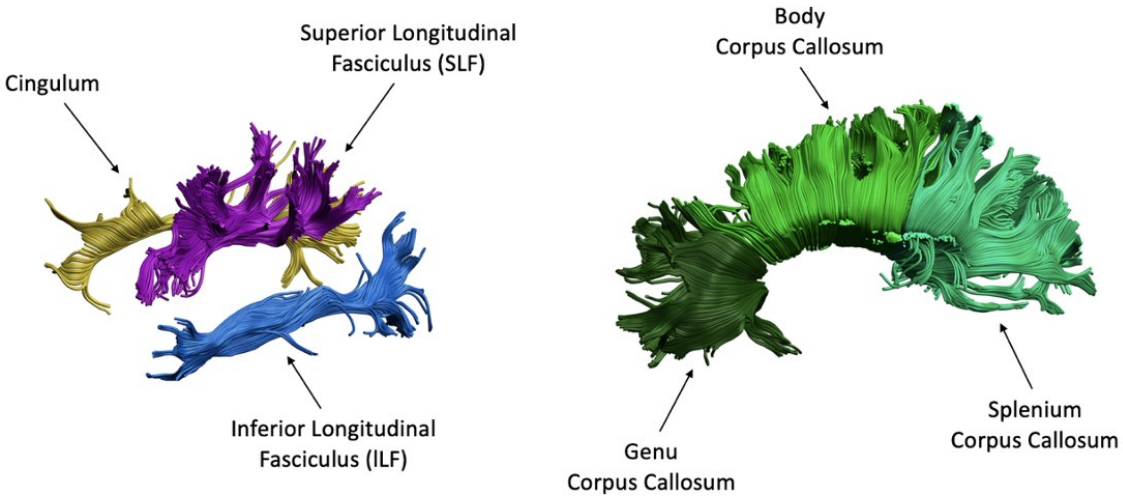


Figure 1.4: Example of the results from a semi-automated tractography analysis.

Probabilistic Tractography

As opposed to the deterministic technique, the probabilistic tractography method attempts to predict a probability distribution of alternative tract orientations per voxel rather than the orientation of the diffusion tensor's principal eigenvector. In addition, it tries to address the limitations of the deterministic technique by generating a probability density function (PDF) for each step of the process and predicting several neural voxel connections from each seed stage (Tournier et al., 2011).

Because they all rely on the same underlying model, probabilistic approaches are not more "correct" than deterministic methods. Nonetheless, the main advantage of probabilistic approaches is that they can estimate the "precision" with which a tract pathway has been reconstructed (Tournier et al., 2011). It is also worth emphasizing that the probability values generated by these algorithms have little to do with the "connectivity" (number of axons, etc.) of the related white matter pathways; they merely represent the degree of certainty that the relation of interest occurs (Tournier et al., 2011).

1.4.5. DTI Limitations

DTI has various limitations including low signal-to-noise ratio (SNR), typically acquired low voxel resolution (2-3 mm), image distortions from the single shot EPI, long scan times (5-10 minutes), and the assumption that each voxel has one coherent set of tracts (Tournier et al., 2011).

The physiological significance of DTI parameters such as FA and MD is not fully understood (Beaulieu, 2014); although they are sensitive to microstructural changes they are not specific. It is sensitive to several elements of axonal integrity (e.g., axon membranes, axon packing, myelination) and the general organization and alignment of groups of axons and fibres in white matter tissue. Also, the directionality of axons cannot be differentiated: afferent vs. efferent,

anterograde vs. retrograde pathways, inhibitory vs. excitatory connections, direct vs. indirect route (Emsell, Van Hecke, Tournier, 2015).

DTI measurements are notoriously noisy, which leads to ambiguity in predicted fibre orientations. Furthermore, because a minor error in the track allows the algorithm to join and pursue a separate white matter route, these flaws can detect slightly different connections placing the deterministic approach's dependability and validity into question (Tournier et al., 2011).

1.5. Thesis Motivation

The cognitive impairments observed in PAE influence several areas of daily living, such as academics, social interactions, and personal development. Neuropsychological literature has demonstrated that people with PAE have significantly impaired self-regulation skills, executive functioning, language and learning. In addition, MRI studies have shown brain abnormalities in individuals with PAE. However, little is known about the relationship between cognition and brain structure in PAE, especially between measures of language, executive functioning and verbal learning, which are the cognitive domains analyzed in this project.

Using DTI to study the underlying structural neurobiology of the cognitive impairment observed in PAE can add to our understanding of the clinical presentation of FASD and offer evidence that can contribute to the improvement of the diagnosis and intervention strategies in FASD. Thus, this study intended to examine associations between frontoparietal and temporal white matter as assessed by DTI tractography, neurocognitive abilities, and age in children and youth with PAE compared to unexposed controls.

Chapter 2

2. Methodology

This study is part of a larger research project looking into the mental health of children and teens exposed to various early risks and the underlying brain structures and processes that influence mental health (Andre et al., 2020; Lebel et al., 2019). Participants performed multiple tests as part of the broader project, including MRI data and cognitive, academic, and mental health screeners. The current study will focus on the DTI and cognitive data from the project mentioned above.

2.1. Participants

This study included 31 children and youth with PAE (18 boys; 7.8-15.9 years, mean 10.3±2.4 years) and 31 unexposed controls (18 boys; 7.1-14.2 years, mean 10.4±2.2 years) (Table 2.1). Recruitment of participants with PAE occurred through FASD clinics, Child & Family Services, organizations throughout Alberta (e.g., Calgary Fetal Alcohol Network, Edmonton Fetal Alcohol Network, Calgary Urban Project Society, First 2000 Days Network), and advertisements in caregiver support groups. Demographic information was collected through a questionnaire that asked about the date of birth, diagnoses, current medications, other family members in the home, household income, and services used. The child's race/ethnicity was not obtained in the demographic questionnaire, and consequently, families were re-contacted over the phone to get the information (Ritter, 2019).

All PAE participants had confirmed alcohol exposure; 13 had a confirmed FASD diagnosis. The absence of PAE was confirmed in controls via the biological mother's report. Children were excluded if they were currently in a mental health crisis or had any contraindications

to MRI. This study was approved by the University of Calgary Conjoint Health Research Ethics Board (REB17-0663).

Unexposed participants were recruited as part of another ongoing project on adolescent brain development. Inclusion criteria included an uncomplicated birth between 37- and 42-weeks' gestation, no history of developmental disorder or psychiatric disease, no history of neurosurgery, and no contraindications to MRI. This study was approved by the University of Calgary Conjoint Health Research Ethics Board (REB13-1346). For both research projects, all participants provided informed assent and parents/guardians provided written informed consent.

Table 2.1: Demographic information

	Unexposed (n=31)	**PAE (n=31)**	**Statistic**
Age (M±SD years)	10.4±2.2 (7.1-14.2)	10.3±2.4 (7.8-15.9)	$U = 461$, $p=0.79$
Gender [N (%) male]	18 (58)	18 (58)	$X^2= 0$, $p=1.0$
Ethnicity [N (%)]			$X^2= 29{,}11$, $p < 0.001$
White	18 (58)	9 (29)	
Indigenous	0 (0)	15 (48)	-
Asian/Pacific Islander	8 (26)	0 (0)	
Multiracial	5 (16)	4 (13)	
Black	0 (0)	3 (10)	
Caregiver Status [N (%)]			$X^2= 54.48$ $p < 0.001$
Biological Parent (s)	31 (100)	2 (7)	
Adoptive Parent (s)	0 (0)	24 (77)	
Foster	0 (0)	1(3)	
Other	0 (0)	4 (13)	

2.2. Neurocognitive Measures

All participants completed the Phonological Processing, Comprehension of Instructions and Speeded Naming subtests of the NEPSY-II (Ritter, 2019). Scaled scores of these subtests were used for analysis; higher scores indicate better performance.

2.2.1. Language

The NEPSY-II is a comprehensive neuropsychological battery that includes a variety of tests assessing attention and executive functioning, language, memory, sensorimotor, social perception, and visuospatial processing (Rasmussen et al., 2013). It is a standardized battery for children aged 3-16 years. The NEPSY-II produces both raw and age-standardized results. The mean standard score for all subtests is 10, with a standard deviation of 3. It has high dependability in internal consistency and test-retest reliability (Korkman, Kirk, Kemp., 2007).

This thesis uses the Comprehension of Instruction subtest that is designed to assess the ability to receive, process and execute oral instructions of increasing syntactic complexity. The Phonological Processing subtest is composed of two phonological processing tasks designed to assess phonemic awareness: (i) phonological segment recognition (requires identification of words from a word segment) and (ii) phonological segmentation (test of elison [elison refers to the cutting off or suppression of a letter]). It is designed to assess phonological processing at the level of word segments and letter sounds). The Speeded Naming subtest is used to evaluate rapid semantic access and production of names of colours, shapes, sizes, letters or numbers (Korkman, Kirk, Kemp., 2007).

Participants with PAE (but not the unexposed group) also completed the California Verbal Learning Test-Children's version (CVLT-C) (n=28) to assess verbal learning and recall in children aged 5 to 16 years (Delis, Kramer, Kaplan, & Ober, 1994), and their caregivers completed the

Behavioral Inventory of Executive Function-Parent Report (BRIEF-PR). The Behavioural Regulation Index, Metacognition Index, and the Global Executive Composite were analyzed for this study (Gioia, Isquith, Guy, & Kenworth, 2013). Higher CVLT-C scores and lower BRIEF-PR scores report better functioning.

2.2.2. Executive Functions

One way to study executive functions in PAE is using evaluation measures completed by parents or legal guardians and, to a lesser extent, teachers. In addition, rating scales assess executive functioning in the real world, providing a more ecologically realistic evaluation of these cognitive capacities than performance-based (i.e., Stroop and Trail Making) measurements provide (Rai et al., 2017a).

The Behavior Rating Inventory of Executive Functions (BRIEF; Gioia, Isquith, Guy, & Kenworth, 2013) has demonstrated good psychometric properties and has been widely used in pediatric research. The BRIEF was created to examine executive functioning in children's daily lives over the previous six months. The BRIEF assesses many executive functions-related behaviours and underlying structures (Inhibit, Shift, Emotional Control, Initiate, Working Memory, Plan/Organize, Materials Organization, Monitor) and two validity scores (Inconsistency and Negativity). In addition, the clinical scales combine to generate two broader Indexes (Behavioral Regulation [BRI]) and Metacognition [MI]) and an overall score, the Global Executive Composite (GEC).

The BRIEF-PR asks participants to respond to questions on a six-point Likert-type scale with N ("Never"), R ("Rarely"), S ("Sometimes"), O ("Often"), V ("Very Often"), or A ("Always"), indicating how frequently the individual being evaluated conducts a given behaviour. Respondents

are instructed to base their responses on observed/performed behaviours. Typically, the administration takes 10 to 15 minutes.

A T-score greater than 65 indicates moderate to high impairment. The T scores are calculated using a normative sample with a mean of 50 and a standard deviation of 10. The BRI measures a child's capacity to manage emotions and behaviour by shifting cognitive sets and using adequate inhibitory control. It consists of the Inhibit, Shift, and Emotional Control scales (Gioia, Isquith, Guy, & Kenworth, 2013). The MI clinical scale measures a child's capacity to initiate, plan, organize, self-monitor, and maintain working memory. It can be defined as a child's cognitive ability to self-manage tasks and check their performance. The MI is closely related to a child's ability to actively problem solve in various situations. It comprises the scales Initiate, Working Memory, Plan/Organize, Organization of Materials, and Monitor (Gioia, Isquith, Guy, & Kenworth, 2013). This test has high internal consistency (α's =0.80-0.98) and test-retest reliability (r's = .82 for parents, .88 for teachers). This study used the parent form due to multiple factors, including the age of the participants and concerns with the ability to complete or understand the rating scale.

While more research is needed in this area, parent report findings are consistent with neuropsychological data, which show that alcohol-exposed children have delayed executive functioning, including measures of problem-solving, planning, concept formation, set-shifting, verbal and nonverbal fluency, response inhibition, and working memory (Mattson et al., 2011).

Compared to the standardization sample, children and youth with PAE had mean BRIEF index t-scores in the clinical range. The majority of research shows that individuals with PAE have poorer cognitive functioning on the GEC, BRI, and MI (McGee et al., 2008; Wozniak et al., 2013). On the other hand, one study discovered a reduced proportion of clinical range GEC scores in

participants with PAE. However, their findings should be regarded with caution because the classification into groups was based primarily on a questionnaire filled out by parents. They were asked whether or not their children had been diagnosed with or were suspected of having PAE (Knuiman et al., 2015).

2.2.3. Verbal Learning

The California Verbal Learning Test- Children's Version (CVLT-C) measures strategies and processes involved in learning and recalling verbal material within an everyday shopping task. It is particularly sensitive to PAE (Lewis et al., 2015).

The test is given to children aged 5 to 16 years to help detect and treat memory deficits. The administration of the test involves several steps. First, a 15-word list (List A) containing five words from three semantic categories is presented for five trials. Following this, a one-time presentation of a distractor list (List B) is shown, followed by a free and semantically cued recall of List A. After a 20-minute delay, long-delayed free and cued recall trials are performed. Finally, the child is given a recognition trial in which they must correctly identify the 15 original words from List A amid distracting objects (Ritter, 2019; Delis, Kramer, Ober, 1994).

The CVLT-C raw scores are transformed into standard scores for each variable based on the normative sample (z-scores, with a mean of 0 and a standard deviation of 1). Negative z-scores indicate poor performance. Furthermore, z-scores are only available in 0.5 increments. The total learning summary score (T-score, List A trials 1-5) has a mean of 50 and a standard deviation of 10 and the internal consistency and alpha reliabilities for the tests are high (above 0.80) (Ritter, 2019; Delis, Kramer, Ober, 1994).

2.3. DTI Data Analysis

DTI images were processed using MATLAB R2020b and ExploreDTI 4.8.6 (Leemans et al., 2009). The pipeline was used as follows:

1. **Signal Drift Correction:** This correction was done using the tool developed by (Vos et al., 2017) and implemented in ExploreDTI. Scanner instability resulting from gradient heating can cause signal drift in various ways (Figure 2.1). The presence of signal drift can be easily examined when multiple $b = 0$ images are acquired throughout the scan. Furthermore, the effect can be minimized by randomization of b-values throughout the acquisition. Whereas this is not a replacement for preventing the effects of signal drift, it is essential to correct for the effects if they occur (Vos et al., 2017).

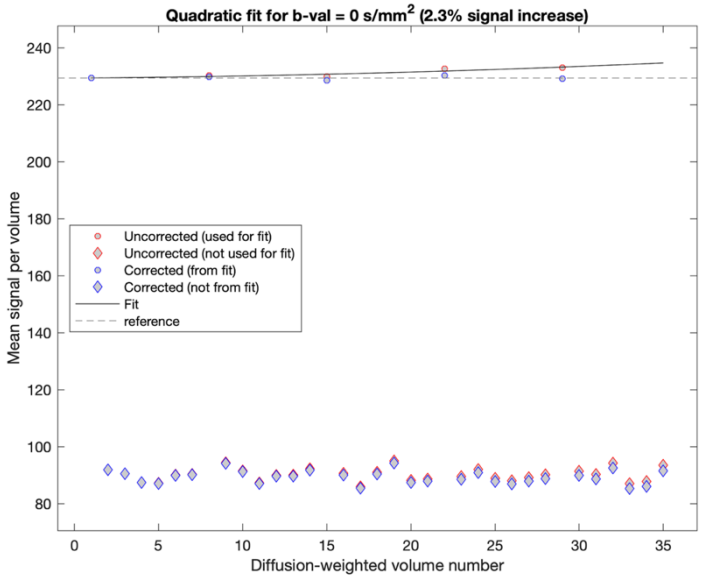


Figure 2.1: Signal drift in one of the participants from this study. The horizontal axis represents the number of diffusion-weighted volume, and the y-axis the normalized signal intensity. The red dots indicate the drift-affected signal, the black line the quadratic fit, and the blue dots the drift corrected signal intensities. The dashed line at the signal intensity is shown as a visual reference for the interpretation of signal drift.

2. **Gibbs ringing correction:** The Gibbs ringing result from high frequencies that result from Fourier Transform to create the images, extreme transitions of image intensity (e.g., cerebrospinal fluid to white matter on b=0 s/mm^2 images) (Van Hecke, Emsell and Sunaert, 2016) (Figure 2.2). This results in errors in diffusion metrics, like MD, near the margins or boundaries such as the genu of the corpus callosum and next to the lateral ventricules (Van Hecke, Emsell and Sunaert, 2016).

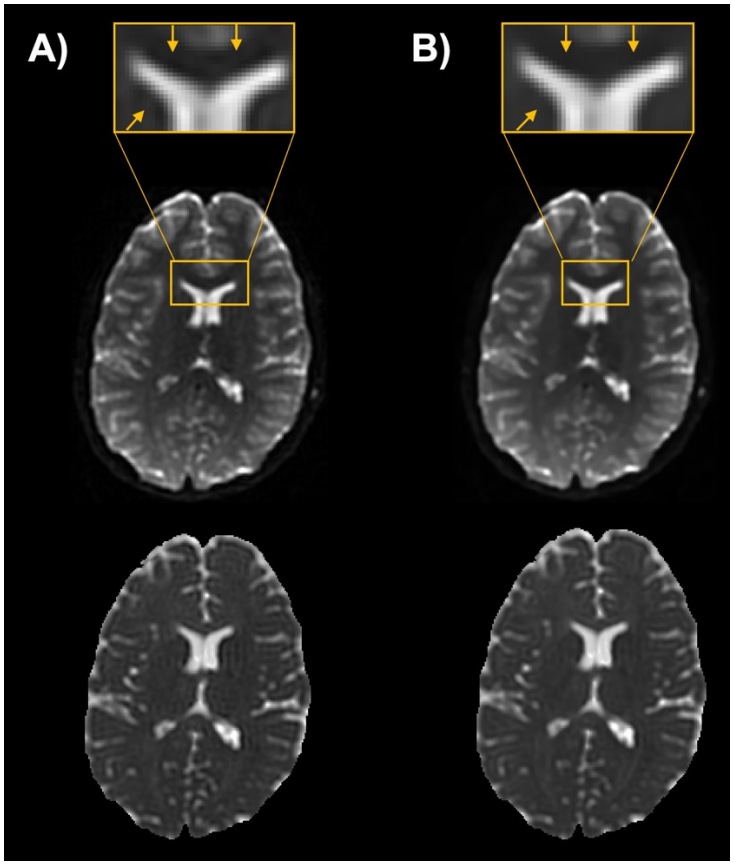


Figure 2.2: Gibbs ringing correction. Column A shows non-diffusion weighted images (top) and MD maps (bottom) before Gibbs ringing correction, and Column B shows non-diffusion weighted images (top) and MD maps (bottom) after Gibbs ringing correction.

3. **Eddy current and head motion correction:** Eddy currents induced by gradient switching can affect the signal readout, leading to distorted images that differ per diffusion gradient direction. Misalignment of the images can also occur if the participant moves their head during the scan. The software aligns all the images of a particular slice, so the correct tissue location's data is processed for the tensor fitting. There is an inherent sensitivity of diffusion imaging to small bulk motions (such as head movements of the patient) (Peterson and Bammer, 2016).
4. **Tensor fitting:** The diffusion tensor estimation was performed with a linear least squares approach with the REKINDLE (Robust Extraction of Kurtosis INDices with Linear Estimation) method consisting of an iteratively reweighted linear least squares approach included in the ExploreDTI software (Leemans et al., 2009; Tax et al., 2015)**.** In the presence of outliers, REKINDLE can estimate diffusion indices more reliably and with a 10-fold reduction in computation time compared to other methods (Tax et al., 2015).
5. **Tractography:** Whole brain tractography was performed by using a DTI based tractography algorithm implemented in ExploreDTI (Basser et al., 2000; Leemans et al., 2009).

2.4. Tractography Analysis

Semi-automated deterministic streamline tractography was performed in native diffusion space for each participant with an FA threshold of 0.2, a turning angle of 30°, a step size of 1 mm, and a minimum streamline length of 10 mm (Figure 2.3). First, on ExploreDTI a set of ROIs (AND/NOT) were defined to extract the white matter tracts based on a FA template from one participant. By using the template and ROIs, the tracts are automatically reconstructed for all the data sets. The participant's FA template was chosen based on the quality assessment of the data,

where one of the criteria was reduced head motion. All these steps were performed by using a built-in function in ExploreDTI.

A specified FA criterion (usually about FA>0.2) is set to not track into low FA voxels, and an angle threshold (below 30°) is set to prevent unlikely sharp turns between adjacent voxels. Tracking comes to a halt if the FA falls below the threshold or the angle between adjacent vectors becomes too large. The movement distance in each tracking period is defined by the step size, which is measured in millimetres and the setting can be the half of the spatial resolution. The length constraint eliminates tracts that are too short (Tournier et al., 2011; Yeh et al., 2021).

Due to the implication of frontoparietal and temporal white matter in cognitive domains such as language, executive functions and verbal learning and memory, the cingulum, inferior longitudinal fasciculus (ILF), and superior longitudinal fasciculus (SLF; without the arcuate fasciculus) were selected as tracts of interest for this analysis. Tracts were manually quality-checked, and additional exclusion regions of interest were drawn as required (Reynolds et al., 2019). Average FA and MD were extracted for each tract in the left and right hemispheres. In addition, the genu, body and splenium of the corpus callosum were examined because, in PAE, callosal abnormalities have been linked to executive dysfunction and verbal learning impairment (Ghazi Sherbaf et al., 2018; Sowell et al., 2001).

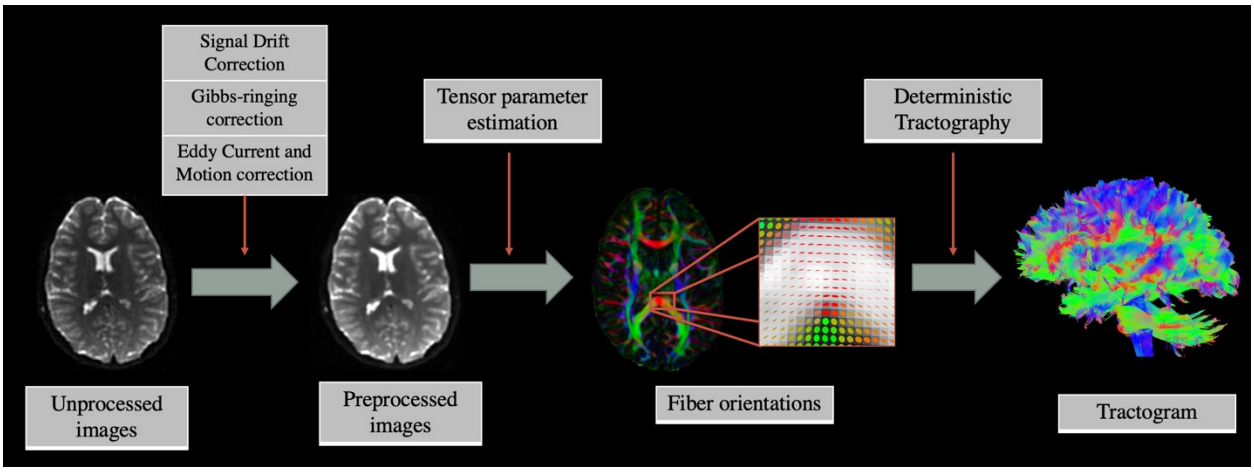


Figure 2.3: Overview of DTI data processing and tractography.

Chapter 3

3. Diffusion tensor tractography of frontoparietal and temporal white matter in children and youth with prenatal alcohol exposure[1]

3.1. Abstract

PAE is associated with brain alterations and neurocognitive deficits, but relationships between those brain alterations and neurocognitive deficits remain unclear. This study aimed to examine the relationship between frontoparietal and temporal white matter, neurocognitive abilities, and age in children and adolescents with PAE compared to unexposed controls.

DTI was obtained from 31 participants with PAE, and 31 unexposed participants aged 7-15 years. Mean diffusivity (MD) and fractional anisotropy (FA) of nine white matter tracts were derived from tractography of the genu, body, and splenium of the corpus callosum (CC) and bilateral cingulum, inferior longitudinal fasciculus (ILF), and superior longitudinal fasciculus (SLF). All participants completed three language subtests from the NEPSY-II. Executive functioning was measured using the Behavior Rating Inventory of Executive Functioning-Parent Rating (BRIEF-PR) and verbal learning was assessed using the California Verbal Learning Test-Children's Version (CVLT-C) in the children with PAE only.

Children with PAE had lower MD in the right SLF compared to unexposed controls. FA was positively related to age in 6/9 tracts and MD negatively related to age in all 9 tracts, and there

[1] A version of this paper has been submitted to a journal. Gomez, MJ., Beaulieu, C., McMorris, C., Gibbard, B., Tortorelli, C., Lebel, C. Diffusion tensor tractography of frontoparietal and temporal white matter in children and youth with prenatal alcohol exposure on April 1, 2022.

were no significant age-by-group interactions. Participants with PAE scored lower than unexposed peers on the NEPSY-II Comprehension of Instructions and Phonological Processing and above population norms (indicating worse performance) on the BRIEF-PR (Behavioural Regulation Index; Metacognitive Index; Global Executive Composite) placing them in the clinical range. There were no associations between cognitive performance and either MD or FA of any of the white matter tracts in the PAE group.

Despite widespread cognitive difficulties, there was only one white matter tract with group differences and there were no correlations between diffusion metrics and cognition in the children and youth with PAE. Further, the participants with PAE demonstrated the typical diffusion parameter-age associations as unexposed controls suggesting similar neurodevelopmental processes of white matter over 7 to 15 years in this cross-sectional sample.

3.2. Introduction

Prenatal alcohol exposure (PAE) is associated with brain abnormalities and neurocognitive difficulties (Uban et al., 2010). Fetal alcohol spectrum disorder (FASD) is the neurodevelopmental disorder related to heavy PAE (Cook et al., 2016), and its estimated prevalence ranges from 2-21% around the world (Lange et al., 2017; Popova et al., 2019). The neurocognitive profile of children with PAE is characterized by impairments in cognitive ability (Chasnoff et al., 2010), executive functioning (Green et al., 2009; Pei et al., 2011; Rasmussen, 2005), visual attention (Mattson et al., 2006), verbal and non-verbal learning (Crocker et al., 2011; Lewis et al., 2015), language (Mattson et al., 2019), and/or motor function (Roebuck et al., 1998).

Previous neuroimaging studies have shown widespread brain abnormalities in children and youth with PAE. Quantitative structural magnetic resonance imaging (MRI) has consistently shown overall reductions of total brain, white matter, and gray matter volumes in children with

PAE when compared to unexposed children (for reviews, see Lebel, Roussotte and Sowell, 2011; Donald et al., 2015). White matter appears to be particularly affected by PAE, with studies reporting microstructural alterations as indicated by diffusion tensor imaging (DTI) metrics such as fractional anisotropy (FA) and mean diffusivity (MD) (Donald, Eastman, et al., 2015; Ghazi Sherbaf et al., 2018; Lebel, Rasmussen, et al., 2008). DTI studies have generally shown lower FA and/or higher MD in white matter regions in children and youth with PAE, including the splenium (Fan et al., 2016; Paolozza et al., 2014, 2016) bilateral cingulum, inferior longitudinal fasciculus (ILF) (Lebel, Rasmussen, et al., 2008; Paolozza et al., 2016), and superior longitudinal fasciculus (SLF) (Fryer et al., 2009; Lebel, Rasmussen, et al., 2008). Contrasting findings of lower MD have been found in the genu of the corpus callosum and the right temporo-parieto-occipital junction in children and youth with PAE compared to unexposed peers (Lebel, Rasmussen, et al., 2008; Li et al., 2008; Treit et al., 2013), as well as more widespread areas in infants and young children with PAE (Kar et al., 2021; Taylor et al., 2014).

Normative development studies show that FA tends to increase and MD decreases with age across white matter, albeit with different regional trajectories (for review see Lebel, Treit and Beaulieu, 2019). Few DTI studies have examined age-related changes in children and youth with PAE, though there is evidence for altered brain development from both cross-sectional (Paolozza et al., 2016; Treit et al., 2017) and longitudinal samples (Treit et al., 2013). The only longitudinal study to date (Treit et al., 2013) showed greater reductions of MD over time in children with PAE, which may suggest compensatory changes.

Studies of the association between white matter microstructure and neurocognitive functioning in individuals with PAE have shown mixed results. In children with PAE, voxel-based analysis (VBA) has shown significant correlations between visuomotor and visual-perceptual

skills and FA in the bilateral splenium (Sowell et al., 2008) and frontal-temporal white matter (Colby et al., 2012), and that math scores are positively related to FA in left parietal regions and the left cingulum and negatively related to FA in the left cerebellum and bilateral brainstem (C. Lebel et al., 2010). Tractography studies have shown that Word ID scores are related to FA of the genu, ILF, and SLF (Treit et al., 2017), as well as MD changes over 2-4 years in the superior fronto-occipital fasciculus and the SLF, but there were no significant correlations with executive functioning (Treit et al., 2013). Working memory scores showed a strong positive association with FA in the genu CC, while MD in the splenium was linked to perceptual organisation and working memory scores, but not verbal comprehension or processing speed (Wozniak et al., 2009). A different tractography study found no relation between FA of multiple brain regions and executive functioning in children and youth with PAE (Paolozza et al., 2016). These studies provide some evidence of associations between white matter and reading, memory, and math abilities in individuals with PAE. However, the associations between key cognitive domains, such as executive functioning, and white matter in children with PAE remain unclear.

Here, we examined nine frontal and temporal white matter tracts in children and youth with PAE compared to unexposed children and youth to determine group differences, assess age-related changes, and examine the association with executive functioning, language, and verbal learning.

3.3. Methods

3.3.1. Participants

This study included 31 children and youth with PAE (18 boys; 7.8-15.9 years, mean 10.3±2.4 years) and 31 unexposed controls (18 boys; 7.1-14.2 years, mean 10.4±2.2 years). Participants were recruited through posters, social media, newsletters, word of mouth, and (for participants with PAE) through the Cumulative Risk Diagnostic Clinic (CRDC) in Calgary,

Alberta (Andre et al., 2020). Demographic information (age, gender, ethnicity) was determined through caregiver reports. Consistent with the Canadian Guidelines (Cook et al., 2016), alcohol exposure was confirmed via the biological's mother self-report, reliable observations by close family or friends, clinical observation, and/or medical, legal or child services records. All PAE participants had confirmed alcohol exposure; 13 had a confirmed FASD diagnosis. Absence of PAE was confirmed in controls via biological mother's report. Children were excluded if they were currently in a mental health crisis or had any contraindications to MRI. Written informed consent were obtained from parents/guardians and assent from the children, and this study was approved by the University of Calgary Conjoint Health Research Ethics Board (REB17-0663).

3.3.2. Neurocognitive Measures

All participants completed the Phonological Processing, Comprehension of Instructions and Speeded Naming subtests of the NEPSY-II (Brooks et al., 2009). Scaled scores of these subtests were used for analysis; higher scores indicate better performance.

Participants with PAE (but not the unexposed group) also completed List A and List B from the California Verbal Learning Test-Children's version (CVLT-C) (n=29) to assess verbal learning in children aged 5 to 16 years (Delis, Kramer, Kaplan, & Ober, 1994). Participant's caregivers completed the Behavioral Inventory of Executive Function-Parent Report (BRIEF-PR) (n=29) (Gioia, Isquith, Guy, & Kenworthy, 2013). The Behavioural Regulation Index, Metacognition Index, and the Global Executive Composite were analyzed for this study. Higher CVLT-C scores and lower BRIEF-PR scores report better functioning.

3.3.3. MRI Acquisition

Diffusion images were acquired on a 3T GE MR750w MRI using a 32-channel head coil at the Alberta Children's Hospital in Calgary, Alberta. The sequence used a spin-echo single-shot

2D EPI parallel imaging ASSET (R2) with 30 diffusion directions at b=900 s/mm^2 and 5 at b=0 s/mm^2, TR=12 s, TE=88 ms, 2.2 mm isotropic resolution interpolated to 1.1x1.1 mm^2 in-plane, 55 2.2 mm axial slices, and total scan time of 7:12 min. T1-weighted anatomical imaging was acquired using an 3D-FSPGR sequence with TI=600 ms, TR=8.2 ms, TE=3.2 ms, 0.8 mm isotropic resolution, and a total scan time of 5:38 min.

3.3.4. Neuroimaging Processing

DTI images were processed using MATLAB R2020b and ExploreDTI 4.8.6 (Leemans et al., 2009). The processing steps included correction for signal drift, Gibbs ringing, subject motion and eddy current-induced artifacts. The b-matrix was accordingly rotated (Leemans & Jones, 2009). The diffusion weighted images (DWI) were non-rigidly registered to the T1-weighted images to correct for echo-planar imaging distortions. Semi-automated deterministic streamline tractography (Lebel, Walker, et al., 2008) was performed with an FA threshold of 0.2, a turning angle of 30°, a step size of 1 mm, and a minimum fibre length of 10 mm. Due to the implication of frontoparietal and temporal white matter in cognitive domains such as language, executive functions and verbal learning and memory (Treit et al., 2013; Wozniak & Muetzel, 2011), the bilateral cingulum, inferior longitudinal fasciculus (ILF), and superior longitudinal fasciculus (SLF) were selected as tracts of interest for this analysis (Figure 1). Tracts were manually quality-checked, and additional exclusion regions of interest were drawn as required (Reynolds et al., 2019). Average FA and MD were extracted for each tract in the left and right hemispheres. We also examined the genu, body and splenium of the corpus callosum because in PAE callosal abnormalities have been linked to executive dysfunction and verbal learning impairment (Ghazi Sherbaf et al., 2018; Sowell et al., 2001).

3.3.5. Statistical Analysis

Statistical analysis was performed using RStudio version 1.1.453 (RStudio Team, 2016). Data visualization was done with the package ggstatsplot (Patil, 2021).

Demographics: The Shapiro-Wilk test was used to test all variables for normality, which showed that age was not normally distributed; thus, a Mann-Whitney U test was used to analyze group differences in age. Categorical demographics were compared using X^2 tests.

Group differences in DTI metrics: Linear regression models were conducted to examine white matter group differences in children with PAE compared to the unexposed group, with FA and MD as the dependent variables, group as the predictor, and age and gender as covariates. Age-by-group interactions were included in the initial model but removed if not significant ($p<0.05$).

Diffusion metrics versus age: Linear regression models were used to investigate the association between DTI metrics and age in children with PAE and unexposed participants.

Group differences in neurocognitive tests: Linear regression models were run to examine language scores differences in children with PAE compared to the unexposed group with the tests scores as dependent variables, group as the predictor, and age and gender as covariates. Age-by-group interactions were included in the initial model but removed if not significant ($p<0.05$). Executive functioning and verbal learning scores for the participants with PAE were compared to population standard values (standard T scores of 50 for the BRIEF-PR, 50 for the List A total of the CVLT-C, and 0 for z scores from the other CVLT-C trials) using one sample t-tests.

Relations between DTI metrics and neurocognitive scores: Linear regression models were used to determine the relation between language measures and diffusion metrics in children with PAE and the unexposed control group, as well as between executive function, and verbal learning measures and diffusion metrics in children with PAE only (measures were not available for the

unexposed control group). The model included the cognitive score as the dependent variable, FA or MD as the predictor, and age and gender as covariates. Age-by-group interactions were included in the initial model but removed if not significant (p<0.05).

Multiple comparisons were addressed using false discovery rate (FDR) correction for 18 tests for white matter group differences (9 regions*2 DTI metrics [FA and MD]), three tests for language score group differences, 36 tests for white matter and age relationships (9 regions*2 DTI metrics [FA or MD] *Group [PAE/Unexposed]), 54 tests for language-white matter associations (9 regions*2 DTI metrics*3* cognitive subtests), 36 tests for verbal learning scores-white matter associations (9 regions*2 DTI metrics*2 cognitive subtests), and 54 tests for executive functions-white matter measures (9 regions*2 DTI metrics*3 cognitive indexes) at q=<0.05 (Benjamini & Hochberg, 1995).

3.4. Results

3.4.1. Demographics

Age and gender did not differ significantly between groups, but significantly more control participants were residing with their biological parents compared to the PAE group (Table 3.1).

Table 3.1: Participant demographics. Significant differences are bolded.

	Unexposed (n=31)	**PAE (n=31)**	**Statistic**
Age (M±SD years)	10.4±2.2 (7.1-14.2)	10.3±2.4 (7.8-15.9)	$U = 461$, $p=0.79$
Gender [N (%) male]	18 (58)	18 (58)	$X^2= 0$, $p=1.0$
Caregiver Status [N (%)]			$X^2= 54.48$ ***p* < 0.001**
Biological Parent (s)	31 (100)	2 (7)	
Adoptive Parent (s)	0 (0)	24 (77)	
Foster	0 (0)	1(3)	
Other	0 (0)	4 (13)	

3.4.2. Neurocognitive Measures

The PAE group had significantly lower Comprehension of Instructions Scores (p=<0.001, q=0.008) and Phonological Processing Standard Scores (p=0.001, q=0.004) of the NEPSY-II compared to controls. Children and youth with PAE scored significantly above population norms on the Behavioural Regulation Index (p<.001, q=0.002), Metacognitive Index (p<.001, q=0.002) and the Global Executive Composite (p<.001, q=0.003) of the BRIEF-PR (Table 3.2).

Table 3.2: Age-standardized cognitive scores for NEPSY-II language subtests, as well as verbal learning (CVLT-C) and executive function (BRIEF) assessments in the PAE group. Lower NEPSY-II and CVLT-C scores indicate worse performance; higher BRIEF-PR scores indicate more problematic behaviour. Population norms mean standard scores were used for the BRIEF-PR (mean T score=50, SD=10), List A total (mean score=50, SD=10) and List B CVLT-C (z-scores= 0, SD=1). Q-values are only provided for tests with $p<0.05$; findings with $q<0.05$ are bolded.

	Unexposed	**PAE**	**t-value**	**p-value (q-value)**
NEPSY-II Standard Scores				
Comprehension of Instructions	11±2	8±3	4.07	**<0.001 (0.008)**
Phonological Processing	10±3	8±3	3.43	**0.001 (0.004)**
Speeded Naming	11±3	9±4	1.45	0.15
CVLT-C				
List A total (T score)		44±16	-1.89	0.07
List B (z score)		-0.5±1.20	-2.04	0.05 (0.06)
BRIEF Parent Form T scores				
Behavioural Regulation Index		67±11	8.35	**<.001 (0.003)**
Metacognitive Index		68±9	10.21	**<.001 (0.002)**
Global Executive Composite		69±9	10.58	**<.001 (0.002)**

3.4.3. DTI of Nine White Matter Tracts

The group mean FA and MD values for all tracts are shown in Tables 3.3 and 3.4, respectively. Compared to the unexposed group, participants with PAE had lower MD in the right SLF (p=0.01, q=0.04) (Figure 3.1.) no other group differences were significant at q<0.05.

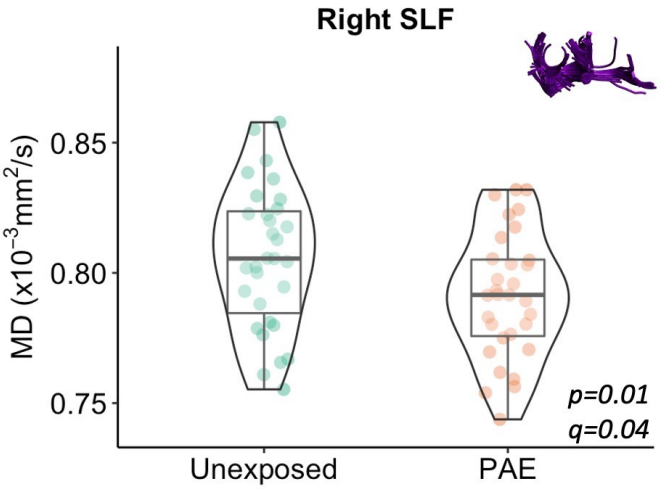


Figure 3.1: The prenatal alcohol exposure (PAE) group had lower mean diffusivity (MD) by 2.5% in the right superior longitudinal fasciculus (SLF) compared to unexposed children

3.4.4. DTI Parameters Versus Age

The majority of tracts (all except the genu and bilateral ILF) showed a positive relation of FA with age (Table 3.3) and all tracts showed a negative correlation of MD with age across groups (Table 3.4, Figure 3.2). There was an age-by-group interaction for FA in the left ILF (p=0.04, q= 0.36; Table 3.4), but it did not survive FDR correction. There were no significant age-by-group interactions for other tracts.

Table 3.3: Fractional anisotropy of white matter tracts in each group, with group differences and relationships with age. L=left; R=right. Q-values are only provided for tests with p<0.04; findings that meet the significance level set at *q*=<0.05 are bolded.

	Fractional Anisotropy					
	Unexposed	**PAE**	**F**	**Group**	**Age**	**Age-group interaction**
	Mean±SD	**Mean±SD**		**p-value (q-value)**	**p-value (q-value)**	**p-value (q-value)**
Genu CC	0.53±0.02	0.53±0.01	1.31	0.73	0.08	0.52
Body CC	0.52±0.02	0.53±0.02	4.15	0.19	**0.002 (0.004)**	0.42
Splenium CC	0.58±0.02	0.59±0.01	5.92	0.02 (0.18)	**0.001 (0.002)**	0.58
R Cingulum	0.47±0.03	0.47±0.03	5.71	0.79	**<0.001 (<0.001)**	0.62
L Cingulum	0.45±0.03	0.44±0.04	8.21	0.34	**<0.001 (<0.001)**	0.60
R SLF	0.44±0.02	0.44±0.02	3.64	0.26	**0.004 (0.006)**	0.78
L SLF	0.45±0.02	0.46±0.02	9.05	0.44	**<0.001 (<0.001)**	0.81
R ILF	0.46±0.02	0.46±0.02	0.88	0.53	0.29	0.40
L ILF	0.46±0.02	0.47±0.02	1.79	0.14	0.16	0.04 (0.36)

Table 3.4: Mean diffusivity of white matter tracts in each group, with group differences and relationships with age. L=left; R=right. Q-values are only provided for tests with p<0.04; findings that meet the significance level set at q=<0.05 are bolded.

	Mean Diffusivity (10^{-3} mm^2/s)					
	Unexposed	**PAE**	**F**	**Group**	**Age**	**Age-group interaction**
	Mean±SD	**Mean±SD**		**p-value (q-value)**	**p-value (q-value)**	**p-value**
Genu CC	0.87±0.02	0.86±0.03	6.10	0.27	**<0.001 (<0.001)**	0.83
Body CC	0.88±0.03	0.86±0.04	5.25	0.10	**<0.001 (<0.001)**	0.46
Splenium CC	0.87±0.03	0.86±0.03	6.67	0.16	**0.0008 (0.003)**	0.65
R Cingulum	0.83±0.02	0.82±0.02	4.50	0.11	**0.001 (0.001)**	0.78
L Cingulum	0.82±0.03	0.81±0.02	9.14	0.03 (0.09)	**<0.001 (<0.001)**	0.06
R SLF	0.81±0.02	0.79±0.02	9.39	**0.01 (0.04)**	**<0.001 (<0.001)**	0.52
L SLF	0.79±0.02	0.79±0.02	9.35	0.54	**<0.001 (<0.001)**	0.36
R ILF	0.83±0.02	0.83±0.02	3.56	0.58	**0.002 (0.002)**	0.10
L ILF	0.82±0.02	0.80±0.02	8.02	0.008 (0.07)	**<0.001 (0.001)**	0.68

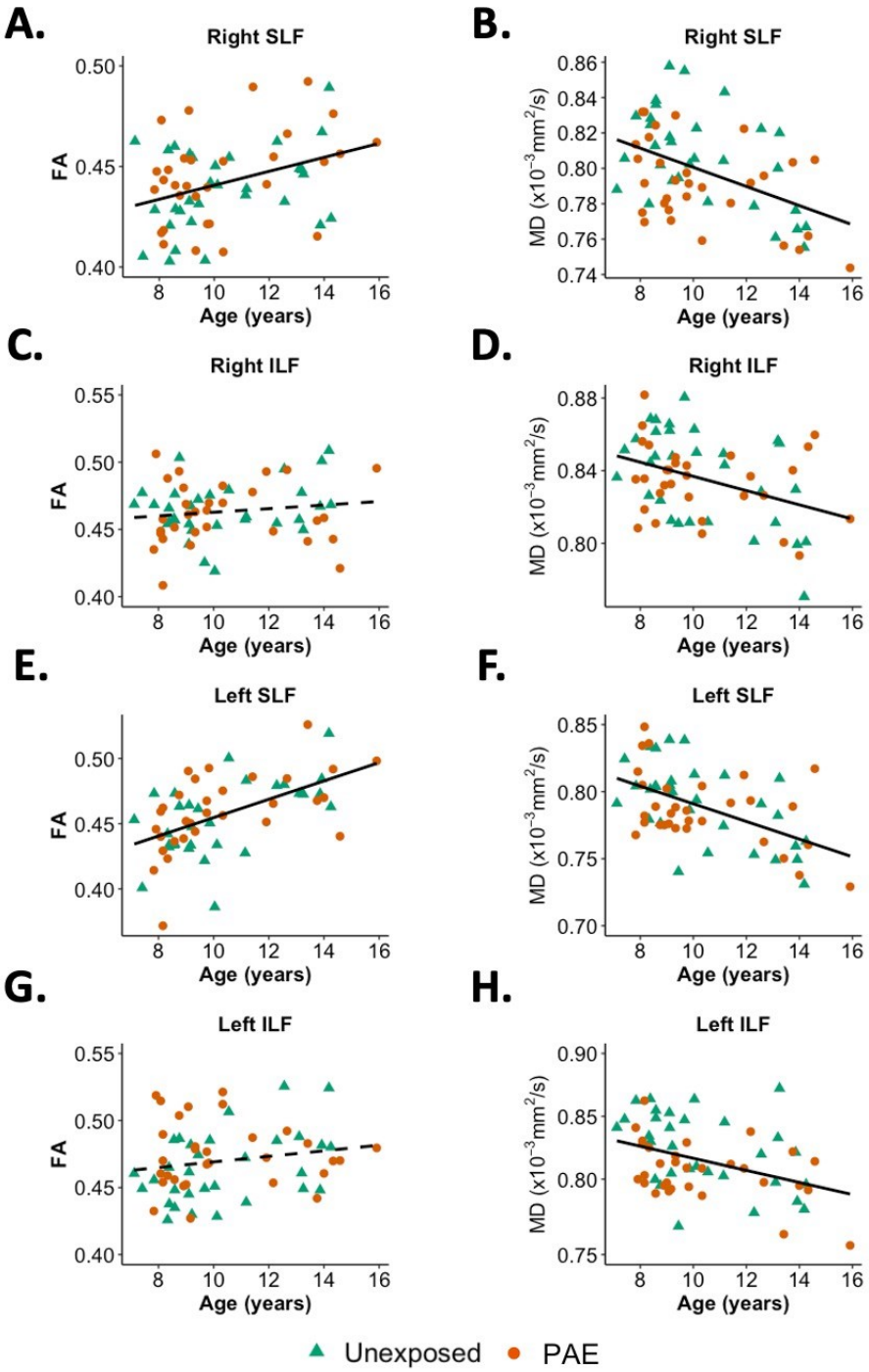


Figure 3.2: The majority of white matter tracts showed significant ($q<0.05$) positive linear association with fractional ansiotropy (FA) and all white matter tracts showed significant negative linear correlations of mean diffusivity (MD) versus age. There were no significant age-by-group interactions (single best fit line shown). Here we show the bilateral superior and inferior longitudinal fasciculi as examples of the diffusion metrics versus age relations. Dotted lines represent non-significant associations.

3.4.5. DTI versus Neurocognitive Measures

Language: There was a positive linear association between Speeded Naming Standard Scores and FA in the left SLF (p=0.02, q=0.54), the left ILF (p=0.03, q=0.40), and between Phonological Processing Standard Scores and MD in the right ILF (p=0.02, q=0.54) (Supplementary Tables 1, 2). However, none of these results survived FDR correction (Figure 3.3). There were no significant group-brain metric interactions.

Executive Function: In the PAE group, there was a positive linear relation between FA in the genu of corpus callosum and the Behavioral Rating Scale (p=0.01, q=0.33) and the Global Executive Composite (p=0.04, q=0.38), as well as between FA in the splenium of corpus callosum and the Behavioural Rating Scale (p=0.03, q=0.42). None of these results survived FDR correction.

Verbal Learning: There were no significant associations between CVLT-C scores and diffusion parameters.

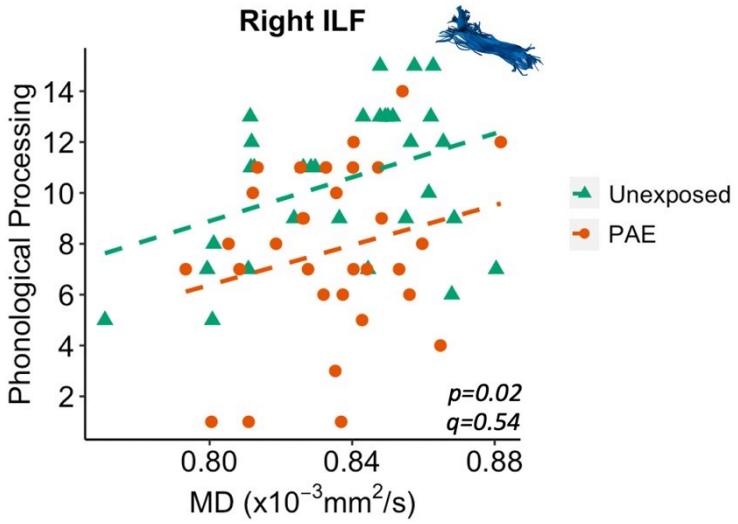


Figure 3.3: Example of a relationship between a cognitive score (phonological processing) and a diffusion metric (mean diffusivity in the right inferior longitudinal fasciculus). No brain-cognitive relationships were significant after multiple comparison correction.

3.5. Discussion

Here, we show lower MD in the right SLF in children and youth with PAE compared to unexposed controls. White matter regions examined showed similar positive associations of FA with age and negative relations of MD with age in both PAE and unexposed groups. Children and youth with PAE showed more language difficulties than unexposed peers, as well as significant executive function impairments. However, the cognitive measures were not significantly related to the diffusion metrics in any tract. The relatively limited brain alterations in this group of children and youth with PAE do not appear to underlie the more widespread cognitive difficulties observed.

The SLF is an association fibre tract that connects the temporoparietal junction region and parietal lobe to the frontal lobe (Wang et al., 2016) and is associated with language abilities, motor control, working memory and metacognition (Dick & Tremblay, 2012; Zheng et al., 2021). Our findings of lower MD in the right SLF are consistent with prior work in infants (Taylor et al., 2014) (Donald, Roos, et al., 2015), young children (Kar et al., 2021), and older children (Andre et al., 2020; Fryer et al., 2009; Lebel, Rasmussen, et al., 2008) reporting lower MD in frontal white matter, including the right SLF specifically (Donald, Roos, et al., 2015). Furthermore, steeper decreases in MD values with age have been observed in the SLF in children with PAE (Treit et al., 2013). However, other work reports higher MD in the SLF in children and youth with PAE (Fan et al., 2016; Fryer et al., 2009), suggesting heterogeneity, perhaps related to participant differences.

Typically, higher FA and lower MD are interpreted to indicate more coherent fibre structure, denser axon packing, and/or more myelination. However, abnormally lower MD in participants with PAE could be explained by accelerated brain development. Accelerated brain changes have been observed in children and youth with PAE that show steeper MD changes compared to unexposed participants (Treit et al., 2013), individuals who were prenatally exposed

to methamphetamines (Cloak et al., 2009), and children that experienced early adversity such as neglect, physical/sexual/emotional abuse and violence (Bick & Nelson, 2016; Hart & Rubia, 2012). Different age ranges and diagnostic profiles (only 13 participants had a confirmed FASD diagnosis) could also contribute to discrepant findings across studies.

Some previous DTI studies have found significant associations between cognitive measures and DTI metrics (Lebel et al., 2010; Sowell et al., 2008; Wozniak et al., 2009), while others reported no significant relationships (Paolozza et al., 2014;Treit et al., 2013; Lebel et al., 2008a). These mixed results could be influenced by different image analysis techniques, age ranges, participant diagnoses, and/or diversity of cognitive assessments. For example, several studies using VBA reported associations (Lebel et al., 2010; Sowell et al., 2008), while others using tractography (Lebel, Rasmussen, et al., 2008; Paolozza et al., 2016; Treit et al., 2013) did not. In addition, complex cognitive processes such as executive functions and language rely on distributed brain networks, rather than single tracts, and cognitive assessments comprise several distinct but related processes (Paolozza et al., 2016; Price, 2018; Tosi et al., 2020), making finding associations between diffusion metrics and cognition more challenging.

There were positive FA-age and/or negative MD-age effects for all white matter tracts, consistent with prior studies in normative development (Clayden et al., 2012; Genc et al., 2018) and in individuals with PAE (Lebel et al., 2008b; Paolozza et al., 2016). We found one age-by group interaction in the left ILF MD, but it did not survive FDR correction. Future studies could explore this interaction in more depth, particularly in larger samples. Other tracts showed no age-group interactions, which suggests similar developmental trajectories in children with PAE and unexposed controls. Limited previous research has shown subtle alterations in developmental trajectories in children with PAE, with steeper reductions of MD from 5-32 years (Treit et al.,

2017). Further longitudinal studies are necessary to better understand developmental trajectories in children with PAE.

There are limitations to this study. First, the small sample size may have insufficient statistical power to detect brain-behaviour relationships, or group interactions in age-related changes. Second, the use of a parent/caregiver-rated questionnaires to assess executive functioning does not necessarily provide a full evaluation of these abilities (Mohamed et al., 2019). Future studies should include performance-based measures to assess executive function.

In conclusion, children and youth with PAE had limited white matter differences from unexposed controls, with lower MD in only the right SLF and no group differences in FA. Cognitive functioning was impaired in the PAE group in most domains. However, cognitive performance was not related to diffusion metrics of the individual tracts, which may reflect a more distributed network supporting cognitive function. Positive FA-age and negative MD-age associations were found in individuals with PAE and unexposed controls, reflecting typical development of DTI metrics. The results presented here show relatively limited brain white matter differences and suggest that complex behaviors such as language and executive function rely on distributed processing and networks in individuals with PAE.

Chapter 4

4. Conclusions

This project examined the relationship between white matter as assessed by DTI tractography, neurocognitive abilities such as verbal learning, language and executive functions and age. Cognition was impaired in PAE, but no relationship was found between brain diffusion metrics in white matter and cognitive scores. Children with PAE had lower MD in the right SLF than unexposed controls. FA was positively related to age in six of nine tracts examined, and MD was negatively associated with age in all nine tracts; there were no significant age-by-group interactions.

The work presented in this thesis addresses several points. First, as was explained in Chapter 1, the literature on the relationship between diffusion metrics and cognitive scores in children and youth is limited, and the results are often mixed (Fan et al., 2016; Lebel et al., 2010; Lebel, Rasmussen, et al., 2008; Paolozza et al., 2014, 2016; Sowell et al., 2008; Treit et al., 2013, 2017; Wozniak et al., 2009). As a result, this study examined group differences in diffusion metrics of specific frontoparietal and temporal white matter and its relation to neurocognitive scores of domains that constitute an important criterion for an FASD diagnosis such as executive functioning and language. Previous research has not looked at the association between the frontoparietal and temporal white matter tracts and cognitive domains analyzed in this study.

Even though there were no group interactions, and the results did not survive multiple comparison corrections, the results obtained in this project suggests that there may be an association between language domains and diffusion metrics in parietal and temporal white matter tracts previously associated with language, such as the ILF and SLF, in PAE and typical development. Regarding executive functioning in PAE, this study reported associations between

frontal and posterior white matter regions diffusion metrics such as the genu and splenium of the corpus callosum and executive functions, which is consistent with the literature indicating the role of frontal areas in executive functioning (Wiebe and Karbach, 2017; Tamnes et al., 2010).

Second, as discussed in Chapter 1, there is limited research on the association between diffusion metrics and age in PAE (Lebel, Rasmussen, et al., 2008; Paolozza et al., 2016; Treit et al., 2013). Therefore, the purpose of this cross-sectional study was to investigate the link between diffusion measures and age in PAE. According to Chapter 3, there were positive FA-age and/or negative MD-age effects for all white matter tracts, which is consistent with previous research in normal development (Clayden et al., 2012; Genc et al., 2018) and in PAE participants (Lebel et al., 2008b; Paolozza et al., 2016), but no age by group interactions were found. These findings show that DTI is still a powerful technique for investigating age-related changes in diffusion metrics of white matter structures in both typical development and neurodevelopmental disorders such as FASD.

Finally, FASD is a heterogeneous neurodevelopmental disorder that represents many diagnostic challenges. For example, it is hard to determine PAE's timing, dosage, and chronicity and differentiate neurocognitive deficits that overlap with other pediatric disorders. In addition, many of the children and youth with an FASD diagnosis have experienced postnatal adversity, such as a change of caregiver, which is not usually seen in their unexposed peers. Taking all this into account, it appears that the interaction between prenatal and postnatal experiences could influence the disruption in neurocognitive abilities observed in FASD and should be considered in future studies.

4.1. Limitations

Unexposed participants did not undertake the full battery of cognitive testing because their data had previously been obtained for a study of healthy brain development. However, they were administered three language subtests that allowed group comparisons in one cognitive domain but not the rest—limiting the comparisons and possible results if the same neurocognitive tests were administered in both groups.

The results shown in the executive functions domain may have been constrained by parent rating of executive functioning. Evaluating performance measures of behavioural and cognitive regulation could have indeed strengthened current findings and allowed for a more accurate clinical description of the impairments reported in the PAE group. According to at least one research study, the performance of children with FASD on tests like the BRIEF-PR is reported to be more severe by instructors than by parents (Rasmussen, 2005). It's unknown if the difference is due to different contextual demands on children's executive functions (school vs. home), rater expectations (e.g., more self-regulation expected in the classroom), or a mix of these and/or other variables (Rai et al., 2017).

Furthermore, this thesis focused on examining specific diffusion metrics (FA/MD) in frontoparietal and temporal white matter tracts and their relationship with neurocognitive scores. A broader approach that includes more tracts, especially when analyzing age-related changes in diffusion metrics and the inclusion of other diffusion metrics such as radial and axial diffusivity could help to increase the robustness of the project. In addition, only white matter structures were examined here; future work could also include grey matter structures.

Recruitment of children and youth with PAE is challenging; this introduces biases in clinical and demographic variables of participants with PAE and unexposed participants. In this

study, ethnicity was not matched between groups, resulting in differences that could impact the results.

Tractography-based diffusion analysis has the benefit of probing a whole white matter tract, but this may limit sensitivity to local anomalies found by voxel-based or along-the-tract techniques and may account for fewer group differences here than prior studies using other methods.

4.2. Future Work

First, PAE studies should explore brain-behaviour interactions in more white matter tracts. For example, the arcuate fasciculus could be included as a parietal-temporal white matter tract and explore correlations with language domains. Furthermore, future research could benefit from double dissociation experimental designs traditionally used in neuropsychology.

Second, studies should include executive functions performance-based measures like subtests of executing functioning from the NEPSY-II, Trail Making Test, Color-Word Interference, along with third-party reports of child behaviour (parents, teachers, other caregivers) like the BRIEF-PR which was used in this thesis, because even though parent reports offer a more ecologically validated assessment of executive functioning, there is evidence showing that these tests could be measuring different constructs in comparison with the performance-based tests of executive functioning (Ten Eycke & Dewey, 2016).

Third, to date, only one longitudinal study has investigated diffusion metrics versus age in individuals with FASD (Treit et al., 2013), and little is known about this relationship. More studies should take a longitudinal approach to explore and understand the developmental trajectories in PAE in both brain structure and cognition. For example, diffusion metrics could be assessed in both white and grey matter. In addition, developmental studies have demonstrated that executive

functioning abilities have a definite time course, with age moderating the strength of the executive functions-PAE relationship (Khoury et al., 2015).

Fourth, better diffusion MRI acquisitions could improve the sensitivity of this technique to the diffusion changes observed in PAE. The improvement of parameters such as higher resolution can reduce partial volume effects and measure smaller tracts. Using higher b-values and more gradient directions can allow for the implementation of more complex models like constrained spherical deconvolution (CSD) beyond DTI to perform tractography analysis through crossing fibre regions and obtain more robust tracts. Likewise, higher b-values also provide the opportunity to generate other diffusion metrics like kurtosis possibly better reflecting water restriction in the white matter tracts.

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Appendix

A. Anatomical Coordinates for the Delineation of White Matter Tracts

The following semi-automated tractography guides are based on Reynolds et al. (2019). Green ROIs represent inclusion of regions where fibres must pass through, and red ROIs represent exclusion regions where fibres cannot pass through these regions.

A.1. Genu of the Corpus Callosum

Sagittal ROIs:

1. AND ROI placed on the anterior portion of the corpus callosum.

Coronal ROIs:

2. NOT ROI placed posterior to the sagittal AND ROI (1). Covers the entire coronal slice.

3. NOT ROI placed posterior to the sagittal AND ROI (1). It covers half of the coronal slice. Coronal NOT excludes the cingulum projections.

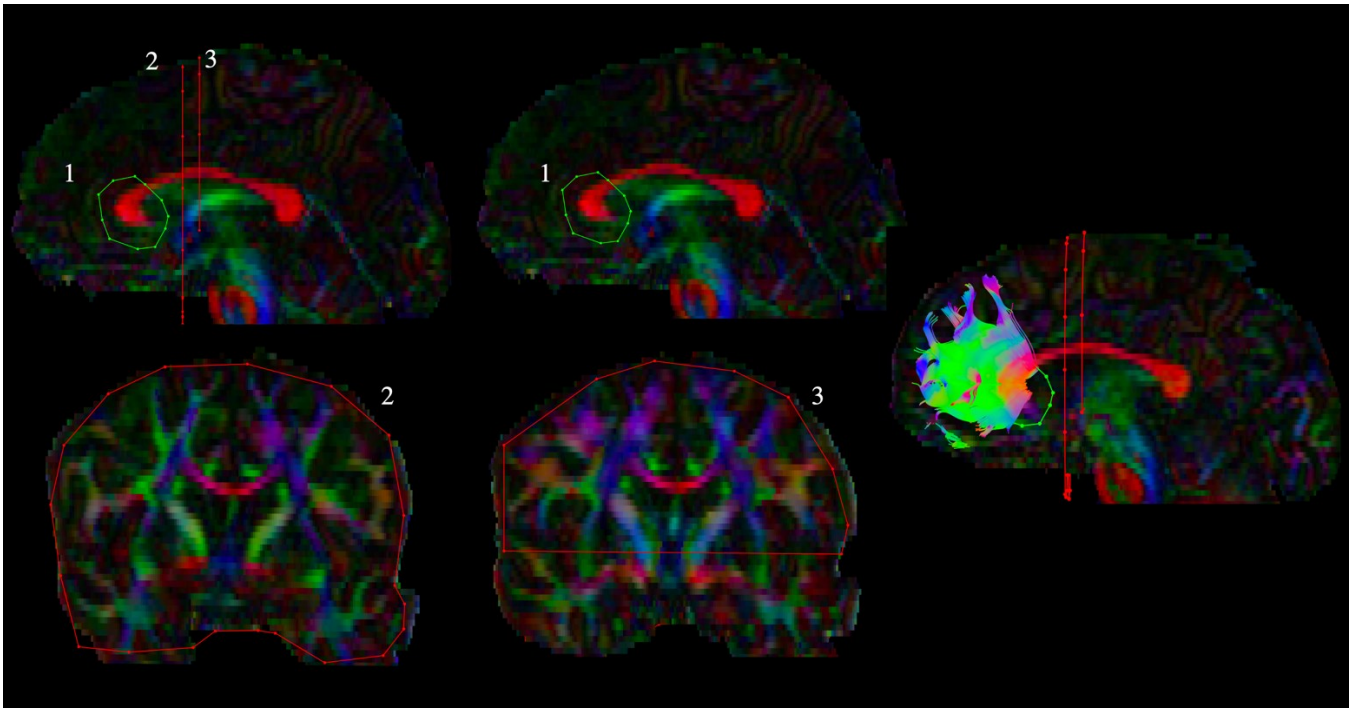


Figure A.1. ROI placement to delineate the Genu of the corpus callosum.

A.2. Body of the Corpus Callosum

Sagittal ROIs:

1. AND ROI placed on the central portion of the corpus callosum.

Axial ROIs:

2. NOT ROI placed below the lowest axial level of the sagittal AND ROI (1).

Coronal ROIs:

3. NOT ROI placed posterior to the sagittal AND ROI (1). Covers the entire coronal slice.

4. NOT ROI placed anterior to the sagittal AND ROI (1).

5. NOT ROI placed around both cingulum bundles to remove cingulum fibres.

6. NOT ROI placed around both cingulum bundles to remove cingulum fibres.

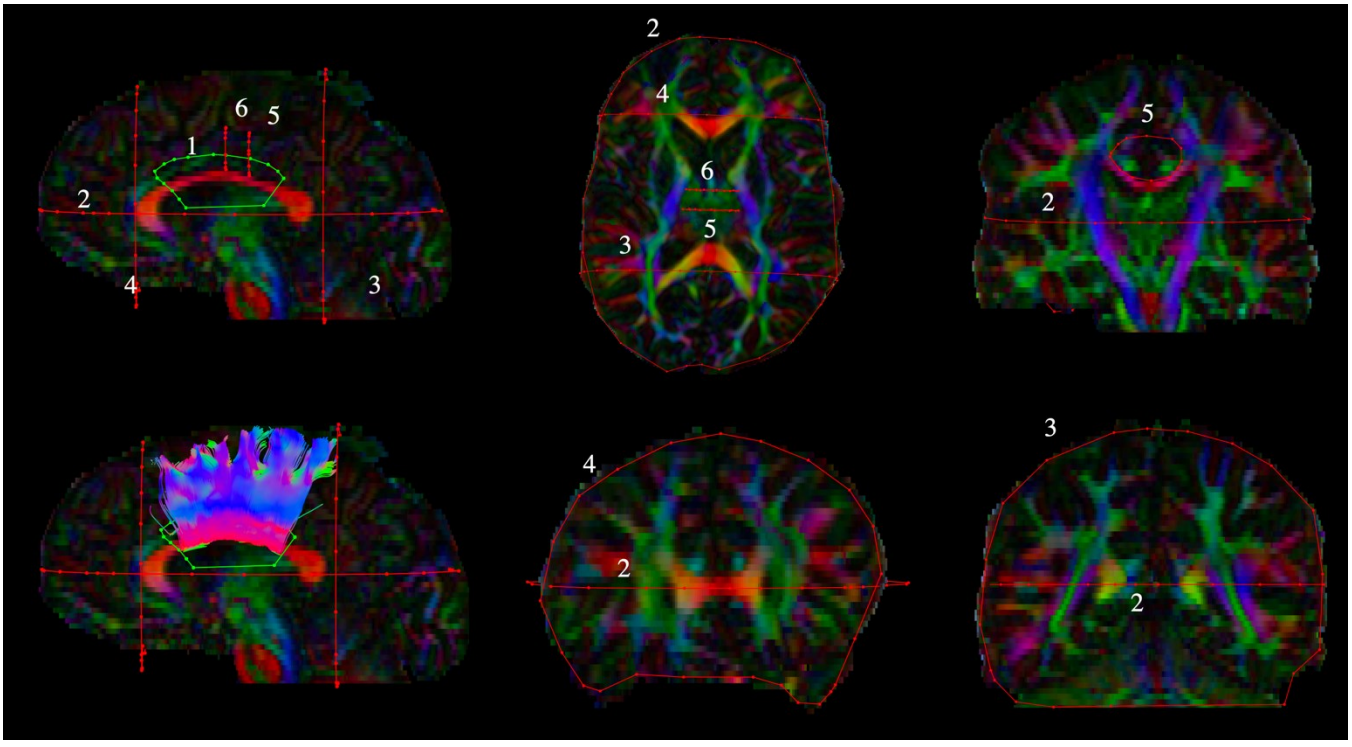


Figure A.2. ROI placement to delineate the body of the corpus callosum.

A.3. Splenium Corpus Callosum

Sagittal ROIs: 1. AND ROI placed on the posterior portion of the corpus callosum

Axial ROIs:

2. NOT ROI placed below ROI 1, from the posterior bound of ROI to the anterior bound of the brain, to ensure fibres are projecting to the posterior/occipital location.

3. NOT ROI placed above ROI 1, from the posterior bound of ROI to the anterior bound of the brain, to ensure fibres are projecting to the posterior/occipital location. This ROI (3) is placed along the edge of (and including) the somatosensory/postcentral gyri to ensure fibres are not projecting to the pre-or post-central gyri (motor and sensory cortices).

Coronal ROIs: 4. NOT ROI placed just below the level of the corpus callosum to the base of the brain, on the left side of the brain. 5. NOT ROI placed just below the level of the corpus callosum to the base of the brain, on the left side of the brain. 6. NOT ROI placed just below the level of the corpus callosum to the base of the brain, on the right side of the brain.

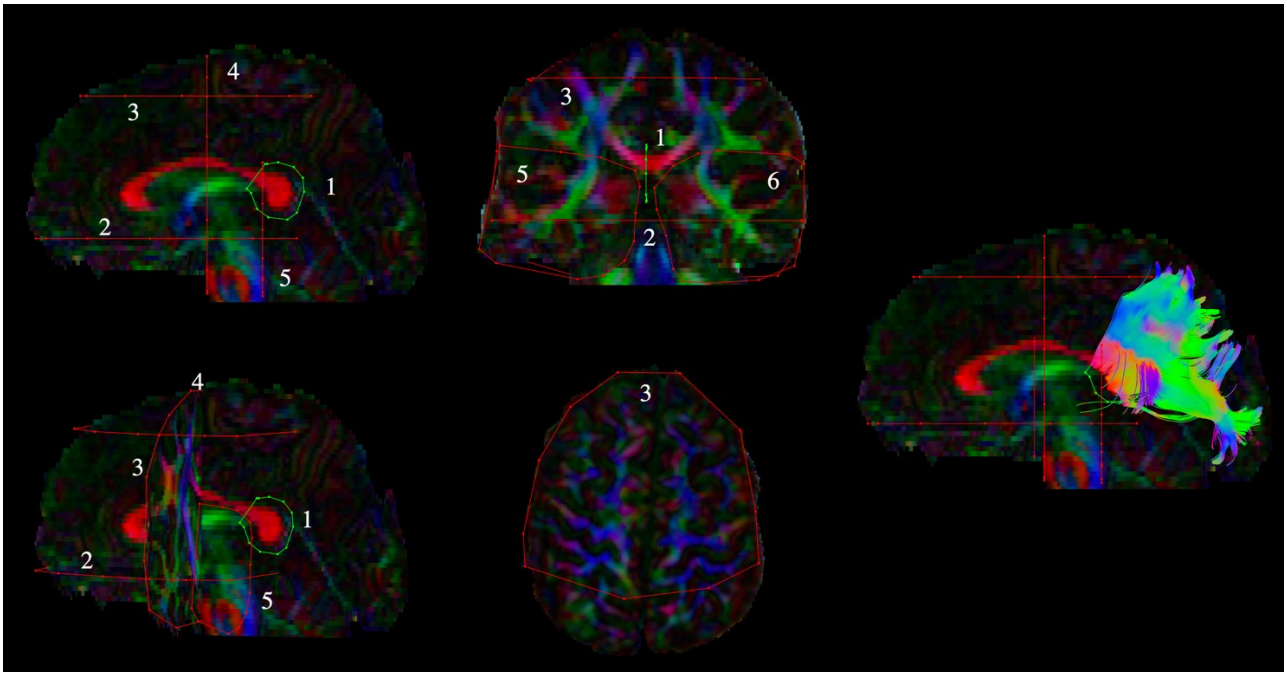


Figure A.3. ROI placement to delineate the splenium of the corpus callosum.

A.4. Cingulum

Coronal ROIs:

1. AND ROIs placed just anterior to the coronal midline slice (inclusion ROI circles the cingulum bundles).

2. AND ROIs placed just anterior to the coronal midline slice (inclusion ROI circles the cingulum bundles).

* Inclusion AND ROIs (1 & 2) are separated by as few as 3-5 coronal slices

Sagittal ROIs:

3. NOT ROI to prevent any fibres crossing the midline.

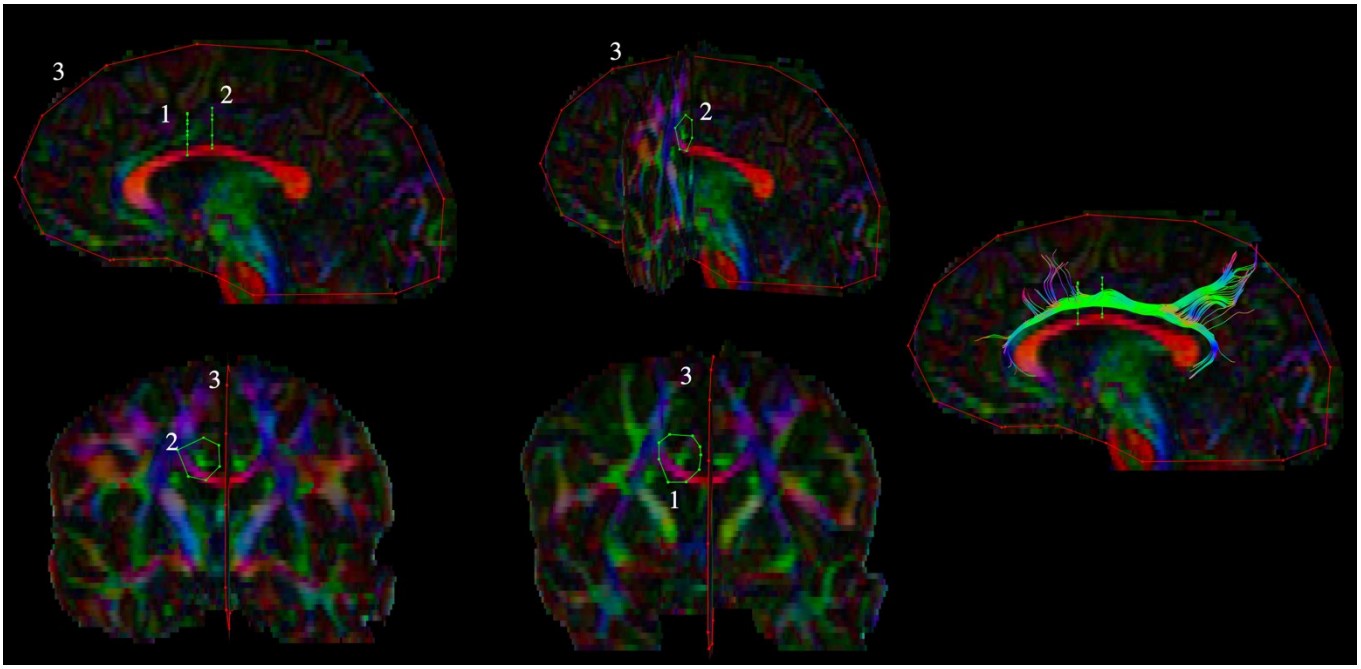


Figure A.4. ROI placement to delineate the cingulum.

A.5. Superior Longitudinal Fasciculus (SLF)

Coronal ROIs:

1. AND ROI placed over the anterior-posterior SLF fibres, where the SLF appears as a well-defined green triangle.

2. AND ROI placed over the anterior-posterior SLF fibres, where the SLF appears as a well-defined green triangle.

Axial ROIs:

3. NOT ROI placed on the base of the splenium to avoid spurious fibres and the arcuate fasciculus.

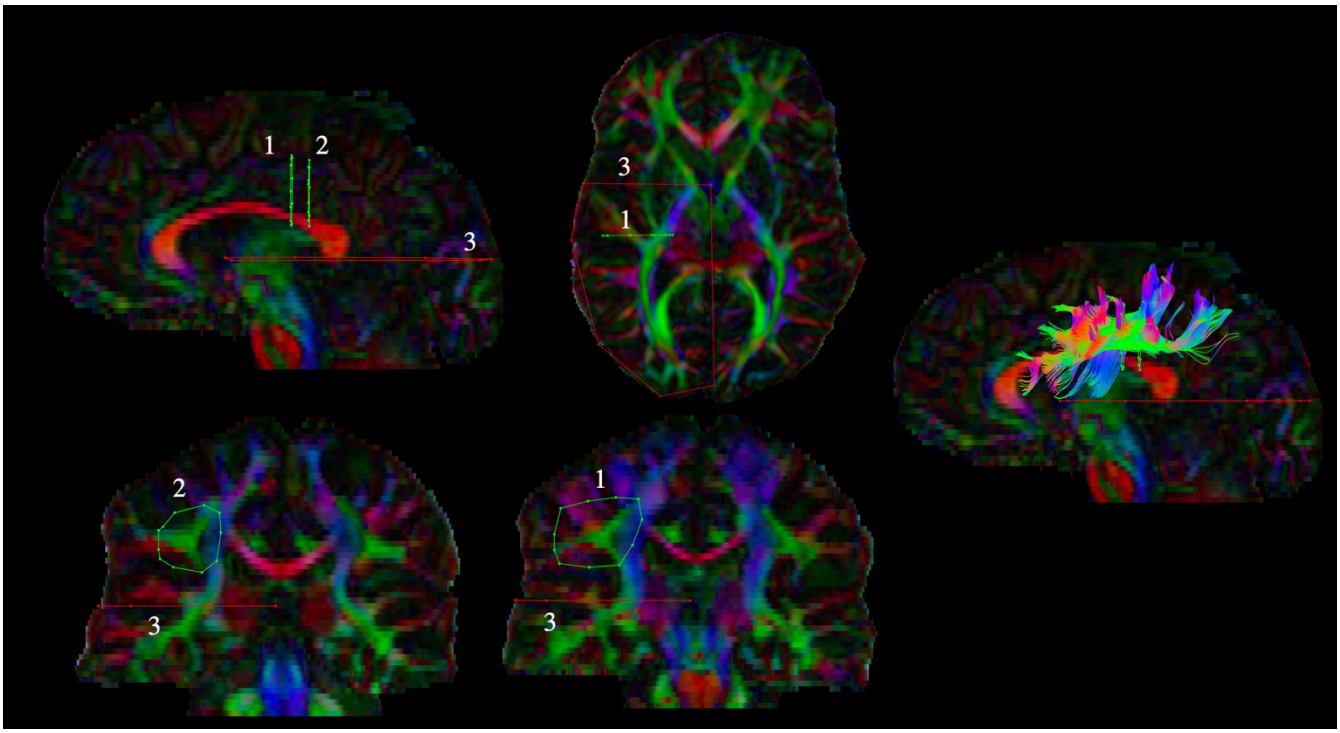


Figure A.5. ROI placement to delineate the SLF.

A.6. Inferior Longitudinal Fasciculus (ILF)

Coronal ROIs:

2. AND ROI placed over ILF fibres passing through the temporal lobe.

3. AND ROI over the ILF fibres (green, anterior-posterior projecting fibres), placed at the posterior bound of the corpus callosum.

5. NOT ROI placed on the same slice as AND ROI 2.

6. NOT ROI covering the uncinate fasciculus.

Sagittal ROIs:

4. NOT ROI covering the entire parasagittal slice to stop fibres crossing the midline.

Axial ROIs:

1. AND ROI around the level of the decussation of the cerebral peduncle, covering the most cohesive green strip of anterior-posterior projecting fibres.

7. NOT ROI placed superior to ILF fibres. 8. NOT ROI placed superior to ILF fibres.

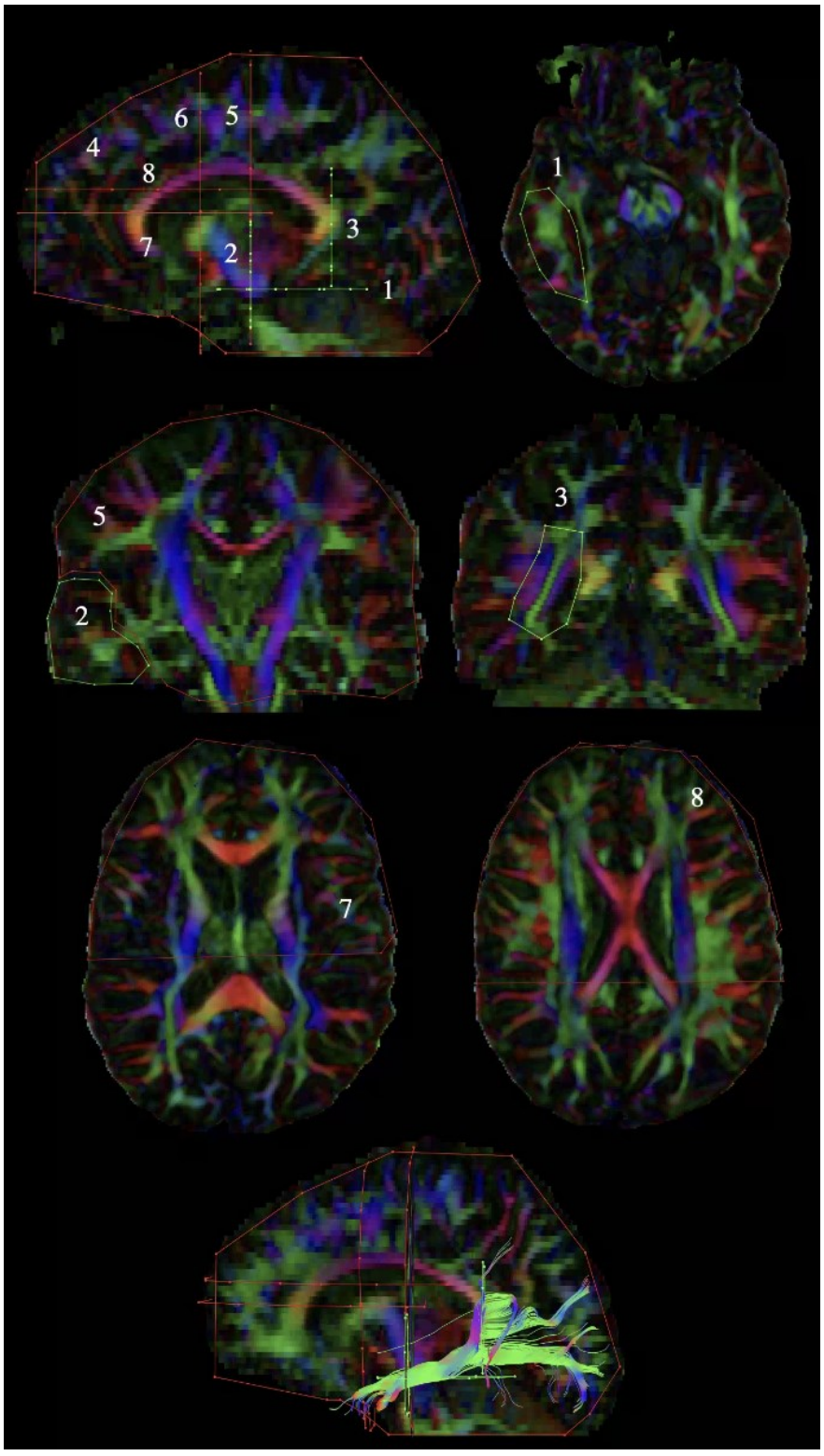
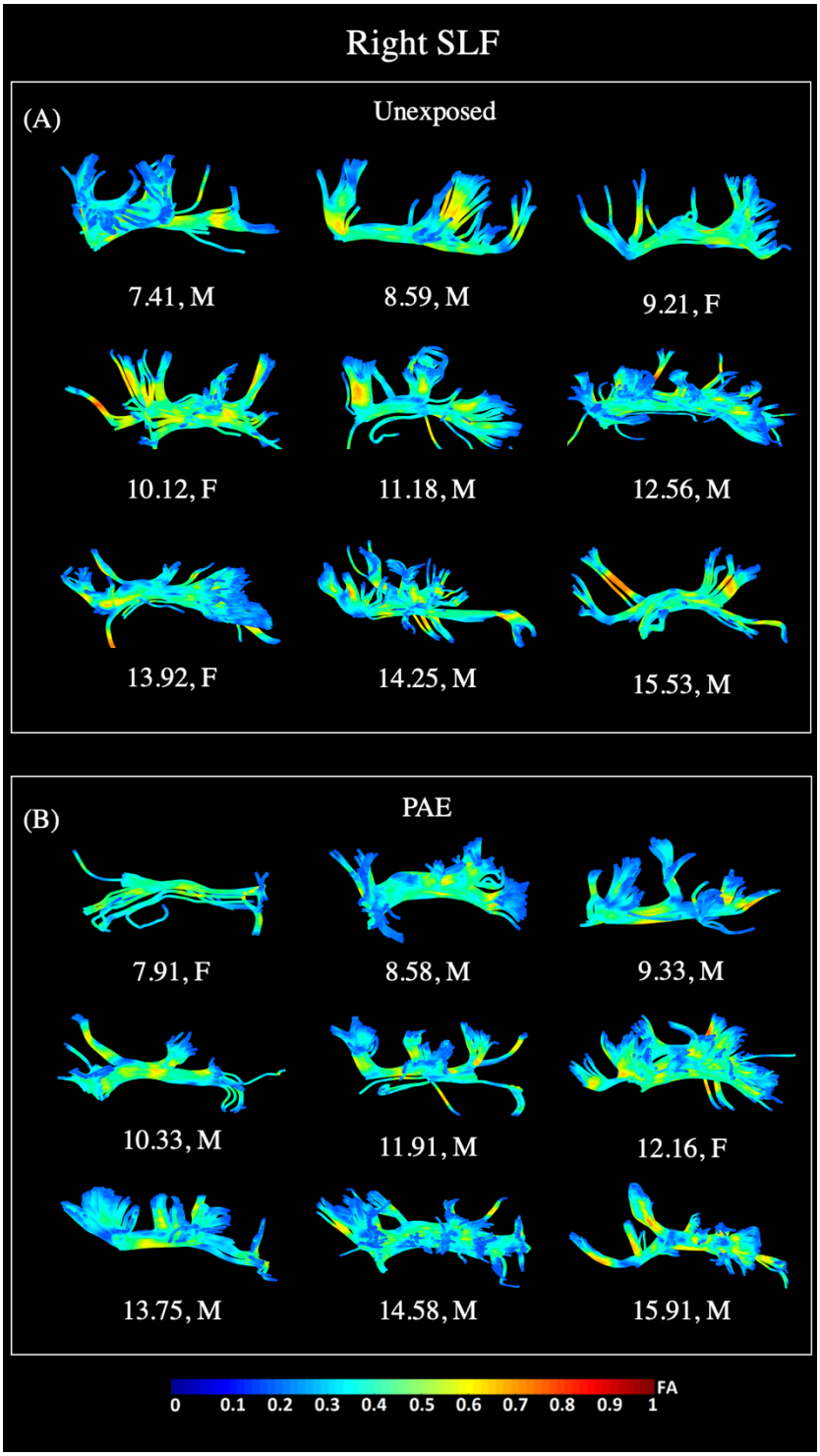


Figure A.6. ROI placement to delineate the ILF.

B. Tractography of the right SLF in 9 representative (A) unexposed participants and (B) children with PAE ordered by age. F= female, M= male. All the tracts are scaled the same.



C. Linear regression results for DTI-cognitive relationships

Supplemental Table 1. Linear regression results examining significant relations between FA values and the NEPSY-II subtests that did not survive the FDR correction. L=left; R=right

Fractional Anisotropy				
	Estimate	**Std. Error**	**t value**	**p-value (q-value)**
Genu CC				
Comprehension of Instructions	8.35	18.56	0.45	0.65
Phonological Processing	-5.09	21.27	-0.24	0.81
Speeded Naming	-20.83	22.57	-0.92	0.36
Body CC				
Comprehension of Instructions	1.55	15.52	0.10	0.92
Phonological Processing	12.59	17.67	0.71	0.48
Speeded Naming	-13.53	18.89	-0.72	0.48
Splenium CC				
Comprehension of Instructions	2.40	20.55	0.12	0.91
Phonological Processing	-16.37	23.41	-0.69	0.49
Speeded Naming	12.35	25.08	0.49	0.62
R Cingulum				
Comprehension of Instructions	9.69	12.07	0.80	0.42
Phonological Processing	18.29	13.67	1.33	0.19
Speeded Naming	5.22	14.82	0.35	0.72
L Cingulum				
Comprehension of Instructions	13.90	11.36	1.22	0.23
Phonological Processing	6.37	13.14	0.48	0.63
Speeded Naming	-1.20	14.07	-0.085	0.93
R SLF				
Comprehension of Instructions	8.77	17.83	0.49	0.62
Phonological Processing	-15.78	20.33	-0.78	0.44
Speeded Naming	8.11	21.81	0.37	0.71
L SLF				
Comprehension of Instructions	19.99	14.85	1.35	0.18
Phonological Processing	-21.12	17.02	-1.24	0.22
Speeded Naming	-43.25	17.52	-2.47	**0.02 (0.54)**
R ILF				
Comprehension of Instructions	20.79	16.83	1.23	0.22
Phonological Processing	2.55	19.50	0.13	0.896
Speeded Naming	-22.84	20.63	-1.107	0.27
L ILF				
Comprehension of Instructions	4.80	14.596	0.33	0.74
Phonological Processing	-15.76	16.58	-0.95	0.34
Speeded Naming	-37.30	17.16	-2.17	**0.03 (0.40)**

Supplemental Table 2. Linear regression between MD values and the NEPSY-II subtests that did not survive the FDR correction. L=left; R=right

Mean Diffusivity (10^{-3} mm^2/s)				
	Estimate	**Std. Error**	**t value**	**p-value q-value**
Genu CC				
Comprehension of Instructions	6.13	14.22	0.43	0.67
Phonological Processing	-2.16	16.29	-0.13	0.89
Speeded Naming	12.48	17.34	0.72	0.47
Body CC				
Comprehension of Instructions	-3.38	10.27	-0.33	0.74
Phonological Processing	-14.65	11.60	-1.26	0.21
Speeded Naming	14.80	12.42	1.19	0.24
Splenium CC				
Comprehension of Instructions	14.39	11.71	1.23	0.22
Phonological Processing	8.92	13.52	0.66	0.51
Speeded Naming	-0.74	14.51	-0.05	0.96
R Cingulum				
Comprehension of Instructions	1.25	17.23	0.07	0.94
Phonological Processing	23.92	19.45	1.23	0.22
Speeded Naming	-18.74	20.92	-0.90	0.37
L Cingulum				
Comprehension of Instructions	-15.58	16.39	-0.95	0.34
Phonological Processing	16.41	18.77	0.87	0.38
Speeded Naming	5.97	20.18	0.30	0.77
R SLF				
Comprehension of Instructions	-15.32	16.38	-0.93	0.35
Phonological Processing	2.32	18.88	0.12	0.90
Speeded Naming	15.92	20.07	0.79	0.43
L SLF				
Comprehension of Instructions	-14.48	15.40	-0.94	0.35
Phonological Processing	28.22	17.36	1.63	0.11
Speeded Naming	11.04	18.92	0.58	0.56
R ILF				
Comprehension of Instructions	-1.24	16.84	-0.07	0.94
Phonological Processing	42.45	18.43	2.30	**0.02 (0.54)**
Speeded Naming	-7.35	20.57	-0.36	0.72
L ILF				
Comprehension of Instructions	-4.59	15.39	-0.21	0.77
Phonological Processing	18.10	17.45	1.04	0.30
Speeded Naming	26.51	18.50	1.43	0.16

Findings that meet the significance level set at q=<0.05 are bolded, q values presented only for uncorrected p values that were significant.