

Structural organization in 9-year-old HIV-infected children
and HIV-exposed children



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MBRFAR002

A thesis presented for the Degree of
DOCTOR OF PHILOSOPHY
in the Department of Human Biology,
Faculty of Health Sciences,
UNIVERSITY OF CAPE TOWN

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UNIVERSITY OF CAPE TOWN
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Abstract

Background:

Despite early initiation of antiretroviral treatment (ART) in children, studies continue to report HIV-related neurodevelopmental damage and delays. Neuroimaging and neuropsychological studies have identified brain regions and cognitive domains vulnerable to the effects of HIV infection and exposure in children. As most studies focus on a single time point, it is unclear if the HIV-related abnormalities reported represent damage or developmental delay. Follow up studies are needed to better understand the long-term consequences of HIV in the ART era. Further, few studies examine links between brain imaging and cognitive outcomes, which provides a better understanding of the consequences of imaging abnormalities.

This thesis includes a follow up study of a Cape Town-based cohort using neuroimaging, neurocognitive and clinical data at age 9 – 10 years. The cohort includes Children Perinatally infected with HIV (CPHIV) from the Children with HIV Early antiRetroviral (CHER) trial, who initiated ART by the age of 2 years. In addition, the cohort includes a control group made up of Children who are HIV Uninfected (CHU) and Children HIV-exposed, but Uninfected (CHEU). The age group in this study represents the beginning of adolescence, a critical period for the maturing brain. In particular, white matter increases in early adolescence to later stabilize in the middle teenage years. In parallel, this growth is related to maturing cognitive abilities allowing for more complex thinking processes.

Diffusion tensor imaging (DTI) measures various aspects of white matter microstructure. DTI data can be explored using different methods, such as voxel wise analysis (VWA) and tractography. Within this cohort, we've previously reported white matter alterations using VWA at ages 5 and 7 years in the inferior/superior longitudinal fasciculus (ILF/SLF), inferior fronto-occipital fasciculus (IFOF), forceps minor, superior corona radiata (SCR), anterior thalamic radiation (ATR) and corticospinal tract (CST), in CPHIV despite early ART, pointing to ongoing HIV related white matter injury associated with myelin loss and axonal degradation. We hypothesize continued diffuse white matter abnormalities in these regions, pointing to chronic damage from at age 5.

Tractography quantifies tract properties within the context of gray matter regions, giving functional context to DTI measures. Tractography also allows for the quantification of structural organization measures. Graph theory measures various aspects of brain organization, such as segregation and efficiency. Network measures can identify changes in structural organization due to disease, brain disorders and age. These measures also reflect cognitive and behavioral outcomes. Studies examining structural organization in CPHIV have reported alterations in gray matter volumes affecting local and network properties, suggesting HIV may influence signal propagation. To fill the gap between imaging outcomes and functional consequences within the population of children living with or exposed to HIV, we used tractography to identify the gray matter regions most dependent on tracts

affected by HIV and the influence of HIV infection and exposure on white matter organization. Further, we explored possible links between tractography and graph outcomes and neuropsychological measures.

Methods: We performed DTI-based VWA and tractography in a cohort of 58 CPHIV, 24 CHEU and 18 CHUU at age 9 – 10 years. Structural measures included DTI parameters, fractional anisotropy (FA), mean diffusivity (MD), axial diffusion (AD) and radial diffusion (RD). Tractography based structural network measures included degree, strength, transitivity, nodal efficiency, and local efficiency as measures of local network properties, and network modularity, global efficiency, and global transitivity as measures global organization. Statistical analysis was performed to identify HIV infection and exposure related differences, as well as explore relationships between imaging outcomes and neuropsychological data.

Results: In the DTI voxelwise analysis, we observed higher MD in the IFOF, ILF/SLF, SCR and forceps minor of CPHIV. Many changes in MD were attributed to above-normal RD and/or AD which point to demyelination and axonal degradation. Furthermore, some regional HIV mediated white matter abnormalities characterized by higher MD were associated with markers of early immune compromise, including CD4% around age 12 weeks and timing of disease severity (age at nadir CD4%).

Using DTI tractography, we observed that tracts with higher mean MD, AD and/or RD included seeds with connections to the insula, putamen, and fronto-temporoparietal regions. Tracts with higher MD, AD and/or RD were within the same hemisphere, with the exception of one interhemispheric connection of higher AD between insula and right caudate. Across participants, higher MD and RD in fronto-temporoparietal connections were associated with lower performance in sequential processing, which measures auditory working memory. Among CHU, we found significant negative correlations between sequential processing and MD in basal ganglia connections to limbic and fronto-parietal regions. Among CPHIV, we found significant negative correlations between sequential processing and MD in a handful of tracts connecting regions in the limbic and temporoparietal junction. Lastly, in the graph theory-based analysis we found lower degree in the inferior temporal gyrus in CPHIV compared to CHU. Further, nodal degree in the inferior temporal gyrus across study participants was associated with auditory working memory. We did not find any HIV exposure effects on DTI measures.

Conclusions: The DTI results presented in this thesis indicate persistent localized white matter damage or delayed development in CPHIV, with some regions influenced by early immune health. In addition, we observe a robust global network despite disconnections in tracts connecting the inferior temporal gyrus of CPHIV. Long term axonal loss and demyelination may result in hypomyelinated axons that are loosely packed in the now widened extra-exonal space. Further, white matter

connectivity in fronto-temporoparietal and limbic regions as well as nodal disconnections in the inferior temporal gyrus was associated with auditory working memory among CPHIV, suggesting these abnormalities contribute to deficits in this domain. In CPHIV, we observe typical networks that are robust to the effects of altered connectivity among regions of the temporoparietal cortex, limbic and subcortical areas. Lastly, we observe no HIV exposure effects on white matter integrity and network measures suggesting differences reported at 7 years in this cohort have resolved.

Acknowledgements

Firstly, I would like to thank my supervisors with whom I developed the objectives of this work and are most influential to the outcomes of this thesis. I'm extremely grateful to my supervisor Dr. Martha Holmes. Without her mentorship, support, and patience this work would have never been possible. I'm grateful for your patience during the time I lost my mother. I would also like to express my deepest appreciation to my co-supervisor Dr. Marcin Jankiewicz who provided technical advice and support and helped me develop early intuitions concerning neuroimaging data. I would like to thank Prof. Ernesta Meintjes who recognised my potential and gave me this opportunity in neuroscience.

This endeavor would not have been possible without the support provided by the NRF/DST South African Research Chairs Initiative; US National Institute of Allergy and Infectious Diseases (NIAID) through the CIPRA network, Grant U19 AI53217; NIH grants R01HD093578, R01HD071664, R21MH096559 and R21MH108346; NRF grant CPR20110614000019421, and the Medical Research Council (MRC).

I would like to thank my peers, Marilize Fourie, Mona Ehmadi, Abdul Ibrahim, Samuel Bayih, Amy Graham, Isaac Khobo, Ndivhuwo Magogondo, Karen Fitzgerald and Keri Woods for their emotional support and delightful company over the years. I'm forever indebted to Joanah Madzime. Her love and support made this journey all the more bearable.

I would also like to thank my family for their undying support and patience. My sisters Tinotenda, Anotidaishe and Nokutenda. I love you wholeheartedly. I would also like to extend my gratitude to my closest friends, Aphiwe Matiwane and Ephraim Maphasa. Together we mastered a balance between virtue and adventure.

Lastly, this thesis is dedicated to my late parents, Shoobridge Mberi and Monica Muradya whose values helped shape how I relate to the world. Your work is done. I now must look to other humans to model a course through life after 48.

DECLARATION

I, ... Farai Mberi, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other university.

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List of abbreviations

ACC	Accumbens
ACR	Anterior corona radiata
AD	Axial diffusivity
ADC	Apparent diffusion coefficient
AF	Arcuate fasciculus
AFNI	Analysis of functional neuroimaging
AMG	Amygdala
AP	Anterior Posterior
ART	Antiretroviral therapy
ATR	Anterior thalamic radiations
BBB	Blood brain barrier
BST	Brain stem
BSTS	Banks of superior temporal sulcus
CAC	Caudal anterior cingulate
cART	combination ART
CAU	Caudate
CC	Corpus callosum
CER	Cerebellum
CHER	Children with HIV Early antiRetroviral
CHEU	Children who are HIV-Exposed, but Uninfected
CHU	Children who are HIV Uninfected
CHUU	Children who are HIV-Unexposed Uninfected
CMF	Caudal middle frontal
CNS	Central nervous system
CPHIV	Children with perinatally HIV infection
CST	Corticospinal tract
CUBIC	Cape Universities Body Imaging Center
CUN	Cuneus
DTI	Diffusion tensor imaging
DW	Diffusion weighted
DWI	Diffusion weighted imaging
ENT	Entorhinal
EPI	Echo planar imaging
FA	Fractional anisotropy
FACTID	Fiber assessment by continuous tracking including diagonals
FID	Free induction decay

fMRI	Functional magnetic resonance imaging
FP	Frontal pole
FUS	Fusiform
GMDS	Griffiths Mental Development Scales
HIV	Human immunodeficiency virus
HPC	Hippocampus
hs-CRP	high sensitive C-reactive protein
ICVF	intracellular volume fraction
IFOF	Inferior fronto-occipital fasciculus
ILF	Inferior longitudinal fasciculus
INS	Insula
IP	Inferior parietal
IRCT	Inversion-of-the-relative-contrast-of-tissues
ISTH	Isthmus cingulate
IT	Inferior temporal
LING	Lingual
LOCC	Lateral occipital
LOF	Lateral orbitofrontal
MD	Mean diffusivity
MEMPRAGE	Multiecho magnetization-prepared rapid gradient echo
MOF	Middle orbitofrontal
MRI	Magnetic resonance imaging
MT	Middle temporal
NODDI	Nuerite orientation dispersion and density imaging
PA	Posterior - anterior
PAL	Pallidum
PARC	Paracentral
PARH	Parahippocampal
PC	Posterior cingulate
PCAL	Pericalcarine
PCUN	Precuneus
PD	Proton density
PHIV	Perinately acquired HIV infection
POPE	Parsorpecularis
PORB	Parsorbitalis
PREC	Precentral
PSTC	Postcentral

PTRI	Parstriangularis
PUT	Putamen
RAC	Rostral anterior cingulate
RD	Radial diffusivity
RF	Radio frequency
RMF	Rostral middle frontal
ROI	Region of interest
SCR	Superior corona radiata
SF	Superior frontal
SLF	Superior longitudinal fasciculus
SMAR	Supramarginal
SNR	Signal-to-noise ratio
SP	Superior parietal
ST	Superior temporal
TE	Time to echo
THAL	Thalamus
TP	Temporal pole
TR	Repetition time
TT	Transverse temporal
UF	Uncinate fasciculus
VBM	Voxel-based morphometry
VDC	Ventral diencephalon
VL	Viral load
VWA	Voxel wise analysis

I. Introduction

1.1.1. Context

In 2020 about 37.7 million individuals were living with the human immunodeficiency virus (HIV) worldwide. Of these, 2.8 million were children born to mothers living with HIV. An estimated 75 000 children (0 – 14 years) were newly infected in eastern and southern Africa, with only 57% receiving antiretroviral therapy (ART) (UNAIDS, 2021). Studies have reported substantial improvement in neurodevelopmental outcomes of children with perinatally acquired HIV (CPHIV) on ART regimens (Laughton *et al.*, 2012, 2018a, 2019; Gómez *et al.*, 2018). However, treatment does not offer complete protection from HIV-related neurological and neurodevelopmental impairments (Laughton *et al.*, 2013; van Arnhem *et al.*, 2013; Nichols *et al.*, 2015; Sophie Cohen *et al.*, 2015; Boivin *et al.*, 2018; Sherr *et al.*, 2018).

Due to the introduction of ART during pregnancy, there has been a decrease in the incidence of vertical transmission of the virus (Connor *et al.*, 1994; Sperling *et al.*, 1996). An estimated 97% of mothers needing ART for prevention of mother to child transmission (PMTCT) are currently receiving treatment worldwide (UNAIDS, 2021). As a result, there is a rising population of children who are HIV-exposed and uninfected (CHEU) (Desmonde *et al.*, 2016), with 4 000 000 CHEU reported in 2020 (UNAIDS, 2021). In utero exposure to HIV may lead to subtle brain abnormalities (Tran *et al.*, 2016) and risk of cognitive deficits (Van Rie *et al.*, 2007; Kerr *et al.*, 2014). Meta-analyses in CHEU reveal consistent evidence of deficits in expressive language and gross motor functions (Wedderburn *et al.*, 2022), while both CPHIV and CHEU children were shown to have lower cognitive and motor outcomes compared with children who are HIV-unexposed uninfected (CHUU) (McHenry *et al.*, 2018).

Gaining a better understanding of HIV-mediated neuropathogenesis in ART treated CPHIV as well as CHEU may offer insights into the unique developmental trajectory of this population. Within childhood, the period of adolescence includes critical neurological changes necessary for the development of adult cognitive abilities. While some studies have examined brain development in these populations during adolescence, little work has been done linking alterations of brain development to cognitive deficits associated with HIV infection and exposure. This thesis adds to the small body of research using both neuroimaging and neuropsychological data in young people living with HIV infection or exposure.

1.1.2. Cohort characteristics: Children with HIV Early antiRetroviral (CHER)

This sub-study includes participants in a well-characterized cohort of children living with HIV who initiated treatment in infancy. The cohort is comprised of CPHIV and Children who are HIV Uninfected (CHU) who came from the randomized CHER trial (Violari *et al.*, 2008; Cotton *et al.*, 2013) and a community vaccine study, respectively (Mahdi *et al.*, 2010). CPHIV have been followed from age 6 weeks at the Family Centre for Research with Ubuntu (FamCRU), Tygerberg Children's Hospital, in Cape Town, South Africa. The CHU were recruited from the same community for a vaccine study running concurrently with the CHER trial. This group includes both CHEU and CHUU. These children are participating in a longitudinal study that includes neuroimaging and neuropsychological testing at ages 5, 7, 9, 11, 15 and 17 years. This thesis focuses on neurodevelopmental data acquired at age 9 years.

The CHER study randomized infants with CD4 percentage (CD4%) > 25% into three treatment arms: ART-Def (ART delayed until CD4% < 25% in first year or CD4% < 20% thereafter, or if clinical disease progression criteria presented); ART-40W (ART initiated before 12 weeks with planned interruption after 40 weeks); and ART-96W (ART initiated before 12 weeks of age with planned interruption after 96 weeks). All CPHIV included in the current analysis had initiated ART by age 76 weeks. First line ART consisted of Zidovudine (ZDV) + Lamivudine (3TC, Epivir) + Lopinavir-ritonavir (LPV/r, Kaletra®) according to safety and efficacy specifications for infants developed by Chadwick *et al.*, 2008 (Violari *et al.*, 2008). Children in the ART-40W and ART-96W arms in whom treatment was interrupted were immediately restarted on ART when CD4% declined or on presentation of evidence of disease progression. Due to evidence of accelerated disease progression following interruption, treatment of only a subset of children in the two arms who initiated treatment before 12 weeks was interrupted (Cotton *et al.*, 2013). As such, these two arms were grouped together in the thesis for comparison with children who had started ART after age 12 weeks. Clinical data (CD4 count, CD4%, CD8 count and viral load) were acquired regularly to monitor immune health and viral load. At the time of scanning, all CPHIV were receiving ART.

Neuropsychological testing was conducted by means of administering a standard test battery to participants at ages 7 and 9 (van Wyhe *et al.*, 2021). The test included the Beery-Buktenika Developmental Test of Visual-Motor Integration (Beery-VMI), which is a test for visual perception and motor coordination. In a typical VMI assessment, a child copies geometric designs ranging from simple line drawings to more complex figures. Performance in this test is scored based on how well the child can reproduce the shapes presented. Lower scores indicate a delay in the development of visual motor skills. Children that perform poorly in this test may have trouble with fine motors skills, particularly hand and hand-eye coordination. The Kaufman Assessment Battery for Children – Second Edition (KABC-II) (Kaufman and Kaufman, 2013) subtests measure performance in

sequential processing (an assessment of auditory working memory), simultaneous processing (visual-spatial processing and problem solving), learning (short-term memory) and planning (executive reasoning). Lastly, Peabody Picture Vocabulary Test – fourth Edition (PPVT-IV) scores (Dunn and Dunn, 2007) represented a reliable measure for receptive language ability in these children, (Eigsti, 2021). The PPVT assesses the richness of vocabulary in test subjects – the number of words that a person can understand. Test subjects are presented with four pictures and from these the children must select one that best illustrates that word's meaning.

1.1.3. Diffusion tensor imaging

Diffusion tensor imaging (DTI) is a neuroimaging method used to characterize the strength and orientation of structure between spatially distributed regions of the brain (Skudlarski *et al.*, 2008). DTI maps water diffusion changes in structurally organized tissues, such as white matter tracts which demonstrate directionally dependent diffusion (Basser., 1996; Beaulieu, 2002a; Curran *et al.*, 2016). HIV infection in children leads to a risk of decreased white matter integrity (Hoare, Fouche, Phillips, John A Joska, *et al.*, 2015; Musielak and Fine, 2016; Hof *et al.*, 2019). Prenatal HIV exposure without infection is associated with altered white matter microstructural integrity in infants and children (Tran *et al.*, 2016; Yadav *et al.*, 2020a).

One approach to DTI data analysis is whole-brain voxel-wise analysis (VWA), which performs exploratory analyses of every voxel containing white matter tracts. The VWA approach detects regional differences in DTI-based measures of water diffusion in statistically significant clusters of voxels in the brain. Another approach to DTI analysis is tractography, which relies on fiber-tract reconstruction. Following the principal direction of diffusion in the voxels of DTI data allows for the reconstruction of white matter tracts within the brain. Analyses of diffusion metrics within these tracks can then be performed.

The brain can be viewed as a network consisting of gray matter regions (i.e., nodes) and axonal connections between regions (i.e., edges), obtained by means of DTI tractography (Mori and Zijl, 2002; Griffa *et al.*, 2013). Graph analysis provides insight into brain organization using a structural connectome framework. Structural connectomes depict large-scale white matter connectivity of the brain (Sporns, Tononi and Kötter, 2005).

Brain network topology characterized by graph theoretical measures is sensitive to structural organizational changes in the developing brain that reflect cognitive performance, behavioral changes, and neurological insults as well as disorders such autism, and attention- deficit/hyperactivity disorder (Cao *et al.*, 2016). Common graph theoretical metrics such as node degree, clustering coefficient, average path length, hubs, centrality, modularity, and robustness are used to characterize aspects of brain organization. These graph metrics, among others, can be used to detect the topological patterns

of brain networks as well as reflect cognitive and behavioral outcomes (Sporns *et al.*, 2004; van den Heuvel *et al.*, 2008).

Additionally, structural covariance networks that depict an interdependence in gray matter morphological changes in structurally connected regions can be constructed.

1.1.4. Neuroimaging and neuropsychological findings within our cohort

Within our cohort, both VWA and tractography have been used to study the microstructural properties of tracts and investigate the associated neurocognitive outcomes (Ackermann *et al.*, 2016; Jankiewicz *et al.*, 2017; Ackermann *et al.*, 2020; Madzime *et al.*, 2021). Using VWA, DTI analyses at ages 5 (Ackermann *et al.*, 2016) and 7 (Jankiewicz *et al.*, 2017) years reported persistent alterations in the inferior fronto-occipital fasciculus (IFOF), inferior longitudinal fasciculus (ILF), corticospinal tract (CST), superior corona radiata (SCR), and forceps minor in CPHIV compared to CHU. These results suggest persistent localized white matter HIV-related damage from age 5 to 7 years. At age 7 years, we further identified localized white matter abnormalities in CHEU compared to CHUU (Jankiewicz *et al.*, 2017).

Also at age 7, tractography work was conducted (Madzime *et al.*, 2021) examining the effects of HIV infection and exposure on white matter tracts within resting state networks. In CPHIV, the analyses identified altered integrity in white matter tracts within the somatosensory, salience, default mode (DM) and motor networks. In addition, Madzime *et al.* reported an HIV exposure effect on white matter integrity in tracts within the visual, posterior DM and motor networks.

In addition to identifying potential ongoing maturational abnormalities related to HIV infection or HIV exposure, we intend to investigate links between brain imaging and neurocognitive outcomes. Cognitive testing complements neuroimaging data, allowing for a deeper understanding of the consequences of HIV-related alterations. Within our cohort, neuropsychological testing has reported evidence of the beneficial effects of immediate ART initiation (ART before 12 weeks) on the neurodevelopment of CPHIV (10 – 16 months of age). At this age, we found significantly higher scores in infants in the ART before 12 weeks group as compared to infants who received deferred ART (ART after 12 weeks) in general, locomotor, personal-social, hearing and speech, eye and hand coordination and performance quotients of the Griffiths Mental Development Scales (GMDS). Furthermore, the combined group of CPHIV had scores comparable to CHU in all but the locomotor tests of the GMDS (Laughton *et al.*, 2012). Similarly, in a longitudinal analysis in the same cohort at 11-, 20-, 30-, 42- and 60-month intervals, neurodevelopmental outcomes between ART-Def, ART-40W, ART-96W, CHEU and CHUU were the same in all GMDS except for locomotor and general Griffiths which were lower in the deferred treatment group (Laughton *et al.*, 2018b). In a cross-

sectional analysis of the same children, group comparisons of Beery-Buktenica mean scores of visual perception were lower in CPHIV compared to CHU at 60 months (Laughton *et al.*, 2018b).

In a longitudinal analysis of 7- and 9-year-old children of the same cohort, significant improvements in scores over time were reported. More specifically, CPHIV scored lower than CHU on tests of motor dexterity at seven years, but performance increased significantly to match that of CHU at nine years. Similarly, CPHIV showed increased performance, progressively, in tests of visuospatial processing and problem solving. However, working memory and executive function performance in CPHIV decreased compared to their CHU counterparts from ages 7 through 9 years. CHU had higher scores for working memory than CPHIV on early ART and CHEU groups at both ages 7 and 9 years. Similarly, ART-Def scored lower than their ART-96w, ART-early, CHEU and CHUU counterparts in tests of motor dexterity at age 7 years but showed typical performance at 9 years. While significant improvements in cognitive tasks is seen, CPHIV remain at risk for cognitive deficits over early school ages regardless of treatment arm (van Wyhe *et al.*, 2021).

Although we have identified cognitive deficits at various ages in this cohort, we have not observed many neurodevelopmental outcomes associated with brain imaging abnormalities. Among CHU, personal social quotient was associated with improved myelination of the forceps minor at age 5 years. Further, a significant correlation where increased radial diffusivity was associated with lower visual perception in the right SLF and left ILF was found across the sample, suggesting ongoing development in this subset of tracts of the visual perception pathway at 5 years of age (Ackermann *et al.*, 2020). Madzime *et al.* found no significant associations of diffusivity measures with neurocognitive outcomes despite finding white matter alterations within defined functional connectivity domains (Madzime *et al.*, 2021).

This thesis seeks to fill gaps in the literature around white matter development in CPHIV and CHEU. To date, there have been seventeen neuroimaging publications using DTI data to explore the effects of HIV-infection and/or HIV-exposure in pediatric populations (Hoare *et al.*, 2012, 2015; 2018, 2019, 2020; Jahanshad *et al.*, 2015; Li *et al.*, 2015; Ackermann *et al.*, 2016; 2020; Tran *et al.*, 2016; Uban *et al.*, 2016; Jankiewicz *et al.*, 2017; Sarma *et al.*, 2019; Yadav *et al.*, 2020a; Madzime *et al.*, 2021; van den Hof *et al.*, 2021; van Genderen *et al.*, 2022). Within these publications, fifteen used VWA (Hoare *et al.*, 2012, 2015; 2018, 2019, 2020; Jahanshad *et al.*, 2015; Li *et al.*, 2015; Ackermann *et al.*, 2016; 2020; Tran *et al.*, 2016; Jankiewicz *et al.*, 2017; Sarma *et al.*, 2019; Yadav *et al.*, 2020a; van den Hof *et al.*, 2021; van Genderen *et al.*, 2022) and two employed DTI tractography (Uban *et al.*, 2016; Madzime *et al.*, 2021). Among these, three were follow up studies (Jankiewicz *et al.*, 2017; Madzime *et al.*, 2021) and thirteen publications focused on or included adolescents (Hoare *et al.*, 2012, 2015; 2018, 2019, 2020; Jahanshad *et al.*, 2015; Li *et al.*, 2015; Uban *et al.*, 2016; Sarma *et al.*, 2019; Yadav *et al.*, 2020a; Madzime *et al.*, 2021; van den Hof *et al.*, 2021; van Genderen *et al.*, 2022). Fifteen studies looked at relationships with cognitive outcomes (Hoare *et al.*, 2012, 2015; 2018, 2019, 2020;

Jahanshad *et al.*, 2015; Li *et al.*, 2015; Ackermann *et al.*, 2016; 2020; Tran *et al.*, 2016; Uban *et al.*, 2016; Yadav *et al.*, 2020a; van den Hof *et al.*, 2021; van Genderen *et al.*, 2022). None of the studies investigating white matter development in CPHIV and CHEU employed network analysis. The only literature looking at network analysis is based on gray matter structural covariance (Yadav *et al.*, 2017; Li *et al.*, 2018). And, four studies included children from our cohort at ages 5 and 7 years (Ackermann *et al.*, 2016; 2020; Jankiewicz *et al.*, 2017; Madzime *et al.*, 2021). Five focused on or included the effects of HIV-exposure (Jahanshad *et al.*, 2015; Tran *et al.*, 2016; Jankiewicz *et al.*, 2017; Yadav *et al.*, 2020a; Madzime *et al.*, 2021).

In summary, there is a small body of literature investigating the effect of HIV infection and *in-utero* exposure on white matter integrity and how HIV-related abnormalities relate to neuropsychological and neurodevelopmental outcomes in children. Little follow up work has been done, making it difficult to interpret findings as HIV damage or delay that may resolve with age. Further, studies include a fair amount of heterogeneity in age and treatment regimens, which does not allow for the comparison of outcomes or drawing larger conclusions about the population. Moreover, no network analysis based on DTI tractography was performed.

In our cohort of CPHIV, followed clinically since infancy and with neurodevelopment assessments (brain imaging and neuropsychological testing) since age 5 years, we present analyses of white matter integrity, connections, and networks in children at 9 years. Children at ages 9 – 10 are entering adolescence, a period of intense white matter development (Giorgio *et al.*, 2010; Brouwer *et al.*, 2012; Ladouceur *et al.*, 2012; Peters *et al.*, 2012). To add to the literature regarding the long-term consequences of living with HIV on the developing brain, we perform follow up VWA. Using VWA, we will establish whether HIV-related changes at 5 (Ackermann *et al.*, 2016) and 7 years (Jankiewicz *et al.*, 2017; Madzime *et al.*, 2021) have resolved or continue. We present DTI and graph theory correlates of neuropsychological performance of CPHIV and CHEU compared to age matched controls. This analysis addresses a key gap in the research literature, evaluating whether neuropsychological function in CPHIV and CHEU is correlated with tractographic DTI and DTI tractography based graph metrics in an early treated cohort with continued clinical monitoring.

1.1.5. Aims and Objectives

The aim of this thesis is to study the influence of HIV infection and exposure on white matter in a cohort of 9-year-old children. This will be accomplished through different methods of analyzing and presenting DTI data. The main questions we will answer are: (1) Does regional HIV-related white matter abnormalities observed at 5 and 7 years continue at age 9/10 years? (2) Does HIV infection and exposure influence structural connections and organization, and do these alterations contribute to neuropsychological deficits?

- Aim 1:** To identify ongoing white matter abnormalities in a cohort of well-characterized children entering adolescence at age 9 - 10 years.
- Hypothesis:** We hypothesize ongoing white matter abnormalities at age 9 years in the ILF/SLF, IFOF, forceps minor and CST in CPHIV on ART, and the CST and posterior corona radiata of CHEU.
- Objectives:** Whole brain voxel-wise DTI analyses at 9 years following the same pipeline and statistical analysis as previous work in this cohort will be performed. Analysis includes HIV infection and exposure groupwise differences as well as associations between DTI measures and both immune health and treatment variables in CPHIV.
-
- Aim 2:** To identify the effects of HIV infection and exposure on white matter connections and organization in a 9-year-old cohort.
- Hypothesis:** We posit the same white matter tracts will be affected as outlined above. Within our cohort, morphometric alterations were found in global gray matter and white matter volumes, and regionally in the accumbens, putamen, pallidum, hippocampus, parietal cortex, lateral occipital, medial frontal regions of CPHIV (Randall *et al.*, 2017) (Nwosu *et al.*, 2017). Moreover, consistent with the morphometric findings, DTI tractography in our cohort demonstrated altered white matter integrity in the somatosensory, salience, default mode, and motor networks involving the putamen and regions of the superior temporoparietal area. In addition, HIV-exposure effects on white matter integrity in tracts within the visual, posterior DM and motor networks were reported (Madzime *et al.*, 2021).
- We hypothesize that CPHIV will have altered local and global measures due to aberrant fronto-temporoparietal structural wirings and demonstrate alterations in nodal properties of putamen, pallidum, accumbens and hippocampus compared to controls.
- We also hypothesize that CHEU will have altered structural connectivity compared with CHUU in the CST and posterior corona radiata of CHEU. Nodal properties of regions connected by the CST and posterior corona radiata in CHEU will be affected.
- Objectives:** This aim will be accomplished using DTI tractography to map white matter connections that link gray matter regions. Graph theory methods will be used to construct structural connectomes. Statistical analysis will identify groupwise differences.
-
- Aim 3:** To identify white matter connections and structural network elements that contribute to cognitive deficits in 9-year-old CPHIV.
- Hypothesis:** Based on previous morphometric and tractography findings in our cohort changes in white matter connectivity and structural organization will affect cognitive performances in CPHIV and CHEU. More specifically, we hypothesize potential association between cognitive outcomes and structural organization underpinned by altered connectivity within and to fronto-temporoparietal from subcortical regions and the limbic cortex, with a predominant involvement of heavily impacted regions such as the insula, putamen, hippocampus, and amygdala.
- Objectives:** Linear regression models will be used to examine associations between neuropsychological scores and DTI outcomes (tractography and graph measures).

II. Background

2.1.1. Pediatric neurodevelopment

Given the evidence of clinical, neuropsychological, and neurological effects related to HIV infection and exposure, studies of children living with and exposed to HIV over time are needed. MRI brain maturation studies have described normal pediatric cerebral growth trajectories. Cerebral volume reaches peak volume at 14.5/11.5 years in males/females respectively (Giedd *et al.*, 1999; Lenroot and Giedd, 2006). From childhood to adolescence, cortical and subcortical components of the brain are dynamic to accommodate for the development of the brain, its connecting structures and booming network of micro-vessels throughout the brain to enable cognitive functioning (Giedd *et al.*, 1999; Lenroot and Giedd, 2006; Webster, Elashoff and Weickert, 2011). Studies report age-related linear increases in white matter volumes alongside exponential increases in microstructural measures, whereas the growth trajectory for cortical gray matter shows a nonlinear pattern, with a characteristic increase during preadolescence and a subsequent decrease after adolescence (Giedd *et al.*, 1999; Lebel and Beaulieu, 2011). Cortical gray matter age-related changes differ across various lobes, whereas white matter slopes are similar in frontal, temporal, and parietal lobes (Giedd *et al.*, 1999; Lenroot and Giedd, 2006). White matter fibers continue to mature beyond adolescence, with this increase offset by a decrease in gray matter leading to a relative steady overall brain volume (Lebel and Beaulieu, 2011).

Early studies have pointed to white matter and deep gray matter structures such as the basal ganglia as primary targets of HIV CNS insults (Martin *et al.*, 2006). As such, the bulk of pediatric neurological studies to date have involved assessment of white matter indicators ranging from signal abnormalities and lesions, reduction in white matter volumes to decreased white matter integrity measured (Hoare *et al.*, 2014; Musielak and Fine, 2016; Van den Hof *et al.*, 2019).

2.1.2. Typical white matter developmental trajectories

Human brain development is a lifelong process characterized by dynamic changes in structure and chemistry (Gogtay *et al.*, 2004). A handful of studies suggest associations between age, sex and genetic differences in pubertal maturation and regional white matter development (Ladouceur *et al.*, 2012; Lenroot *et al.*, 2008; Brouwer *et al.*, 2012; De Bellis *et al.*, 2001).

A structural MRI study assessing sex and age dependent white matter maturation reported linear increases in white matter volume with age well into adulthood across white matter of the frontal, temporal, parietal, and occipital lobes with males presenting a rapid increase during adolescence (Lenroot *et al.*, 2008). Volumes of gray and white matter areas such as the corpus callosum differ by sex and age with females exhibiting slower age-related decreases and increases in gray matter and,

white matter as well as corpus callosal areas volumes, respectively, compared to their male counterparts (De Bellis *et al.*, 2001). The authors suggest that these sex-dependent differences are reflected in the timing of neuronal pruning and myelination between male and female adolescents.

From birth to early adulthood white matter fibers display differential maturational patterns characterized by regional age and sex-dependent linear and curvilinear volumetric and exponential microstructural growth trajectories (Taki *et al.*, 2013). Significant age and sex-dependent increase in white matter volume with males exhibiting more rapid increases than females (Giedd *et al.*, 1999). Linear increases in white matter volume in childhood and adolescent populations may reflect more established connectivity and integration of spatially distributed regions (Hüppi *et al.*, 1998; Neil *et al.*, 1998; Song *et al.*, 2002). Similarly, significant sex–age interactions on FA and MD were also shown. Girls displayed a greater rate of fiber density increase with age when compared with boys in associative regions (reflected in MD values). However, girls displayed a trend toward increased organization with age (reflected in FA values) only in the right hemisphere, while boys displayed this trend only in the left hemisphere (Schmithorst *et al.*, 2008). In contrast, gray matter structures generally exhibit an inverted U-shaped developmental trajectory. Gray matter volumes reach their developmental peak in the childhood-to-adolescence transition period (Lenroot and Giedd, 2006). Neural activity dependent gray and white matter growth patterns exhibit some degree of synchronicity in time to give rise to functional networks (Demerens *et al.*, 1996; Ishibashi *et al.*, 2006). This coordinated developmental process occurs in tandem with the temporal development of known cognitive and behavioral milestones (Luna *et al.*, 2004; Fornari *et al.*, 2007). Altered microstructural development is associated with cognitive impairment in higher order functions, inhibitory control, working memory and executive functions (Goddings *et al.*, 2021; Lebel *et al.*, 2019).

Post-mortem studies in infants describe myelination following a posterior-to-anterior and inferior-to-superior pattern for white matter maturation (Yakolev and Lecours, 1967). Similarly, a few MR studies have examined changes in white matter maturation that support this pattern (Colby, Van Horn and Sowell, 2011; Krogsrud *et al.*, 2016). Post-mortem studies in infants in their first 2 years of life reveal myelination occurs earlier in infancy and progresses faster in the occipital regions than in posterior parietal, frontal, and temporal white matter relative to other regions in the brain (Kinney *et al.*, 1988). In general myelination is governed by the following key rule of thumb: with some overlap, white matter proximal to the midline matures before distal areas, projection before association, and motor areas mature only after sensory areas from birth up to adulthood (Volpe, 2000). In vivo imaging of white matter tracts in newborns and infants have revealed delayed myelination in association tracts and intracortical regions relative to projection pathways and deep lying white matter such as the cingulum and fornix which are prominent in limbic area connectivity and commissural pathways (such as the corpus callosum) (Hermoye *et al.*, 2006). This maturation event coincides with

a drop in myelin supply in an abundance of axonal presence throughout childhood into adulthood. As a result, myelin sheaths in association tracts tend to be thinner with greater axonal load per oligodendrocyte (Yakovlev, 1967; Kinney *et al.*, 1994). Differential white matter growth patterns may dictate individual tract vulnerabilities to HIV-mediated white matter insults.

2.1.3. HIV Central Nervous System (CNS) infection

Early studies have shown immediate CNS HIV penetration and replication after infection in both children and adults (Shaw *et al.*, 1985; Davis *et al.*, 1992). Brain microglial cells have been described as playing a central role in CNS infection due to their high susceptibility to HIV infection and persistence as reservoirs of the virus (Rock *et al.*, 2004; Castellano *et al.*, 2017; (Cenker, Stultz and McDonald, 2017) whereas astrocytes are believed to play a more central role in CNS infection in children (Saito *et al.*, 1994).

Since the brain is still developing in childhood, HIV-infection and subsequent CNS invasion may disrupt or delay neurological growth leading to impairments in specific neurocognitive domains that take place alongside the development of associated brain structures (Inder and Huppi, 2000; Webster, Elashoff and Weickert, 2011). Studies have shown that children living with HIV may present with damage across the whole brain, as in the case of HIVE, which results in cognitive deficits and delayed or loss of developmental milestones (Van Rie *et al.*, 2007). Perinatally acquired HIV infection (PHIV) or exposure to the virus in newborns is also associated with cerebrovascular disease and lesions (Patsalides *et al.*, 2002). Ventricular enlargement, cortical and subcortical atrophy together with damage in the frontal white and gray matter, basal ganglia calcification and corpus callosum damage are the most common anomalies reported in PHIV (Hoare *et al.*, 2014).

2.1.4. Clinical and treatment variables in relation to HIV neurological manifestation

The effect of HIV and ART on the developing brain is a subject of continued exploration. Neuropsychological testing offers an indirect measure of the effects of HIV in the CNS (Grund *et al.*, 2013). Cognitive domains governing a child's working memory, executive function and processing speed have been discovered to be the most affected, with deficits in visual memory and visual-spatial ability also incident in CPHIV (Phillips *et al.*, 2016).

Understanding the factors affecting disease progression and their associations with neurodevelopmental and behavioral outcomes may offer insight. An example of this is the clear utility of CD4+ T-cell count and HIV-RNA for disease stage and progression assessment. Low blood CD8+ T-lymphocytes and an increase in monocyte counts in the brain have been identified as possible key factors leading to neurologic complications in perinatally infected children (Sánchez-Ramón *et al.*, 2003). Higher viral load at enrolment is associated with poorer cognitive and fine-motor functioning (Jeremy *et al.*, 2005), whereas viral suppression during infancy or early childhood is associated with

improved neurocognitive outcomes in school-aged CPHIV (Crowell *et al.*, 2015). CPHIV on delayed treatment (55% of participants who initiated ART after 12 months of age and all had a positive HIVE diagnosis) present with severe clinical manifestations because of CNS invasion such as progressive encephalopathy or a halt in neurodevelopment, including missed or lost milestones (Tardieu *et al.*, 2000; Donald *et al.*, 2015).

While improvements in cognitive ability are observed among children who receive treatment (Laughton *et al.*, 2012, 2018a, 2019), neurocognitive performance of children living with HIV on ART is still not equivalent to healthy, matched controls (Cohen *et al.*, 2015; Ravindran *et al.*, 2014; Jeremy *et al.*, 2005; Puthanakit *et al.*, 2010). Neuropsychological impairments in CPHIV also occur due to (and persist even in the absence of) factors such as prenatal drug exposure, low level of maternal education, poor mother–child interaction, changes in care-givers due to HIV related deaths of parents, and socioeconomic factors (poverty and malnutrition), which can influence test performance (Phillips *et al.*, 2016; Cohen *et al.*, 2015).

Nearly all children born to a mother living with HIV are exposed to HIV/ARV *in-utero* and during the post-natal period (Griner *et al.*, 2011; Jao *et al.*, 2016; Connor *et al.*, 1994; Sperling *et al.*, 1996; Desmonde *et al.*, 2016; UNAIDS, 2021). ART is responsible for a host of dysfunctions of intracellular organelles as well as disruptions in neuronal cell structure and function, leading to the thought that ART treatment may contribute to the risk of cognitive deficits (Liner, Ro and Robertson, 2010). HIV mediated maternal immune activation and the use of ART to prevent vertical transmission may have unanticipated consequences on the developing brain (Blumberg, Gelbard and Epstein, 1994; Sirois *et al.*, 2013). Prenatal exposure to HIV in CHEU infants may lead to abnormal white matter microstructural organization (Tran *et al.*, 2016) and subtle deficits in the domains of language cognition, motor function and behavior (Van Rie *et al.*, 2007; Kerr *et al.*, 2014).

2.2. MRI concepts – An overview

Magnetic resonance imaging (MRI) is a noninvasive imaging technique used to produce high-resolution images of the soft tissue that make up the internal organs of the human body. Typical MRI experiments are based on the interaction of a nuclear spin with an external magnetic field B_0 . This interaction produces a torque that causes the proton spin to rotate in a cone shaped motion about B_0 . Imaging is achieved by the manipulation of a sum of spins in a sample with a selection of magnetic fields followed by the detection of the resulting precession (Brown *et al.*, 2014). A more elaborate introduction to MRI concepts used in this work are explored in the sections that follow.

2.2.1. Proton spin – magnetic field interaction

Each hydrogen nucleus is a positively charged proton in constant rotation about its own axis producing a magnetic field – the proton magnetic moment. The strength and orientation of this

effective current loop can be summarized by the term ‘magnetic dipole moment’ vector (μ). When B_0 is applied, the magnetic moment vector precesses around B_0 at a radiofrequency (ω_0) – referred to as the Lamor frequency (Brown *et al.*, 2014). Precession angular frequency (ω_0) is linearly proportional to B_0 as in the equation below:

$$\omega_0 = \gamma B_0 \quad [2.1]$$

where γ (gyromagnetic ratio specific a given nucleus) is a constant that connects the spin and magnetic moment and B_0 which gives the strength of the static magnetic field in Tesla (T). For Hydrogen γ is 2.68×10^8 rad/s/Tesla.

At equilibrium, spins continue to precess in alignment with B_0 . Spin count parallel to the magnetic field exceeds that of spins precessing anti-parallel to it by an extremely small margin. This difference in spin states is referred to as the ‘spin excess’. A measurable NMR signal is given by the product of the proton magnetic moment component and spin excess multiplied by spin density. This is referred to as the ‘longitudinal equilibrium magnetization’ M_0 . To initiate precession the magnetization vector is flipped in the direction orthogonal to the external field direction. Typically, M_0 is rotated by a radiofrequency pulse ($\pi/2$ -pulse). The resulting ‘transverse magnetization’ has magnitude M_0 and begins to precess clockwise in the x-y plane. The magnetization produced by a sum of spins causes fluctuations in the magnetic flux in an adjacent ‘receive’ coil by means of Faraday’s law of induction. Thus, ‘magnetic resonance’ in MRI is achieved by the provision of a radiofrequency pulse at the Lamor frequency which brings about precession. Thus, a spatial encoding magnetic field is applied across the sample producing a signal with frequency specific to a given locus according to $\omega_{(x)} = \gamma B_{(x)}$. Measuring the signal at specific loci in the sample brings about a complete MRI image.

2.2.2. T_1 and T_2 Contrast mechanisms

Tissue delineation in MRI can be achieved using spin echo sequences based on the inherent differences in exponential decay properties in the tissue, T_1 and T_2 relaxation times and proton density (PD) [Fig. 2.1]. TE depicts the time of echo generation and, thus, also describes and controls the degree of T_2 weighting in the measured signal and, therefore, in the reconstructed image. Similarly, the repetition time (TR) depicts the time between excitations and, thus, how strong T_1 recovery of different tissues influences image contrast in the form of T_1 weighting. Hence, both TE and TR are important parameters for influencing contrast in spin echo imaging. By observing the behavior of exponential decays, we can see that T_1 -weighted images, and spin density images can be achieved by a combination of short TR ($TR \leq T_1$), and short TE [Fig. 2.1a]. A long TE ($TE \simeq T_2$) and

long TR will yield both proton density and T2-weighted images and the contrast between tissues with different T2 is enhanced. For long TR (relative to T1) and short TE (relative to T2), the image will be sensitive only to the tissue spin density.

T_1 , the spin-lattice relaxation time governs changes in the longitudinal component of the magnetization M_z . It represents the speed of recovery of M along the z axis and B_0 [Fig. 2.1a]. Temporal changes in magnetization along the transverse plane (M_{xy}) [Fig. 2.1b] by are dependent on T_2 relaxation time. After the application of an $\pi/2$ -pulse, the longitudinal magnetization displays an exponential form showing the evolution from the initial value, $M_z(0)$, to the equilibrium value, M_0 .

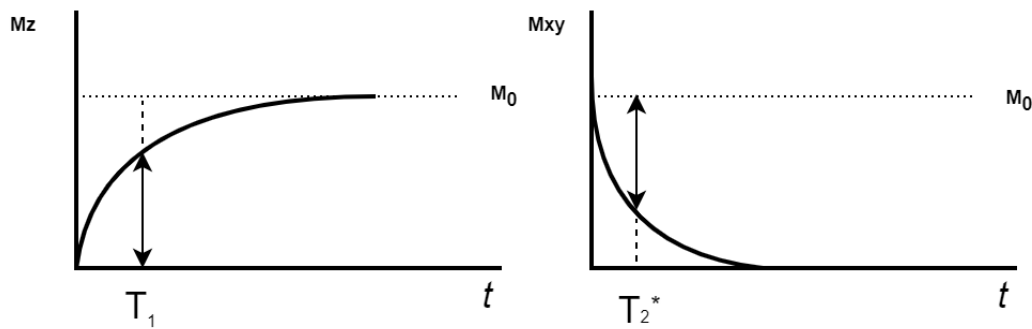


Figure 2.1: Longitudinal (M_z) and the transverse (M_{xy}) magnetization after a 90° excitation pulse. M_z and M_{xy} is described by the time constants T_1 and T_2^* , respectively. Corresponding regrowth of M_z from the initial value $M_{z(0)} = 0$ to the equilibrium value M_0 and, decay of the magnitude of M_{xy} from an initial value ($M_{xy(0)} = M_0$). Image adapted from (Jung and Weigel, 2013).

When an excitation pulse $\pi/2$ -pulse is applied at the Larmor frequency (ω_0), the longitudinal magnetization (M_z) of spins is flipped into a plane perpendicular to the main field (M_{xy}). Rapid dephasing of spins follows. This signal decay is caused by static field inhomogeneities. The resulting signal decay is described by the characteristic relaxation time T_2 . Irregularities in the magnetic field can also induced by mutual polarization between spin neighbors. These spin-to-spin interactions are influenced by Brownian motion. The decay time, T_2^* represents a combination of external field induced (T_2') and thermodynamic (T_2) effects. Both types of decay, T_2 and T_2' relaxation can be combined to make the relaxation time T_2^* (T2-star) according to:

$$\frac{1}{T_2^*} = \frac{1}{T_2} + \frac{1}{T_2'} \quad [2.2]$$

Due to T_2^* processes, individual spins lose their phase coherence, and the overall signal gets attenuated generating a free induction decay (FID). It turns out, a portion of this loss of transverse magnetization due to T_2' is recoverable. This can be achieved by using a refocusing pulse in the spin echo sequence. A brief introduction of the spin echo technique to manipulate MR effects is provided in the section that follows.

2.2.3. Spin-echo

To achieve a spin-echo sequence, two radiofrequency pulses are applied in succession. The first is an excitation pulse ($\pi/2$ -pulse) followed by one or more refocusing pulses (π -pulse). When the $\pi/2$ -pulse is applied, the magnetization of the sample flips 90° and precess about the transverse plane (xy). Almost instantaneously, the spins begin to dephase relative to each other, as they experience different field strengths. Hence, some spins precess faster or slower than ω_0 , which results in a loss of coherence of the spins. The π -pulse is then applied in the transverse plane, inverting the phase accumulated since the time ($t = 0$) when the $\pi/2$ -pulse was applied. This recovery of the loss in phase coherence following the application of a sequence of $\pi/2$ and π -pulses is called the spin-echo. Signal sensitivity to diffusion alone can be accentuated with modifications to spin-echo techniques (Stejskal and Tanner, 1965). Typically, diffusion imaging pulse sequences contain diffusion-weighting gradients (Bernstein, King and Zhou, 2004). For our case we consider a twice-refocused spin echo (TRSE) sequence. Through the acquisition of an additional SE signal, TRSE technique is able to offset residual eddy-current magnetic fields (Reese *et al.*, 2003), beyond recovery of signal from off-resonance effects (Bernstein, King and Zhou, 2004). Diffusion of water molecules causes a phase shift of the transverse magnetization resulting in the attenuation of the MRI signal. Using diffusion tensor imaging (DTI), tissue delineation can be achieved by measuring the extent of signal attenuation as a function of tissue type and its associated structural, physical, and physiological properties. DTI is discussed at length in the sections that follow.

2.2.4. Diffusion tensor imaging

DTI can be used to assess changes in white matter. It is based on the principle of the random movement of molecules due to thermal energy (Brownian motion). Cellular membranes and organelles influence the behavior of water (Alexander *et al.*, 2007). Structurally organized tissues, such as white matter, present directionally dependent diffusion (anisotropy) (Pierpaoli and Basser, 1996; Curran *et al.*, 2016). Pathological changes in tissue structure also alter diffusion (Alexander *et al.*, 2007). DTI is an imaging tool that has a wide range of applications in demonstrating injury to the brain such as in ischemic stroke (van Gelderen *et al.*, 1994), multiple sclerosis (Cassol *et al.*, 2004) and cerebral edema (Nath *et al.*, 2004). Water diffusion in axons is anisotropic due to their geometry (i.e., long fibrous tracts). Based on the behavior of water molecules, DTI studies can map changes in the diffusion of water in white matter tracts (Beauleu *et al.*, 2002).

DTI may be used to map and characterize the three-dimensional diffusion of water as a function of spatial location. The diffusion tensor describes the magnitude, the degree of anisotropy, and the orientation of diffusion anisotropy (Alexander *et al.*, 2007). DTI comes with a set of objective indicators that describe and indicate white matter damage without the need for contrast agents and

chemical tracers, making it an ideal non-invasive imaging modality in pediatric patients (Neil *et al.*, 1998, 2002; Behrens *et al.*, 2003).

Measuring diffusion in MRI involves the incorporation of strong diffusion-weighted gradients (G_{diff}) to sensitize measurements to diffusion (Fig. 2.2). Typically, two gradient pulses of equal magnitude and similar polarity are applied on either side of a 180° RF pulse such that they cancel out when water molecules are not in motion and cause a random phase shift proportional to distance travelled for molecules that are displaced, simultaneously. This phase shift results in signal attenuation and is the basis of DW contrast in diffusion tensor imaging (DTI). The highest phase shift is evident in spins diffusing along the applied diffusion gradient and thus show the least signal intensity.

The diffusion tensor

In white matter, diffusion is largely anisotropic due to preferential orientation of myelin fibers. Diffusion sensitizing gradients may be applied along the direction of principal diffusion to extract information about diffusion along this axis. Anisotropic diffusion in tissues where diffusion shows a directional dependence can be expressed in the following equation (Basser *et al.*, 1994):

$$\ln \left[\frac{S(g, TE)}{S(TE)} \right] = - \sum_{i,j}^{x,y,z} b_{i,j} \cdot D_{i,j} \cdot \quad [2.3]$$

$$= -(b_{xx}D_{xx} + b_{yy}D_{yy} + b_{zz}D_{zz} + 2b_{xy}D_{xy} + 2b_{yz}D_{yz} + 2b_{xz}D_{xz})$$

where $b_{i,j}$ represents b-matrix row and column elements, i and j , respectively. These quantities are related to ij^{th} direction ($i = x, y, \text{ and } z; j = x, y, \text{ and } z$) (Shetty *et al.*, 2014). $S(TE)$ is the gradient free echo intensity. To achieve DTI, a gradient-time integral describes the integration of trapezoidal bipolar pulse gradients into the spin-echo sequence producing a gradient echo, while $S(g, TE)$, as follows (Basser *et al.*, 1994):

$$b_{ij} = \gamma^2 g_i \cdot g_j \left[\left(\Delta - \frac{\delta}{3} \right) + \frac{\varepsilon^3}{30} - \frac{\delta \varepsilon^2}{6} \right]. \quad [2.4]$$

Studying [Eq. 2.3], it becomes apparent that a linear relationship between the log of the echo attenuation and each component of D can be established. Diffusion in white matter is characterized using the apparent diffusion tensor, D (Basser *et al.*, 1994). In anisotropic tissues, scalar coefficients are insufficient to characterize diffusion, thus a tensor, D is required. D adequately describes three-

dimensional (3D) molecular diffusion i.e., along x, y and z directions (diagonal terms i.e., D_{xx}, D_{yy}, D_{zz}) and assesses correlation between these directions (off-diagonal terms i.e., $D_{xy}, D_{yx}, D_{yz}, D_{zy}, D_{xz}, D_{zx}$) (Le Bihan *et al.*, 2001):

$$D = \begin{bmatrix} D_{xx} & D_{xy} & D_{xz} \\ D_{yx} & D_{yy} & D_{yz} \\ D_{zx} & D_{zy} & D_{zz} \end{bmatrix} \quad [2.5]$$

2.2.5. Diffusion tensor properties

Quantitative DTI measures of white matter properties of include fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD). These parameters are calculated from eigenvalues λ_1 , λ_2 and λ_3 of D . An ellipsoid model - a three-dimensional representation of the diffusion displacement of molecules in time in the X, Y, and Z planes - is often used as a visual representation of the components of D [Eq. 2.5]. In a given ellipsoid [Fig. 2.3] are eigenvectors (ϵ_1 , ϵ_2 and ϵ_3), which describe the orientation of the axes while the radius of the ellipsoid along these axes is proportional to l_1 , l_2 , and l_3 which represent the corresponding magnitude of anisotropy (Curran *et al.*, 2016).

The eigenvalues of the diffusion tensor provide diffusion coefficients along the orientations defined by its respective eigenvectors (Pierpaoli *et al.*, 1996). A common representation of isoprobability surfaces of the Gaussian diffusion propagator estimated by DTI is the diffusion ellipsoid (Basser, 1995), with axes along the three eigenvectors and magnitude equal to the respective root mean square (RMS) diffusion displacements. The shape of the ellipsoid reveals the anisotropy degree of the tensor. The tensor can be broken down into linear, planar, and spherical components (Alexander *et al.*, 2012). These tensors provide a basis for describing valid white matter properties. For example, one would expect a tensor where the linear component is the highest in white matter. In such cases the principal eigenvector corresponds with the principal fibre orientation of the underlying tissue structure (Pierpaoli *et al.*, 1996).

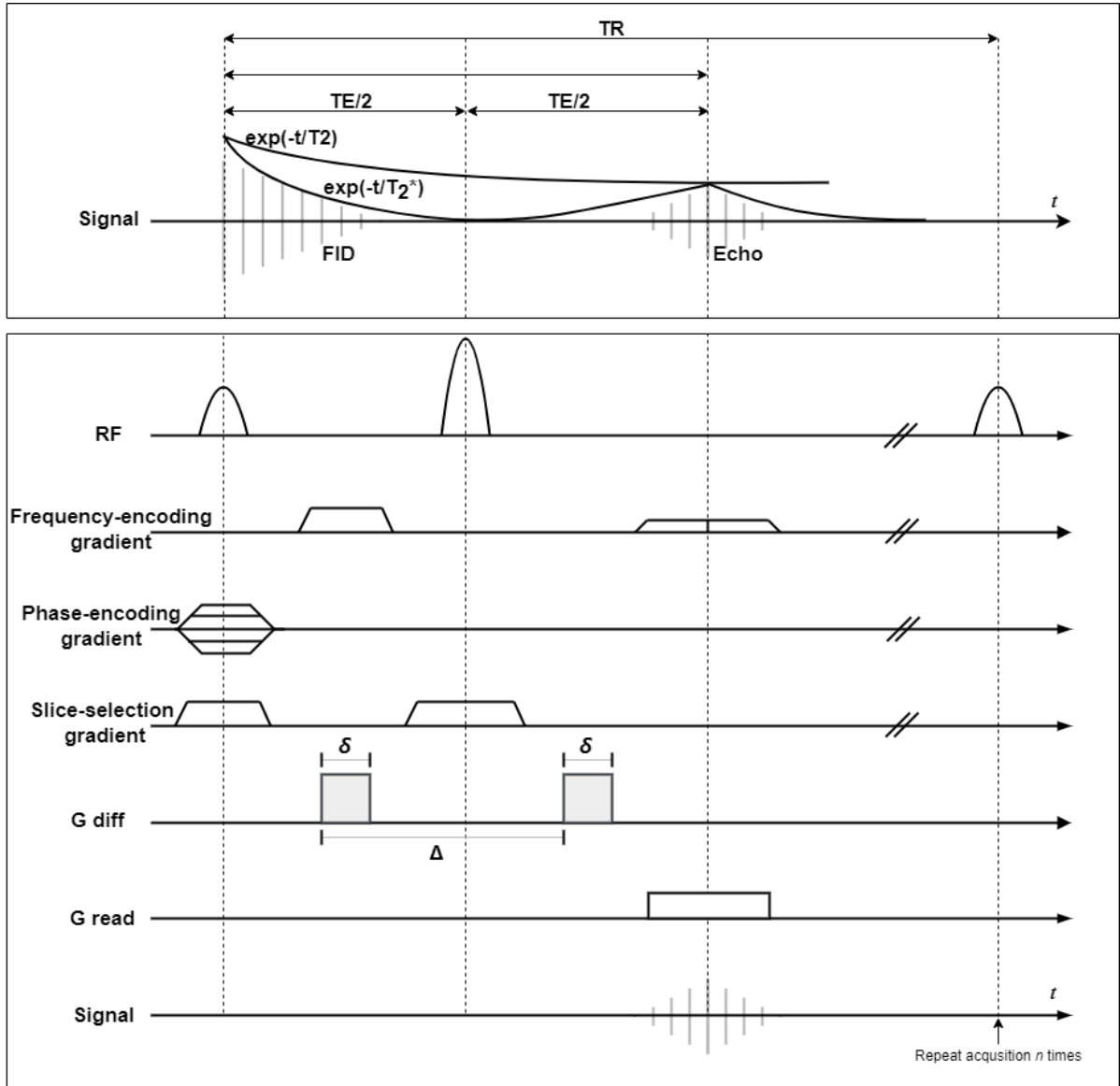


Figure 2.2: A. The Spin Echo sequence consists of a $\pi/2$ -pulse and a π -pulse. Rephasing of spin isochromats is complete at TE , signal decay solely due to field inhomogeneities is described by T_2' . Observing the behavior of T_2^* where stochastic and magnetic field fluctuations are considered; a reduced signal amplitude is observed at TE . T_2^* can be decomposed to T_2 and T_2' according to Eq. [2.2]. **B.** A pulse sequence diagram of a diffusion-weighted spin-echo pulse sequence. Gradient pulses (G diff) here share polarity due to an imposed spin-phase effect about 180° by a second radiofrequency pulse in the x, y, and z directions. The sequence is repeated according to the matrix size n in the phase-encoding direction. Adapted from (Jung and Weigel, 2013).

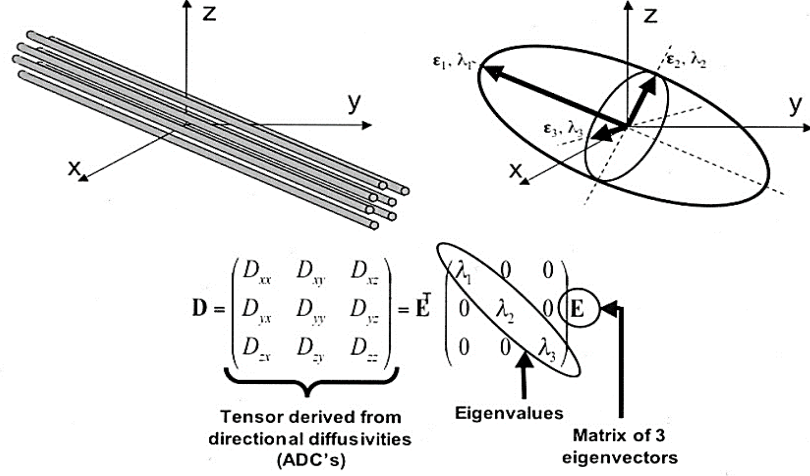


Figure 2.3: Diffusion tensor ellipsoid with associated eigenvectors (ϵ_1 , ϵ_2 and ϵ_3) and eigenvalues (λ_1 , λ_2 and λ_3) and the matrix from which the tensor is computed. (Jellison *et al.*, 2004)

From the diffusion tensor scalar DTI parameters can be calculated. MD can be obtained as the mean of the tensor's eigenvalues or in general as the average sum of three ADCs measured in three orthogonal directions (Basser, 1995).

$$MD = \frac{\lambda_1 + \lambda_2 + \lambda_3}{3} \quad [2.6]$$

FA is a normalized expression of the variance of the tensor eigenvalues (Basser, 1995). This metric quantifies diffusion asymmetry within a given voxel and values closer to 0 represent isotropic tissue and values closer to 1 represent an almost perfect anisotropic tensors produced by more linear and coherent tissue.

$$FA = \sqrt{\frac{3}{2} \frac{(\lambda_1 - (D))^2 + (\lambda_2 - (D))^2 + (\lambda_3 - (D))^2}{\lambda_1^2 + \lambda_2^2 + \lambda_3^2}} \quad [2.7]$$

Studies have linked reduced FA values, indicative of lower diffusional asymmetry, to damaged white matter tracts, structural disruption, or poorer myelination (Beaulieu, 2002b; Tae *et al.*, 2018). MD, a scalar measure of overall diffusivity, is affected by cellularity, oedema, necrosis, myelination, structural organization, and axonal packing (Beaulieu, 2002b; Song *et al.*, 2003; Tae *et al.*, 2018).

Diffusion parallel and perpendicular to the axis of axons, AD and RD, provide more direct measures of axonal injury/degeneration and the degree of myelination, respectively (Beaulieu, 2002b):

$$AD = \lambda_1 \quad [2.8]$$

$$RD = \lambda_2 + \lambda_3 \quad [2.9]$$

Interpretation of DTI measures

Table 2.1. Summary of relationships among DTI measures FA, MD, AD, and RD in different clinical cases (CHU> CPHIV). CHU is the reference group.

Case	ΔFA	ΔMD	ΔAD	ΔRD	Clinical interpretation
A	-	-	-	-	No pathological changes, e.g., typical white matter
B	↓	↑	-	↑	Demyelination / Dysmyelination (Recovering myelination)
C	↓	↑	↑	↑	Severe dysmyelination (Extreme astrocyte hypertrophy) (Increased interstitial space)
D	↓	-	↓	-	Mild dysmyelination (Mild astrocyte hypertrophy)
E	↓	-	↓	↑	Axonal degradation / Mild dysmyelination

Studies have reported white matter alterations due to direct viral toxicity (Liu *et al.*, 2017) and indirectly through persistent indolent HIV associated immune activation and inflammation mediated cellular invasion, demyelination, and axonal atrophy, despite ART and viral suppression (Kapetanovic *et al.*, 2010; Hileman and Funderburg, 2017; Blokhuis *et al.*, 2019; Sarma *et al.*, 2021). The result is hypomyelinated axons and/or degenerating axons that are loosely packed in a widened extra-exonal space (Naismith *et al.*, 2010; Aung, Mar and Benzinger, 2013; Winklewski *et al.*, 2018). Vasogenic edema, an extra-axonal fluid accumulation associated with a compromised blood brain barrier (BBB), is the likely cause of the increase in size of the extracellular matrix (Stokum, Gerzanich and Simard, 2016). Lower FA and higher MD in CPHIV and CHEU populations, suggest cerebral edema and/or neuro-inflammation associated axonal damage and/or demyelination (Yadav *et al.*, 2020a). Alternatively, increased cellularity due to an influx of inflammatory cells and demyelination debris in MS may result in general restricted water diffusion (Wang *et al.*, 2011). In adult subjects, decreased AD, RD, and MD seen in HIV/ART may reflect macrophages and microglia infiltration due to active viral replication within the CNS or cytotoxic edema (Wright *et al.*, 2012). The polarity in directional

diffusion appear to suggest a possible means to delineate between edema associated with inflammation related cellular infiltration and subsequent intracellular water influx (cytotoxic edema) and increased extracellular water content (vasogenic edema).

Dysmyelination

Mutant mice have been imaged to identify DTI biomarkers for white matter insults and myelin malformations in diseases that affect humans. Mutant *jimpy* mice which carry a recessive gene on their X-chromosome that leads to myelin malformations (Nave *et al.*, 1986; Harsan *et al.*, 2007). Dysmyelinating disorders, represented by Pelizaeus-Merzbacher disease (PMD) and other leukodystrophies, are characterized by myelination abnormalities, leading to incomplete, patchy, or irregular myelin sheaths (Harsan *et al.*, 2006). Above-normal values of MD, AD, and RD (Table 1. C.) were recorded in PMD mice modelling inflammation associated edema. In this model, astrocytic hypertrophy, a cellular proliferation event in severely dysmyelinated *jimpy* brains where most axons or bundles of fibers are entirely wrapped by astrocyte cytoplasmic processes, is observed. These cytoplasmic structures arrange themselves longitudinally along the principal axis of the axons. This exaggerates the parallel diffusivity component (AD) (Ono *et al.*, 1995; Harsan *et al.*, 2007 ; Naismith *et al.*, 2010; Chiang *et al.*, 2014). Myelin deficient *shiverer* mice displayed increased RD and no changes in AD (Table 1. B) in the absence of axonal degradation and inflammatory associated mechanisms (Song *et al.*, 2002). *Shiverer* mice have hypomyelinated axons due to homozygous recessive alleles that code for defective myelin basic protein.

Demyelination

Demyelination takes the form of disruption of previously formed myelin, as in multiple sclerosis (MS) (Harsan *et al.*, 2006). MS is a neurodegenerative inflammatory disease, characterized by demyelination and axonal loss. This combination of effects has a negative impact on axonal packing. Similarly, wallerian degeneration, characterized by lower FA and AD and, higher RD [Table 1. E] (Pierpaoli *et al.*, 2001), represents the stripping of myelin sheaths and axonal filament degradation in neuronal populations in positions adjacent to site of stroke can be detected due to changes in anisotropy (Table 1. E) (Werring *et al.*, 2000; Ni *et al.*, 2013). Similarly, an attenuated parallel diffusivity in optic and trigeminal nerves due to lack of axonal coherence was observed in twitcher mice used to model Krabbe disease (Ono *et al.*, 1995).

Cerebral edema

DTI measures acquired from trigeminal nerve phantoms and transgenic mice designed to mimic vasogenic edema in multiple sclerosis (MS) demonstrated increased RD and AD associated overall diffusivity increases due to an increased extra-axonal space (Wang *et al.*, 2011, 2014; Chiang *et al.*, 2014).

Acute and chronic white matter insults

Diffusion parameters are dynamic in acute and chronic disease, with the diffusion tensor everchanging in time to reflect the underlying disease related tissue microstructure. Studies have reported acute RD increases in myelin deficient mice (Song *et al.*, 2002, 2005), while patients with recovering from multiple sclerosis (MS) present with progressive reductions in RD (Fox *et al.*, 2011). In traumatic brain injury, the membrane of a dying neuron degenerates, thus reducing restriction in diffusion along directions perpendicular to the axon, increasing λ_2 and λ_3 , and reducing anisotropy (Table 1. E) (Arfanakis *et al.*, 2002). It is well described that AD increases relate to improved axonal health (Bockhorst *et al.*, 2008; Kumar *et al.*, 2013). Alternatively, anisotropy is a function of the packing density of axons within a voxel (Pierpaoli and Basser, 1996; Beaulieu, 2002b). In acute axonal injury, AD decreases possibly due to the increased debris from the disrupted membrane barriers (Song *et al.*, 2003). However, inflammation, cellular invasion, gliosis, and oedema complicate the interpretation of changes in anisotropy in demyelinating diseases (Aung, Mar and Benzinger, 2013). Dramatic decreases followed by steady increases in AD due to vasogenic oedema have been reported in cuprizone induced spinal cord injury in mice models (Kim *et al.*, 2007). A similar pattern was observed in human chronic optic neuritis (ON) models, an inflammatory condition affecting the optic nerve, with AD eventually rising to above-normal levels (Naismith *et al.*, 2009). Diffusion parameters are dynamic in acute and isolated optic neuritis, with an initial acute decrease in axial diffusivity. The acute decrease in axial diffusivity at onset correlated with visual contrast sensitivity. Increased MD, AD and, RD in chronic ON, with RD correlating with functional, structural, and physiologic tests of vision in chronic ON (Naismith *et al.*, 2009). Interestingly, in long-term optic neuritis, linear mixed modeling assessing the relationship of DTI to different categories of vision loss revealed that RD can discriminate between severity of cases while AD does not reflect any clinical outcomes (Naismith *et al.*, 2010). AD decreases are correlated with acute axonal atrophy but not during sustained demyelination (Xie *et al.*, 2010). The power of AD as a measure of tissue directionality in some cases may be reduced (Naismith *et al.*, 2010; Aung, Mar and Benzinger, 2013; Winklewski *et al.*, 2018). Taken together, these examples show that using both AD and RD allows for better interpretation of the data, particularly in disease states. Further, due to the dynamic nature of disease, careful considerations are to be made when interpreting DTI measures. Particularly, a clear distinction between the acute and chronic stages of disease makes DTI measures more powerful as a prognostic tool.

2.2.6. DTI Artifacts

Motion artifacts

During acquisition subject physiological and head motion can cause signal dropout artifacts or a shift in spatial location of the voxelwise DTI signal (geometric distortions). Fast EPI-acquisition and

cardiac-gated techniques can be used to mitigate physiological motion artifacts. Retrospective geometric distortions can be corrected by uniform phase restoration, while prospective head motion correction can be achieved by incorporating navigator echoes in spin echo or gradient echo sequences.

Eddy current distortions

The application of gradients during DTI acquisition induces ‘eddy currents’ in the scanner environment producing additional magnetic fields. As a result, undesirable effects that adversely affect the DTI signal such as a change in gradient field dependent b-value and geometrical distortions during readout of the DW images. Reliable computation of quantitative DTI parameters from the diffusion tensor rest provided that gradient field parameters are constant during a scan. This is not the case in DTI acquisitions. Instead, additional magnetic fields introduce significant systematic deviation (bias) in the estimated diffusion parameters. Eddy current distortions may be corrected through prospective and retrospective correction schemes.

Image noise

Noise is an inherent feature in DTI because the diffusion signal is determined from signal attenuation in each direction. This can introduce a significant bias in the estimates of quantitative diffusion parameters. Increased SNR in DTI images can be achieved by the application of more diffusion gradient directions and/or acquisition averages. However, Improved SNR is often at the cost of lengthy scan times. Alternatively, post-processing noise-removal filtering and regularization techniques may be applied. However, due to the low-pass nature of most smoothing filters, the SNR enhancement is often accompanied by spatial blurring, which may cause partial volume effects or voxel averaging effects, the choice of filter size significantly affects the outcome of statistical inferences.

2.2.7. Voxel-wise analysis

VWA of DTI data is an exploratory technique that evaluates focal differences diffuse in the brain. Due to individual anatomical variation between images of subjects, VWA involves the spatial normalization of DTI images to a common atlas and thus the spatial location of voxels is assumed to be equivalent between subjects. The quality of this registration steps is nontrivial as it has a direct influence on downstream analyses. While improved voxel correspondence may be achieved by performing VWA on an intersect of voxels across the study population (Liu *et al.*, 2009), only a subset of voxels is tested and subjected to highly penalizing multiple comparison corrections at the voxel level. Furthermore, focal alterations in peripherally located regions of whole tracts are not captured in favor of reducing alignment errors and avoiding partial volume effects (Smith *et al.*, 2006). Tract-based spatial statistics (TBSS) is one such example of VWA that evaluates changes in

the centers of whole tracts (Smith *et al.*, 2006). This technique is, however, unable to provide insights into long-range fiber-tract integrity and structural connectivity between brain regions.

2.2.8. Tractography and tract-graphs

The tractography-based approach can generate three-dimensional fiber-tract reconstructions of pathways between brain regions of interest (ROIs). Following the computation of the tensor, the principal direction of diffusion along the fiber is determined at each voxel (Basser *et al.*, 2000; Catani *et al.*, 2002). This is the eigenvector associated with the largest eigenvalue of the tensor. Fibers can be modelled in the form of streamlines across voxels by following the principal eigenvectors in the current direction of propagation using algorithms such as the improved “fiber assignment by continuous tracking” (FACTID) (Taylor and Saad, 2013). Studies have shown the pivotal role of white matter connectivity models for the understanding of typical brain function and associated developmental trajectories and in disease (Assaf and Pasternak, 2008; Horsfield and Jones, 2002; Ciccarelli *et al.*, 2008). In addition, studies investigating the use of tractography in the reconstruction of whole-brain white matter networks for graph theory analysis revealed useful topological properties, such as small worldness and hubs (Hagmann *et al.*, 2008; Gong *et al.*, 2009; Heuvel and Sporns, 2011). Moreover, aberrant topological organization of white matter networks have been reported in demyelinating diseases such as multiple sclerosis (Shu *et al.*, 2011).

DTI tractography is sensitive to the quality of data and results vary with tracking parameters. Typical probabilistic tractography algorithms determine the most likely course of reconstruction by performing Monte Carlo simulations modeling uncertainty in fiber orientation in each voxel. However, probabilistic tractography produces different streamlines with each run (Reid, Cespedes and Pannek, 2020).

The choice of DTI metrics to analyze is no trivial task. Similarly, graph analysis based on diffusion metrics is equally challenging and requires cautious implementation and interpretation. Connectivity between two gray matter regions may be quantified as the number of axons within the connection. Due to low spatial resolution, streamlines reconstructed through tractography are not a representation of individual axons. Typically, a voxel contains millions of axons coursing through it and an average of their trajectories makes up a streamline (Smith *et al.*, 2020). Thus, streamline count is limited as a quantitative measure of connectivity. Alternatively, combining tractogram and fiber density information from the diffusion model may be a more appropriate measure of connectivity (Smith *et al.*, 2020). Newer methods such as neurite orientation dispersion and density imaging (NODDI) (Zhang *et al.*, 2012), can provide information about axonal density as the intracellular volume fraction (ICVF) (Lampinen *et al.*, 2017).

Diffusion imaging relies on certain biological assumptions, such as the single tensor model in DTI. The single tensor model assumes that water diffusion is Gaussian and can only infer a single dominant

fiber orientation within each voxel. In regions with crossing fibres, this assumption can lead to inaccuracies in fibre orientation estimation and subsequent fibre tract reconstruction. These assumptions may not always hold true in complex brain regions or pathological conditions. Diffusion imaging does not provide a direct measure of the complex brain microstructure that make up the huge network of long-range axonal connectivity, and the ground truth of the reconstructed white matter tracts is often unknown. Validation of tractography results can be challenging and model validation is carried out using DTI phantoms (Drobnjak *et al.*, 2021). There is significant variability in the diffusion properties of white matter tracts between individuals, which can make it challenging to draw general conclusions or make group comparisons (Carew *et al.*, 2007). Tractography can overcome alignment problems prevalent in VWA methods by working in subject space and for similar reasons do not necessarily require pre-smoothing (Smith *et al.*, 2006). However, the distribution of DTI property values such as FA within white matter regions is non-Gaussian because not all axons course through the full length of the fiber, and aberrations may be focal within the fiber. Thus, simple averaging over large ROIs is non optimal (Liu *et al.*, 2009, 2012). Diffusion measures in sections along each fiber tract offer a different avenue to understanding longitudinal white matter maturation and its role function in typical and diseased brains (Yeatman *et al.*, 2012).

Connectivity

In DTI derived brain networks, connectivity is a quantitative measure of the number of axons within the connection between proximal and distal grey matter regions (Smith *et al.*, 2020). Additionally, regional variation in myelination, axonal diameter and axonal density associated with pruning of synaptic connections (Giedd *et al.*, 1999; Lebel *et al.*, 2008; Gong *et al.*, 2009; Lebel and Beaulieu, 2011), represent the weight of the edge between i and j . As such, group level connectivity matrices can be compared to identify abnormal connectivity patterns in the brain.

Thresholding

Thresholding is commonly used to mitigate the effects of spurious connections resulting from tractography (Hagmann *et al.*, 2008; Fornito, Zalesky and Breakspear, 2013; Sotiropoulos *et al.*, 2013; Váša *et al.*, 2018). In most cases this involves the selection of an arbitrary threshold (Colon-Perez *et al.*, 2016; Civier *et al.*, 2019). Computation of weighted graph-theoretical metrics such as global efficiency, characteristic path length, betweenness, centrality, vulnerability, clustering coefficient and modularity is heavily influenced by more influential, disproportionate values on the heavy tails of the connectivity strength distributions (Civier *et al.*, 2019) [Fig. 2.4]. Consequently, heavy tail strength distributions of dense weighted connectomes may confer shorter lengths to stronger connections to distal nodes compared to longer lengths for paths to adjacent nodes connected by weak connections [equation 1.20] (Civier *et al.*, 2019). Hence, weighted networks enable the

characterization of the brain network organization without the application of arbitrary thresholds (Colon-Perez *et al.*, 2016).

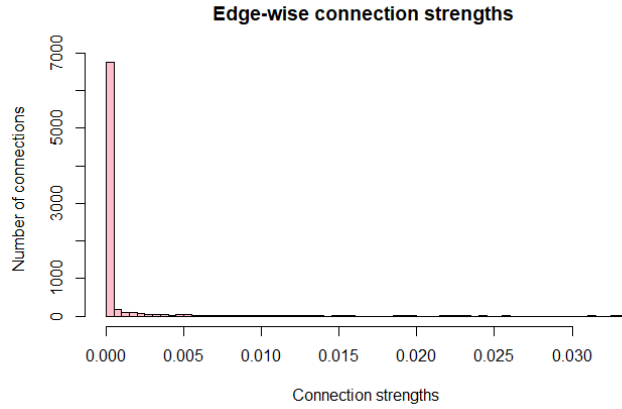


Figure 2.4. A histogram of pairwise connection strengths in a representative CHU subject. Stronger connection strengths form the heavy tail of the distribution.

2.2.9. Graph theoretical brain connectivity analysis

The structural connectome is a comprehensive description of the structural connections that link a network of regions that make up the brain. In this framework the brain can be conceptualized as graphs. Graphs (G) in the context of the brain can be used to model pairwise white matter connectivity (edges, E) between gray matter regions (vertices, V) according to:

$$G = (V, E, \omega) \quad [2.10]$$

where E is the graph edge set:

$$E = \{\{i, j\} \mid \Psi(i, j) > 0 \forall 1 \leq i, j \leq q\} \quad [2.11]$$

and $\omega: E \rightarrow \Psi(E)$ is the weighted function that assigns at each edge $e \in E$ its weight; q is number of vertices in V .

Strength

Strength is simply a weighted average of the measured connectivity strength among all a region's connections. The strength, k_i is defined as follows:

$$s_i = \sum_j \hat{a}_{ij} = \sum_j a_{ij} \cdot \omega(e_{ij}), \quad [2.12]$$

where $\omega(e_{ij})$ is the fractional number of tracks (fNT), NT scaled by the total number of streamlines in edge set $|E|$ according to (Tinaz *et al.*, 2017):

$$\omega(e_{ij}) = \frac{x_{ij}}{\sum_{ij} x_{ij}} \quad [2.13]$$

Integration

Characteristic path length

Characteristic path length of a network of nodes is a global metric and is the mean shortest path length [Eq. 1.14] between all possible pairwise connections. It is a measure of integration of information processing. Shorter characteristic path lengths promote functional integration of the network and thus a greater ease in information transfer between nodes. C_i is the mean path length between node i and the other nodes that make up the rest of the network, and $q = |V|$:

$$C = \frac{1}{q} \sum C_i = \frac{1}{q(q-1)} \sum_{i,j \in V}^q s_{i,j} \quad [2.14]$$

where $s_{i,j}$, is the shortest path length that represents an aggregate of weights in the shortest path between nodes i and j :

$$s_{i,j} = \sum_{a_{u,v} \in G_{i \leftrightarrow j}} a_{u,v} \quad [2.15]$$

where $G_{i \leftrightarrow j}$ is the shortest path between i and j .

In weighted graphs, ‘length’ between pairwise connections is the reciprocal connectivity strength (Civier *et al.*, 2019). Thus, paths made of stronger connections have a low connectivity length and represent shorter paths.

Global efficiency

Global efficiency is a measure of integration. It is a measure of parallel information processing. Efficiency (Latora and Marchiori, 2001). The Global efficiency of a graph is the mean inverse shortest path length for all pair of nodes:

$$G = \frac{1}{q(q-1)} \sum_{i,j \in V}^q s_{i,j}^{-1} \quad [2.16]$$

where $q = |V|$ and $s_{i,j}$, is the shortest path from i to j .

Global efficiency is highest for dense networks, while sparse networks characterized by shorter paths show the least efficiency.

Measures of Segregation

Modularity

Modularity is the degree to which the brain is parcellated into distinct functionally related partitions of highly interconnected nodes (modules). Typical modular structures are estimated by means of Q-metric computation and optimization (Blondel *et al.*, 2008):

$$Q = \frac{1}{2m} \sum_{i,j} \left[A_{ij} - \frac{k_i k_j}{2m} \right] \delta(c_i, c_j) \quad [2.17]$$

Clustering coefficient

The weighted clustering coefficient, $c_{i,o}$ is the sum of triangle intensities (Onnela *et al.*, 2005):

$$c_{i,o} = \frac{1}{k_i(k_i - 1)} \sum_{j,m=1}^N [\hat{\omega}(e_{ij}) \hat{\omega}(e_{jm}) \hat{\omega}(e_{mi})]^{1/3} \quad [2.18]$$

where $\hat{\omega}$ are edge weights scaled by the maximum edge weight in the network:

$$\hat{\omega}(e_{ij}) = \frac{\omega(e_{ij})}{\max(\omega(e))} \quad [2.19]$$

2.3. Region specific age-related sex differences in white matter maturation: DTI studies

White matter development in infants generally follows a defined spatio-temporal sequence that correlates with cognitive capacity. *In vivo* quantification of white matter changes through time reveals a cascade of maturational events. Typically, axonal organization underlies coherent fibers leads. More organized axons likely translate as increased in anisotropy (FA and AD) due to higher diffusivity along the axons and decreased radial diffusivity (RD) (Beaulieu *et al.*, 1996). In parallel, negligible changes occur in the extracellular matrix and membrane density, meaning MD is expected to be constant. Proliferation and maturation of precursors to myelination i.e., oligodendroglia that wrap around axons are associated with decreases in the extracellular matrix and an increase in membranes density. These changes result in a decrease in overall diffusivity (MD, AD and RD) [for review Beaulieu, 2002].

A handful of studies suggest apparent associations between age, sex and genetic differences in pubertal maturation and white matter development (Ladouceur *et al.*, 2012). Studies report a general

trend during adolescence (age 12–18 years) showing increasing fractional anisotropy (FA) with age and decreasing mean diffusivity (MD) with age, findings primarily due to decreasing radial diffusivity with age (Schmithorst and Yuan, 2010). In a DTI study, longitudinal age-related differences in regional white matter maturation were observed among children, adolescents, and young adults. Sex dependent differences in white matter maturation were observed with female tracts achieving full maturity earlier than males across projection and association tracts (Asato *et al.*, 2010). A structural MRI study assessing sex dependent and age dependent white matter maturation reported linear increases in white matter volume with age well into adulthood across white matter of the frontal, temporal, parietal, and occipital lobes with males presenting a rapid increase during adolescence (Lenroot *et al.*, 2008). Similarly, significant sex by age interactions were seen for cerebral gray and white matter volumes and corpus callosal areas. Specifically, males had more prominent age-related gray matter decreases and white matter volume and corpus callosal area increases compared with females. The authors suggest that these sex-dependent differences are reflected in the timing of neuronal pruning and myelination between male and female adolescents (De Bellis *et al.*, 2001). A study investigating longitudinal white matter development using deformation-based morphometry and fiber tractography to measure white matter volumetric and microstructural changes in zygotic twins aged 9 – 12 years found whole brain and regional white matter volume increases in a number of projection, commissural and association tracts (Brouwer *et al.*, 2012). A pattern characterized by a longitudinal increase in regional fractional anisotropy (FA) with a corresponding increase in axial diffusivity (AD) and a decrease in radial diffusivity (RD) was observed in this group of early adolescent group (Brouwer *et al.*, 2012). (Asato *et al.*, 2010) also found general decreases in RD with age pointing to continued myelination in older children. In a tractographic study examining age-related regional variations of the corpus callosum over a wider age range (5 – 59 years) revealed FA increases and decreases in MD during childhood and slightly slower decreases of FA and increases of MD at older ages (Lebel *et al.*, 2010). Another MRI study using voxel-based morphometry (VBM) and DTI found age-related increases and decreases white matter and GM volumes, respectively, to occur concurrently with FA increases attributable mainly to AD increases bilaterally in the arcuate fasciculus (AF) and corticospinal tract. These findings suggest structural changes associated with brain maturation in adolescence present a bias for the establishment of long-distance connections in different white matter tracts, specifically in the AF and CST (Giorgio *et al.*, 2010).

2.4. Pediatric HIV DTI studies

2.4.1. HIV-related diffusivity changes

To date, twelve DTI studies investigating white matter outcomes in pediatric HIV infection in ART-treated and ART-naïve have been done (Hoare *et al.*, 2012, 2018; Hoare, Fouche, Phillips, John A. Joska, *et al.*, 2015; Li *et al.*, 2015; Sarma *et al.*, 2019). Decreased FA and increased MD are thought

to be indicative of loss of axonal integrity. Lower FA and higher MD and RD in the corpus callosum (CC) and higher MD in the superior longitudinal fasciculus (SLF) have been demonstrated in ART-naïve children compared with controls (Hoare *et al.*, 2012). However, studies have shown localized low FA, high MD values within CPHIV on ART treatment compared to their uninfected counterparts (Hoare *et al.*, 2014; Musielak and Fine, 2016). Implicated regions include the CC, cerebellar peduncles, fornix, superior and posterior corona radiata (SCR/PCR), frontal and parietal white matter, pre- and postcentral gyrus, superior fronto-occipital fasciculus, and superior longitudinal fasciculus (SLF) (Hoare *et al.*, 2012, 2018; Hoare, Fouche, Phillips, John A. Joska, *et al.*, 2015; Li *et al.*, 2015; Sarma *et al.*, 2019). Within CPHIV on ART treatment, decreased FA and increased MD are thought to indicate loss of axonal integrity (Hoare *et al.*, 2014; Musielak and Fine, 2016). Lower FA than controls in the CC, superior and posterior corona radiata (SCR/PCR), frontal and parietal white matter, pre- and postcentral gyrus, and SLF has been found in adolescents stable on ART (J. Li *et al.*, 2015). In pediatric patients with HIV-mediated white matter damage regions of increased RD and decreased AD are reported (Hoare, Fouche, Phillips, John A Joska, *et al.*, 2015).

In cross sectional analyses of our early-treated cohort of CPHIV at ages 5 and 7 years, white matter alterations in the inferior and/or superior longitudinal fasciculi (ILF/SLF), inferior fronto-occipital fasciculus (IFOF), forceps minor, anterior thalamic radiation (ATR), uncinate fasciculus (UF) and corticospinal tract (CST) were previously reported (Ackermann *et al.*, 2016; Jankiewicz *et al.*, 2017). While deficits in the UF were seen only at age 5 years and those in the ATR only at age 7 years, all other tracts demonstrated deficits at both ages. Consistent with these observations Yadav *et al.*, reported similar regional white matter alterations (Yadav *et al.*, 2020b). More recent work using voxelwise analysis to investigate white matter outcomes in perinatally infected adolescents and youth found significant higher AD, RD, and MD in CPHIV compared with CHU. At follow-up, voxel-wise analysis showed significant lower FA, and significant higher MD, AD and, RD (van den Hof *et al.*, 2021). Lower global FA and higher global MD and RD were reported in a cross-sectional analysis of PHIV adolescents matched for age, sex, ethnicity, socioeconomic status, and adoption status (van Genderen *et al.*, 2022). Tractographic analysis in our cohort at age 7 years found altered WM integrity in the somatosensory, salience, default mode, and motor networks of CPHIV compared with CHU. The superior temporal cortex, superior frontal cortex, and putamen were affected in all four networks and have also been reported to demonstrate morphological alterations in the same cohort (Madzime *et al.*, 2021).

2.4.2. HIV-related effects on brain organization

To our knowledge, two studies have used a network approach to examine structural organization in CHPIV. Both studies investigating structural covariance networks of PHIV children and adolescents

report alterations in focal gray matter volumes affecting node and network properties, particularly, shifts in hubs (Li *et al.*, 2018; Yadav *et al.*, 2018), suggesting HIV may influence information transfer.

2.4.3. Association of DTI measures with clinical outcomes

Studies have also reported associations between DTI measurements of children and adolescents living with HIV and clinical measures. DTI measurements in children and adolescents reported correlations between regional alterations and past disease severity (nadir CD4%, and peak viral loads) (Uban *et al.*, 2015). Regional white matter alterations have been linked to both HIV viral load and past disease severity, as reflected by nadir CD4 lymphocyte count (CD4) or percentage (CD4%), and peak viral loads (Cohen *et al.*, 2015a; Uban *et al.*, 2015). In adolescents with perinatal infection who initiated ART when clinically indicated, FA values were negatively correlated with the duration of ART but positively associated with age at ART initiation in the right and left frontal white matter (Li *et al.*, 2015). The authors posit that earlier and longer HIV treatment may be due to more virulent strains having a greater impact on white matter development. Neuronal damage, as reflected by decreased FA, was associated with being on second-line combination ART (cART), low hemoglobin, and younger age in the fornix, cerebellar peduncles, fronto-occipital fasciculus, and the cingulum. Children with increased MD, reflecting neuronal damage, in the corpus callosum, fornix, fronto-occipital fasciculus, and superior longitudinal fasciculus were younger, had reduced albumin and hemoglobin, increased total protein, and increased viral load (Hoare, Fouche, Phillips, Joska, *et al.*, 2015).

2.4.4. Associations of DTI measures with neuropsychological outcomes

Associations with cognitive performance are also reported in children and adolescents living with HIV. Higher MD has been associated with lower IQ, lower digit span, and poorer motivation, a lower FA with lower digit span as well as increased anger and disruptive behavior (Cohen *et al.*, 2015; Hoare *et al.*, 2018). Among CPHIV at age 10 years, high-sensitive C-reactive protein (hs-CRP), a marker of systemic inflammation was associated with neurocognitive impairment in the general intelligence, visual spatial acuity and executive function domains. In addition, whole brain MD increased with higher hs-CRP values (Hoare *et al.*, 2020). Within our cohort, negative correlations between visual perception and RD in the right SLF and left ILF were reported at age 5 using VWA (Ackermann *et al.*, 2020). However, at age 7 we reported no associations between neuropsychological outcomes and tractography outcomes within resting state networks as well as VWA (Madzime *et al.*, 2021; unpublished analysis). These differences could be due to methodological and/or age differences. Taken together, these findings suggest the possibility that poor white matter integrity and inflammatory mechanisms may contribute to some cognitive deficits in CPHIV despite ART.

However, the few studies to date that have combined both DTI and neurocognitive outcomes use different methods and cognitive outcomes making it difficult to draw specific conclusions.

2.4.5. HIV-exposure effect on DTI measures

To date, four studies have used DTI to study the potential influence of HIV/ART exposure in uninfected infants and children. Tran et al. (2016) reported a region of higher mean FA in the middle cerebellar peduncles in CHEU neonates compared to neonates who are HIV-unexposed and uninfected (Tran *et al.*, 2016). In contrast, a 2015 study of CHEU and children who are HIV-unexposed and uninfected (CHUU) aged 5 to 15 years found no group differences (Jahanshad *et al.*, 2015), while a 2020 study reported regions of lower FA and higher/lower MD in a small number of 10- to 13-year-old CHEU compared to their CHUU peers (Yadav *et al.*, 2020b). The authors posit that ART exposure may affect the maturing brain and consequently their cognitive function. In our cohort, we previously reported regions of lower MD bilaterally in the CST and higher FA in the right posterior corona radiata in CHEU compared to CHUU at age 7 (Jankiewicz *et al.*, 2017). In addition, higher FA in CHEU compared to CHUU was reported in the visual, posterior default mode, and motor networks. Higher FA is indicative of higher white matter integrity (Madzime *et al.*, 2021).

III. Ongoing white matter alterations in children living with HIV are associated with early immune compromise: a DTI study at 9 years.

3.1. Introduction

In the background, we have established that changes in white matter tissue structure due to HIV infection lead to altered diffusion properties (Neil *et al.*, 2002; Alexander *et al.*, 2007) that can be quantified using DTI. Measures such as FA, MD, AD and RD characterize axonal and myelin properties as well as the components of the extracellular matrix between them (Beaulieu, 2002a; Song *et al.*, 2002; Tae *et al.*, 2018). Previous DTI studies in pediatric populations living with HIV on ART have shown global and localized FA reductions and/or MD increases compared to their uninfected counterparts. Implicated regions include the CC, cerebellar peduncles, fornix, SCR and PCR, frontal and parietal white matter, pre- and postcentral gyrus, superior fronto-occipital fasciculus, and SLF (Hoare *et al.*, 2012, 2018; Hoare, Fouche, Phillips, Joska, *et al.*, 2015; Li *et al.*, 2015; Sarma *et al.*, 2019). Within CPHIV on ART treatment, decreased FA and increased MD are thought to indicate loss of axonal integrity (Hoare *et al.*, 2013; Musielak and Fine, 2015).

A few studies have reported associations of clinical measures with DTI measurements in children and adolescents living with HIV. Specifically, regional white matter alterations have been linked to both HIV viral load and past disease severity, as reflected by nadir CD4 lymphocyte count (CD4) or percentage (CD4%), and peak viral loads (Cohen *et al.*, 2015a; Uban *et al.*, 2015). In adolescents with perinatal infection who initiated ART when clinically indicated, FA values were negatively correlated with the duration of ART but positively associated with age at ART initiation in the right and left frontal white matter (Li *et al.*, 2015).

In previous cross-sectional analyses of the early-treated CHER cohort of CPHIV at ages 5 and 7 years, white matter alterations were evident in the ILF/SLF, IFOF, forceps minor, ATR, UF, CST or SCR and cingulum (Ackermann *et al.*, 2016, 2020; Janckiewicz *et al.*, 2017; Madzime *et al.*, 2021). While deficits in the UF were seen only at age 5 years and those in the ATR and cingulum only at age 7 years, all other tracts demonstrated deficits at both ages.

Among CHEU, studies using DTI have reported small regional abnormalities. None of these studies have examined associations with clinical variables, since these are rarely examined in children who are uninfected. Work investigating HIV/ART exposure effects in our cohort reported regions of lower MD bilaterally in the CST and higher FA in the right posterior corona radiata in CHEU compared to CHUU at age 7 (Janckiewicz *et al.*, 2017). Additional regions of significantly higher FA and/or lower RD were reported in the connections of the cingulum (some of them interhemispheric)

and, in the left F. major and SLF of CHEU using tractography at age 7 years in CHEU compared to CHUU (Madzime *et al.*, 2021).

In order to understand the ongoing development of white matter in this cohort, we present a follow up DTI study. This chapter contains VWA performed in the same manner as at 5 and 7 years of age. We investigate voxelwise group differences in MD, FA, AD and RD in CPHIV compared to CHU, and CHEU vs. CHUU. We hypothesize ongoing white matter abnormalities at age 9 years in the ILF/SLF, IFOF, forceps minor, ATR, and SCR in CPHIV on ART, and the CST and posterior corona radiata in CHEU. To better understand to possible mechanism contributing to HIV-related group differences, we include associations of immune health and treatment variables with DTI measures in affected regions.

3.2. Methods

3.2.1. Participants

Participants were 72 CPHIV and 53 CHU (mean age $\pm$ standard deviation (SD) = 9.4 ± 0.4 yr). The CPHIV came from Children with HIV Early antiRetroviral (CHER) trial (Violari et al., 2008; Cotton et al., 2013) and randomized into treatment arms based on CD4 percentage (CD4%) as described in section 1.2. CHU were recruited from the community and a vaccine study (Mahdi et al., 2010) running concurrently with the CHER trial. This group includes both CHEU and CHUU (27 CHEU, 26 CHUU).

3.2.2. Image Acquisition

A 3 Tesla Skyra MRI scanner (Siemens, Erlangen, Germany) was used to image children without sedation at the Cape Universities Body Imaging Centre (CUBIC) located at Groote Schuur Hospital, adjacent to the University of Cape Town Faculty of Health Sciences. Study protocols were undertaken with the approval of the Human Research Ethics Committees of the Faculties of Health Sciences of both the Universities of Cape Town and Stellenbosch. Written informed consent and oral assent was provided by parents/guardians and participating children, respectively.

Structural T1-weighted (T1w) images were acquired in the sagittal orientation using a multiecho magnetization-prepared rapid gradient echo (MEMPRAGE) sequence (van der Kouwe et al., 2008) (voxel size = $1.0 \times 1.0 \times 1.0$ mm³, FOV = 224 mm², 176 x 1.0 mm sagittal slices, TR = 2530 ms, TI = 1100ms, TEs = 1.69/3.54/5.39/7.24 ms, flip angle = 7°, GRAPPA factor 2), and two DTI sets with opposite phase encodings (anterior-posterior (AP) and posterior-anterior PA)) using a twice-refocused spin echo sequence (voxel size = $2.0 \times 2.0 \times 2.0$ mm³, matrix size = $122 \times 122 \times 74$, FOV = $244 \times 244 \times 148$ mm³, TR/TE = 9800/92 ms, 30 non-collinear gradient directions with diffusion weighting (DW) factor $b = 1000$ s mm⁻², and 5 non-DW $b = 0$ s mm⁻² (b_0) acquisitions).

3.2.3. Image Processing

Structural and DW images were converted from DICOM to NiFTi format using AFNI's *dcm2nii_x* tool for processing in TORTOISE v.3.1.4 (Pierpaoli et al., 2010; Irfanoglu et al., 2015). To obtain a TORTOISE-compatible T2-weighted (T2w)-like contrast for co-registration to the b_0 image during distortion correction (Irfanoglu et al., 2015), the inversion-of-the-relative-contrast-of-tissues (IRCT) method was applied to the T1w images from each subject. DTI artifacts that may affect the DTI intensity read out and ways to correct them are discussed in section 2.2.6. We implemented the

following retrospective techniques to correct for motion and eddy current distortions: Any DW volumes demonstrating visible motion-induced distortions or signal drop-out were discarded from both AP and PA acquisitions. The optimal number of DW and non-DW volumes is characterized by parameter $r = (\text{number of } b_0\text{'s})/(\text{number of } b_0\text{'s} + \text{AP/PA directions})$ with an optimal value for fiber tracking in range of 0.1-0.2, (Alexander and Barker, 2005; Mukherjee *et al.*, 2008). On average in our data set, 3 b_0 images and 28 AP and PA directions (ratio, $r=0.10$) were retained for processing. Correction for motion and eddy current distortion involved affine registration to our T2w-like image using DIFF_PREP. EPI distortion correction was performed in DR-BUDDI using the 2 opposite phase encoding directions (AP and PA), whereafter these were combined. Overall, 25 subjects (14 CPHIV, 11 CHU) were excluded solely due to motion. Summary statistics for subjects who were retained is presented in Table 1.

After pre-processing, the AFNI *3dDWItoDT* module (Cox, 1996) was used to fit diffusion tensors nonlinearly and calculate DTI parameters (FA, MD, AD and RD) in each voxel. To achieve spatial alignment between the resulting diffusion parameter maps of the different subjects, we used *3dQwarp* and *3dNwarpApply* in AFNI to first register each subject's FSL-skull-stripped T1w image to a 2 mm isotropic Haskins pediatric template (Molfese *et al.*, 2011) and then resample it into MNI space (Evans *et al.*, 1993). The resulting warping transformation of each subject was then applied to his/her diffusion parameter maps. Regional atrophy that may occur due HIV infection (David *et al.*, 2023; George *et al.*, 2009; Sakai *et al.*, 2021) can be corrected by this nonlinear registration of subject tensor maps to a template. Subject-specific white matter masks (S_i) were generated by thresholding each participant's FA map at $FA \geq 0.2$. From the intersection of these masks ($S_1 \cap S_2 \cap S_3 \dots \cap S_n$), we generated a sample white matter mask composed only of voxels classified as white matter in all subjects (Mori and van Zijl, 2002; Descoteaux *et al.*, 2009). Analysis within this "WM skeleton" accounts for residual misalignments and makes the comparison of FA and MD values between groups reliable (Smith *et al.*, 2006).

Table 3.1. Demographic and clinical characteristics for participants who provided usable data. The CHU group comprises both children perinatally HIV-exposed, but uninfected (CHEU) and children who are HIV-unexposed and uninfected (CHUU), and the CPHIV group children who received ART either before or after 12 weeks of age. Data are presented for groups combined and split by sub-groups.

Demographics	Children who are HIV Uninfected (CHU)					
	All CHU		CHEU		CHUU	
Number of subjects (n female, % female)	42 (19, 45.2%)		20 (7, 35%)		22 (12, 54.5%)	
Age at scan $\pm$ sd (yr)	9.51 $\pm$ 0.49		9.49 $\pm$ 0.47		9.53 $\pm$ 0.51	
	Children with perinatally acquired HIV (CPHIV)					
	All CPHIV		ART before 12 w		ART after 12 w	
Number of subjects (n female, % female)	58 (28, 48.3%)		45 (21, 46.7%)		13 (7, 53.8%)	
Age at scan $\pm$ sd (yr)	9.29 $\pm$ 0.25		9.30 $\pm$ 0.25		9.27 $\pm$ 0.29	
Clinical and Treatment measures	All CPHIV		ART before 12 w		ART after 12 w	
	mean	SD	mean	SD	mean	SD
Clinical Measures at enrolment						
Enrolment CD4 (cells/ μ L)	1900	781	1857	808	2052	688
Enrolment CD4%	35.2	9.6	34.2	9.5	38.8	9.2
Enrolment CD8 (cells/ μ L) ¹	1640	1130	1624	1153	1695	1094
Enrolment CD8% ¹	29.4	10.1	29.4	9.7	29.2	11.7
Enrolment CD4/CD8 ¹	1.42	0.69	1.39	0.68	1.52	0.74
Clinical Measures at scan ^{2,3}						
CD4 at scan (cells/ μ L) ^{2,3}	1091	427	1031	377	1286	531
CD4% at scan ^{2,3}	38.8	6.9	38.1	6.9	41.1	6.9
Treatment variables						
Age at ART initiation (w) Median [IQR]	9.2	[7.4; 12.0]	8.1	[7.3; 9.7]	37.0	[23.9; 41.4]
Age at 1 st VL suppression (w) ⁴ Median [IQR]	46.9	[32.9; 71.0]	34.4	[32.1; 50.4]	73.9	[48.3; 109.6]
Number ART interrupted, n (%)	-	-	36 (80%)	-	0	-
Age at ART interruption (w) ⁵ Median [IQR]	-	-	51.4	[48.1; 102.9]	N/A	N/A
Duration of interruption (w) ⁵ Median [IQR]	-	-	35.3	[24.9; 52.3]	N/A	N/A
Measures of Disease Severity						
Nadir CD4 (cells/ μ L) Median [IQR]	637	[516; 724]	645	[534; 720]	480	[340; 817]
Age at nadir CD4 (w) Median [IQR]	225.6	[78.3; 444.9]	266.6	[93.9; 451.4]	41.1	[25.7; 332.9]
Nadir CD4%	20.6	5.8	20.5	5.7	21.0	6.3
Age at nadir CD4% (w) Median [IQR]	74.0	[38.6; 128.8]	91.3	[58.7; 135.7]	29.7	[21.9; 46.7]
HIVE diagnoses, n (%)		-		-		-

SD standard deviation, w weeks, IQR interquartile range, VL viral load

Mean (SD) reported for variables with a normal distribution and skewed data are presented as Median [IQR]

¹CD8 data missing for 2 children in the early-treated group (ART before 12 w); ²Data collected within 4 months of scan in all except 3 children; ³data missing for 3 children in the early-treated group; ⁴Suppression defined as viral load <400 copies/mL; ⁵Only for the 36 children in the early-treated group in whom treatment was interrupted.

3.2.4. Voxelwise Analysis

Group differences in FA and MD were examined within each voxel in our sample white matter mask. For these two metrics, voxel-based comparisons were performed with the FSL module *randomise*, uncorrected for multiple comparisons, using a general linear model that includes sex and age at scan as possible confounders (Winkler *et al.*, 2014). Additionally, corresponding AD and RD group comparisons were then carried out within voxelwise intensity masks that survive cluster wise correction. Group comparisons included the following: CPHIV vs. CHU, CHEU vs. CHUU, and within the CPHIV group, between children who initiated ART before and after 12 weeks. Monte-Carlo simulations (N=5000) were performed using AFNI's *3dClustSim* to threshold diffusion maps to estimate the distribution of significance values picked up due to chance (Type-1 error) (Forman *et al.*, 1995, Nichols and Holmes, 2002). A Gaussian mono-exponential mixed model that best describes the smoothness of the data was estimated in AFNI using the (spatial) autocorrelation function (ACF) method implemented by the *3dFWHMx* program (Cox *et al.*, 2017). These parameters were then used in *3dClustSim* to calculate more accurate cluster size thresholds ($C = C(p, \alpha)$) (Cox, 2017). Cluster size thresholds were based on a voxelwise threshold $p_{th} = 0.005$ and whole brain family-wise error (FWE) $\alpha = 0.05$ (nearest neighbors NN = 3, two-sided voxelwise thresholding). Cluster size thresholds of 171 mm³, 183 mm³ and 193 mm³ were found for the CPHIV vs. CHU, CHEU vs. CHUU, and ART before 12 w vs. ART after 12 w comparisons, respectively. For each subject, cluster averages of diffusion parameters (FA/MD, AD, RD) were extracted from clusters showing significant group differences, and group means reported. We also performed two-tailed students t-tests to determine whether observed FA/MD differences are attributable to differences in AD, RD, or both. MNI space spatial coordinates, JHU ICBM-DTI-81 White-Matter Labels and JHU White-Matter Tractography Atlas (Mori *et al.*, 2005) were used to identify the white matter tracts in which clusters of significant differences are located. To determine spatial correspondence between intensities at the different ages, clusters were represented as either spheres (5 years) and cubes (7 years). Spheres and cubes of 5mm radius were generated using *3dUndump* by specifying the peak or center of gravity (COG) coordinates of the cluster within the MNI template space.

3.2.5. Clinical associations

To elucidate mechanisms underlying HIV-related white matter alterations among CPHIV, we examined associations of clinical measures with the mean DTI parameters (FA or MD, AD and RD) of each cluster where we found significant group differences. Depending on normality, we used either Pearson or Spearman correlation tests to examine associations of DTI parameters with measures of early immune health (CD4% at study enrolment), immune health around age 9 years (CD4% at scan), indicators of disease severity and timing (nadir CD4% and the age at which this occurred), and

treatment-related variables (ages at ART initiation and first VL suppression, defined as VL < 400 copies/mL).

3.2.6. Correction for multiple comparisons

The risk of type 1 error is increased in VWA analysis. In this thesis, results from the voxelwise analysis were FWE-corrected for multiple comparisons as described in section 3.2.4. The conservative Bonferroni-correction for multiple comparisons corrections were employed this analysis. We did not perform correction for multiple testing in partial correlations of clinical and treatment-related variables with DTI parameters as this work was exploratory.

3.3. Results

3.3.1. Voxelwise analysis

We present data from 58 CPHIV (ART before 12 weeks = 45, ART after 12 weeks = 13) and 42 CHU (CHEU = 20, CHUU = 22). Compared to their uninfected peers, vertically infected children on ART present with white matter regions of significantly lower FA and higher MD, mostly attributable to increases in both AD and RD. We found regions bilaterally in the superior corona radiata (SCR), IFOF and forceps minor (F. minor). We also found one cluster in each of the left ATR, left SLF and right forceps major (F. major) (Table 3.2; Figure 3.1). We did not find any regions showing differences in either FA or MD in the CHEU vs. CHUU comparison, nor the ART before and after 12 weeks comparison.

Table 3.2 | Peak and center of gravity (COG) coordinates (in MNI space) of clusters showing lower FA or higher MD and corresponding changes AD and RD in CPHIV than CHU.

Cluster Location		Size (mm ³)	FA		AD (10 ⁻³ mm ² s ⁻¹)			RD (10 ⁻³ mm ² s ⁻¹)		
Peak (mm)	COG (mm)		CHU	CPHIV	CHU	CPHIV	<i>p</i>	CHU	CPHIV	<i>p</i>
L Inferior fronto-occipital fasciculus (-36; -17; -8) (-34.4; -16.3; -5.41)		212	0.507 (0.007)	0.460 (0.006)	1.166 (0.010)	1.159 (0.007)	0.615	0.518 (0.009)	0.570 (0.007)	<0.001
Cluster Location		Size (mm ³)	MD (10 ⁻³ mm ² s ⁻¹)		AD (10 ⁻³ mm ² s ⁻¹)			RD (10 ⁻³ mm ² s ⁻¹)		
Peak (mm)	COG (mm)		CHU	CPHIV	CHU	CPHIV	<i>p</i>	CHU	CPHIV	<i>p</i>
L Inferior fronto-occipital fasciculus (-41, -7, -15) (-34, -31.4, 3.28)		2076	0.749 (0.005)	0.782 (0.003)	1.234 (0.006)	1.261 (0.005)	0.001	0.506 (0.005)	0.542 (0.004)	<0.001
R Inferior fronto-occipital fasciculus (39, -27, -6) (5.9, -24.1, -0.145)		422	0.786 (0.005)	0.819 (0.004)	1.225 (0.007)	1.252 (0.006)	0.006	0.567 (0.006)	0.602 (0.005)	<0.001
L Superior corona radiata (-23, -26, 31) (-21.4, -15.5, 37.6)		911	0.708 (0.004)	0.730 (0.003)	1.093 (0.006)	1.125 (0.006)	<0.001	0.515 (0.004)	0.532 (0.004)	0.005
R Superior corona radiata (17, 19, 27) (19, -7.71, 36.7)		644	0.723 (0.004)	0.748 (0.004)	1.112 (0.007)	1.141 (0.006)	0.003	0.529 (0.005)	0.552 (0.005)	0.001
R Forceps major (34, -52, 0) (32.8, -50.2, 10.6)		624	0.774 (0.005)	0.808 (0.004)	1.272 (0.009)	1.313 (0.006)	<0.001	0.525 (0.006)	0.556 (0.005)	<0.000
L Forceps minor (-18, 49, 4) (-16.7, 50.9, 3.22)		204	0.754 (0.005)	0.781 (0.005)	1.184 (0.008)	1.207 (0.010)	0.087	0.540 (0.007)	0.568 (0.008)	0.006
R Forceps minor (16, 45, 15) (15.5, 47.2, 16.7)		195	0.736 (0.004)	0.759 (0.004)	1.147 (0.009)	1.176 (0.008)	0.018	0.531 (0.006)	0.551 (0.006)	0.022
L Anterior thalamic radiations (-25, 8, 17) (-24, 1.52, 23.8)		293	0.680 (0.004)	0.701 (0.003)	1.046 (0.007)	1.071 (0.006)	0.009	0.497 (0.004)	0.517 (0.003)	<0.001
L Superior longitudinal fasciculus (-51, -10, 24) (-40.1, -11.2, 28.1)		227	0.718 (0.005)	0.741 (0.004)	1.058 (0.007)	1.081 (0.005)	0.008	0.548 (0.005)	0.572 (0.005)	0.002

Values are group means (SE) of FA and MD, as well as AD and RD, for each cluster; *p*-values are from 2-tailed t-tests; L left; R right.

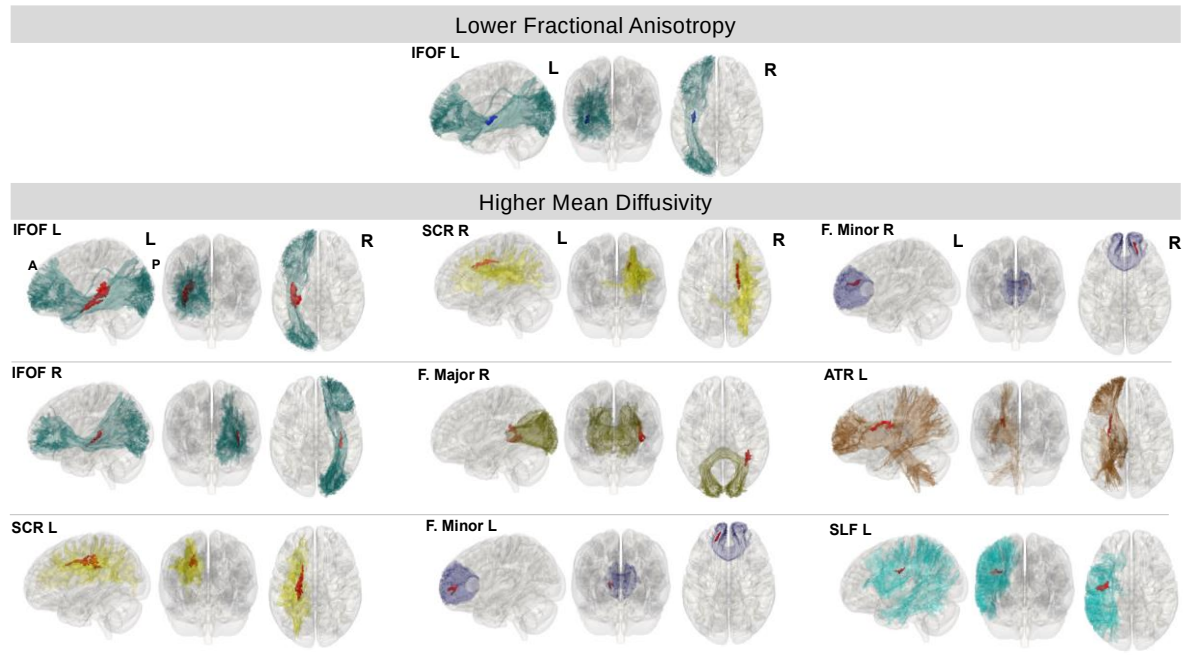


Fig 3.1. Clusters showing either lower FA (in blue; top row) or higher MD (in red) in CPHIV compared to CHU. The clusters were overlaid on masks of the corresponding tracts (JHU White-Matter Tractography Atlas and JHU ICBM-DTI-81 White-Matter Labels). (IFOF: inferior fronto-occipital fasciculus; SCR: superior corona radiata; F. major: forceps major; F. minor: forceps minor; ATR: anterior thalamic radiation; SLF: superior longitudinal fasciculus; L left; R right).

3.3.2. Associations with and clinical/treatment-related variables

Among CPHIV, we do not find any associations (at $p < 0.05$) of DTI parameters in any of the clusters showing HIV-related changes with the clinical measures of immune health examined (CD4% at enrolment, CD4% at scan, nadir CD4%), age at ART initiation, nor age at nadir CD4%.

Few associations were found between DTI parameters and age at 1st VL suppression. Increasing age at VL suppression was associated with higher MD (Spearman $r = 0.27$, $p=0.04$) and RD (Spearman $r = 0.28$, $p=0.04$) in the left SLF, with higher MD in the right F. major (Spearman $r = 0.26$, $p=0.05$), and with higher RD in the left IFOF (Spearman $r = 0.27$, $p=0.04$) (Fig. 3.2).

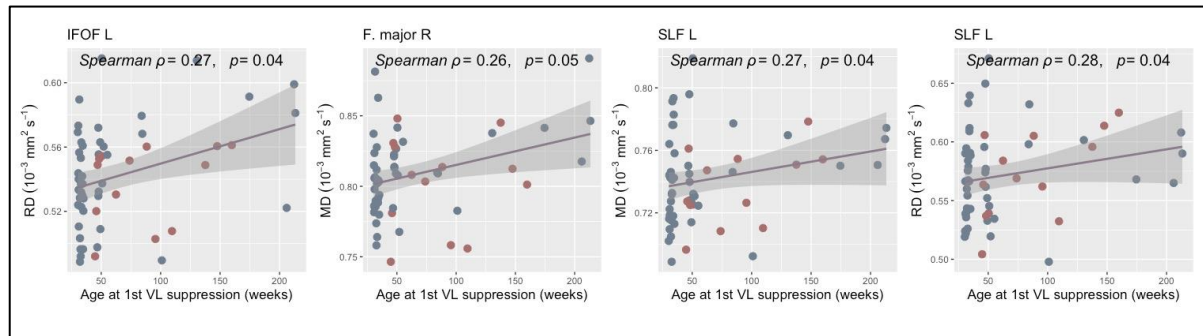


Fig 3.2. Plots showing associations (significant at $p < 0.05$) between DTI parameters averaged across the cluster and age at first viral load suppression. Data points are color coded by age at ART initiation (grey: ART before 12 wks; red: ART after 12 wks). IFOF: inferior fronto-occipital fasciculus; F. major: Forceps major; SLF: superior longitudinal fasciculus; L left; R right.

3.4. Discussion

In this follow-on study of a cohort of CPHIV who initiated ART early and were previously imaged at 5 and 7 years, we find ongoing white matter microstructural alterations in five white matter tracts previously implicated (bilaterally in the IFOF, F. minor and SCR, L SLF and L ATR), and new damage in the R F. major. Among CPHIV, we did not find associations of DTI parameters in any of the clusters showing HIV-related changes with clinical measures of immune health, age at ART initiation, nor age at nadir CD4%. However, age at 1st VL suppression was associated with MD in the L SLF, R forceps major and L IFOF clusters, while AD in the L SLF, RD in the L ATR, and MD in both the L forceps minor and L ATR clusters were higher in children in whom ART had been interrupted compared to those on continuous treatment. These findings indicate that delayed VL suppression and treatment interruption contribute, in part, to HIV-related white matter abnormalities in specific regions at age 9.

Contrary to our results at 7 years, we did not find regions showing exposure-related differences among CHU. The absence of differences at age 9 years suggests that the reported differences at age 7 represented developmental delays that have subsequently resolved.

3.4.1. Ongoing white matter alterations in CPHIV

Table 6.5 in the appendix summarizes the findings from previous VWA studies in this cohort (5 and 7 years) with the current results, in order to observe overlapping cluster regions. The results presented in this chapter demonstrate regions that likely reflect persistent white matter damage reported from age 5 or 7 years, as well as new abnormalities that may represent developmental delays or damage. There is a great deal of overlap in the spatial locations of HIV-related VWA intensities between 7 and 9 years. Particularly, clusters in the tracts connecting the fronto-temporoparietal regions such as IFOF, ILF, SLF, and ATR, where peak and/or center of gravity coordinates occupied relatively similar positions on these tracts. The largest cluster (L IFOF; Size 2076 mm³) is the most representative cluster occupying a space across the temporal and parietal lobes. Similarly, clusters in the projection tracts (i.e., CST/SCR) were detected at ages 7 and 9. Clusters in the forceps minor were seen from age 5 through 9.

Regions with HIV-related differences at 5, 7 and 9 years

The current findings overlap with previously reported regions of white matter abnormalities in this cohort at age 5, particularly in the left SLF and ATR and in clusters bilaterally in the IFOF, F. minor and SCR. At age 5, we reported higher MD in the left IFOF. At ages 7 and 9, we find a region of decreased mean FA in the left- IFOF. Decreased FA in this tract was associated with higher RD and no change in AD which may reflect dysmyelination (Song *et al.*, 2002; Winklewski *et al.*, 2018). We

also find a region of increased mean MD bilaterally in the IFOF. The IFOF is a large and complex tract connecting the parietal and occipital lobes to the frontal lobes. Development of the IFOF, marked by white matter diffusivity changes, continues into adulthood which makes this fiber bundle vulnerable to disruption at 9 years (Lebel and Beaulieu, 2011). While the IFOF is primarily associated with semantic language processing and transmission (Motomura *et al.*, 2014) more recent studies have demonstrated that it carries information between the salience network to the executive control network and is likely to be involved in goal-oriented behavior (Waller *et al.*, 2017; Conner *et al.*, 2018). This is in congruence with an rs-fMRI study in our cohort at age 7, where HIV related alterations were observed in the salience and executive control networks (Toich *et al.*, 2018). Research has shown that there is an inherent relationship between structure and function; correlations between DTI and fMRI measures show white matter microstructure plays a role in mediating brain function through linking brain regions (Tang and Bassett, 2018).

We found a clusters of increased MD in the left- and right forceps minor present at ages 5 and 7 (C. Ackermann *et al.*, 2016; Jankiewicz *et al.*, 2017). The forceps minor forms part of the radiata of the CC connecting the lateral and medial surfaces of the frontal lobe. The forceps minor may relate to executive function (Mamiya, Richards and Kuhl, 2018). Post-mortem studies reveal myelination occurs earlier and progresses faster in the occipital regions than in posterior parietal, frontal and temporal white matter (Kinney *et al.*, 1988). As at age 7, increased MD in this tract was associated with increased RD with no change in AD which may reflect impairments in myelination in 9-year-olds. However, we found regions of higher MD, AD, and RD in the forceps minor of CPHIV 5-year-olds, pointing to both dys- and/or demyelination and axonal damage. Interestingly, a recent study reported an inverse relationship between nadir CD4% and AD in the forceps minor in CPHIV adolescents (Uban *et al.*, 2015) pointing to disease related damage.

Regions with HIV-related differences at 7 and 9 years

In our cohort at age 7 and 9, DTI VWA results revealed persistent alterations in the IFOF, CST/SCR, SLF and F. minor. We also found alterations in several clusters bilaterally in the SCR and the left ATR previously seen at age 7 but not present at 5 years (Ackerman *et al.*, 2016; Jankiewicz *et al.*, 2017). At 7 years, we found HIV-related MD increases in the left ATR, with this cluster overlapping regions in the SCR (Jankiewicz *et al.*, 2017). Similarly, we found a region of increased MD in the left SCR of CPHIV at 9 years compared to CHU that occupies the relative space as the region in the left ATR reported at 7 years.

Regions with HIV-related differences at 5 and 9 years

An earlier study of this cohort at age 5 years identified clusters in the right CST with reduced FA in CPHIV compared to CHU (Ackermann *et al.*, 2016; Jankiewicz *et al.*, 2017). The CST is a white

matter motor pathway starting at the motor cortex and synapses in the spinal cord to connect to lower motor neurons that innervate special muscles for movement (Brackmann and Fetterman, 2007). The CST spreads to fill the cortex with radiations known as the SCR which contain fibers that connect the thalamus, the cortex and subcortical gray matter. The CST and SCR play key roles in cognitive, perceptual and motor systems domains in the cortex for a more refined execution of planned movement (Gage *et al.*, 2018). Crucial changes in the CST start as early as 24 weeks as CST axons fill the length of the cervical spinal cord followed by gray matter innervation (Eyre *et al.*, 2000; Eyre, 2007). Further, the CST projection pattern is refined soon after birth (Eyre *et al.*, 2001). This period of CST maturation coincides with perinatal HIV/ART exposure in CPHIV and makes this fiber bundle particularly vulnerable to disruption. To our knowledge no other studies report alterations in the CST (Hoare *et al.*, 2014; Musielak and Fine, 2016; Van den Hof *et al.*, 2019).

As at age 5 (C. Ackermann *et al.*, 2016) we report a cluster of increased MD in the left-SLF. Similarly other studies have reported alterations in the SLF characterized by increased MD and lower FA. ART-naïve children present with higher MD in the SLF and CC in infected children stable on little to no ART compared to healthy controls (Hoare *et al.*, 2012). The SLF connects the frontal, occipital, parietal, and temporal lobes. It is well described that the primary functional role is transmission of speech and language (Kamali *et al.*, 2015; Conner *et al.*, 2018).

In the CPHIV vs. CHU comparison at 5 years we found a cluster of reduced FA in the left frontal F. minor (Ackermann *et al.*, 2016). Increased MD was also recorded in the left-frontal region of the F. minor in CPHIV at 9 years. However, we did not report group effects within this tract at 7 years using VWA (Jankiewicz *et al.*, 2017). Interestingly, using DTI tractography at 7 years we identified a handful of tracts in the left forceps minor with reduced FA in the salience and motor resting state networks (RSN) and increased MD in the salience and default mode networks of the same children (Madzime *et al.*, 2020). A potential reason for the difference in methodological outcomes could be that VWA analysis loses statistical power due to stringent multiple comparison corrections at the voxel level, and VWA only allows for the detection of clusters of reduced volume due to stringent thresholding and registration steps that are characteristic of this method (Liu *et al.*, 2009; Smith *et al.*, 2006).

Regions with HIV-related differences at 9 years

We report new clusters in the forceps major at age 9 suggesting white matter vulnerabilities to HIV continue between scanning sessions as the cohort matures.

Coherent white matter fibers are tightly packed with myelin and thus demonstrate anisotropic water diffusion. Myelin and axonal loss lead to reduced anisotropy. This results in increased perpendicular

diffusion (higher RD), increased overall diffusivity (higher MD), and decreased tissue directionality (lower FA and/or AD). At 9 years, alterations were predominantly characterized by increases in MD and were attributed to above-normal AD and RD. Studies have reported age-related AD increases in typical development to be associated with axonal pruning (Bockhorst *et al.*, 2008). On the other hand, higher RD in white matter is associated with complications in myelination (Song *et al.*, 2002). However, increased RD and AD may also be associated with extra-axonal water content (Wang *et al.*, 2011, 2014; Chiang *et al.*, 2014). At ages 5 and 7, we reported reduced FA or higher MD that were largely attributed to higher RD in the L CST, pointing to chronic HIV related white matter injury associated with myelin deformities and axon degradation in this tract (Ackermann *et al.*, 2016). Similarly, additional regions of lower FA or higher MD with corresponding increases in RD were observed in the left and right SCR, left ATR, right F. minor and left IFOF AT 7 years (Jankiewicz *et al.*, 2017). In addition, we reported neurometabolite abnormalities in CPHIV at age 9 years in the basal ganglia pointing to cell loss (Robertson *et al.*, 2018). At age 9 years we only observe FA and MD alterations associated with increases in both AD and RD. We speculate that in longstanding HIV infection, overall diffusivity increases within fibers due to an increase in extra-axonal space. As a result, fewer, hypomyelinated axons pack loosely in the extra-axonal space (Naismith *et al.*, 2010; Aung, Mar and Benzinger, 2013; Winklewski *et al.*, 2018). Hence, the present study found fewer differences in FA in these tracts despite significant mean differences in AD between the CPHIV and CHU groups. HIV-mediated disruptions in white matter structures at the onset of myelination and throughout maturation may result in long-lasting myelin sheath malformations, axonal and loss in white matter tracts. Differential white matter growth patterns may dictate individual tract vulnerabilities to dys- and or demyelination. Increased MD, AD and RD may reflect HIV-related changes in structural connectivity driven by a combination of altered maturation events. Furthermore, subtle ongoing inflammatory mechanisms are associated with white matter alterations and poorer cognitive outcomes in CPHIV, despite ART and viral suppression (Kapetanovic *et al.*, 2010; Hileman and Funderburg, 2017; Blokhuis *et al.*, 2019; Sarma *et al.*, 2021). Investigating the associations of these inflammatory markers with DTI measures in CPHIV may provide insight on the underlying mechanisms of HIV-related white matter microstructural changes.

3.4.2. Clinical associations with DTI metrics

We explored links between clinical variables and white matter measures within the aforementioned clusters among the CPHIV. As reported at previous ages, we did not find clinical variables associated with the reported clusters. These findings suggest the white matter abnormalities reported may involve more complicated mechanisms than overall immune health.

In this analysis, we did observe associations when we examined specific groups of CPHIV. Younger age at 1st VL suppression was associated with higher AD in the right F. minor, while lower AD was associated with younger ages at 1st VL suppression in the left IFOF and left ATR in children who initiated ART after 12 weeks (Table 3). These results may point to early ART initiation having neuroprotective effects.

Previous neuroimaging work in this cohort also demonstrated associations with immune health in infancy, suggesting long term consequences of early immune health on brain development. At age 5, we reported positive associations between metabolite levels related to neuronal and cellular integrity in the basal ganglia and CD4/CD8 ratio at study enrolment. At age 7 years, we found baseline CD4% and CD4 count to be associated with higher functional connectivity in the basal ganglia, salience, and somatosensory networks (Toich *et al.*, 2018). Our current and previously published results indicate infant immune health has long-term consequences on brain development. Additionally, associations with age at viral suppression suggest early viral suppression provides regional white matter protection.

No corrections for multiple comparisons in computing these correlations were performed as potential statistical relationships between DTI and clinical measures were exploratory to generate new hypotheses for future work (Rothman, 1990; Curtin and Schulz, 1998; Cabin and Mitchell, 2010). Uncorrected *p*-values were used as a measure of the strength of correlation.

3.4.3. ART initiation in CPHIV

A study looking at white matter development in adolescents with perinatally acquired HIV found reduced FA in the frontal white matter to be negatively associated with duration of treatment and positively correlated with age at ART initiation (Li *et al.*, 2015). The authors speculate that while ART is neuroprotective, early and prolonged ART may expose white matter to potential neurotoxicity (Li *et al.*, 2015). However, the adolescents in this study-initiated ART significantly late (50+ months) compared to the children in our cohort.

At an earlier age, we reported lower FA in the left CST of children who initiated ART before 12 weeks compared to children who initiated after 12 weeks. This difference was attributed to early treatment interruption in the before 12 weeks group (Ackermann *et al.*, 2016). At age 7 years no differences were found based on age of treatment initiation (Jankiewicz *et al.*, 2017). As at 7 years, we continue to find no significant group differences between children who initiated ART before and after 12 weeks but all within the first 24 months. These results point to a sustained recovery from neurodevelopmental delays due to art interruption.

Further, we failed to find any significant associations with age at ART initiation. However, among children who initiated ART after 12 weeks, older age at ART initiation was associated with higher RD in the right F. minor and left ATR and higher MD in the left SLF. Interestingly, younger age at ART initiation was associated with higher AD in the right F. minor. Moreover, lower CD4% at enrolment was associated with higher AD in the left ATR. This uncharacteristic result can be attributed to the study design where children who initiated ART after 12 weeks would have had their lowest known CD4% percent earlier due to early ART, losing the power of nadir CD4%, a predictor of neuropsychological impairment (Ellis *et al.*, 2011). However, these results involve a small sample of our cohort, and must be interpreted with caution.

3.4.4. CHUU vs. CHEU

Few studies have looked at white matter development in CHEU. And to date there are no DTI studies have followed up on their CHEU cohorts. Prenatal exposure to HIV in CHEU infants may lead to abnormal white matter microstructural organization (Tran *et al.*, 2016) and subtle deficits in the domains of language cognition and motor function and behavior (Van Rie *et al.*, 2007; Kerr *et al.*, 2014), while significantly older children (~10-year-olds) do not show any exposure differences in FA or MD in the CHUU - CHEU comparison (Jahanshad *et al.*, 2015). At 7 years we reported clusters of higher FA in the posterior corona radiata and CST in CHEU children (Jankiewicz *et al.*, 2017). Contrary to our findings at age 7, we find no clusters of significant FA and MD differences throughout the white matter tracts of CHEU children at 9 years. Our results suggest the findings at 7 years represented delays in white matter development, and that by age 9 years white matter maturation in CHEU children has caught up to their CHUU peers.

These results are similar to a magnetic resonance spectroscopy (MRS) work done in our cohort. An MRS study in the basal ganglia found no exposure effects at age 7, but significant reductions in metabolite levels were reported at age 9 years (Robertson *et al.*, 2018). A follow up study at age 11 years showed the metabolite reductions observed in the basal ganglia had resolved. Interestingly, at 11 years metabolite reductions were reported in white and gray matter voxels (Graham *et al.*, 2020).

Taken together, the MRS and DTI studies in our cohort point to age specific exposure effects representing development delays, not damage.

3.4.5. Limitations and future work

Longitudinal analysis was not performed, which limits the conclusions we can draw regarding the influence of HIV on white matter development. However, the children in this cohort have provided

neuroimaging data well into their teens and have also been monitored for disease response since ~6 weeks-old and are about the same age which allows for cross sectional and longitudinal assessment of neuroimaging correlates of HIV disease. We could not establish the timing and duration of PMTCT in the mothers living with HIV and so there are questions about the homogeneity of the ART-exposure group. White matter diffusivity outcomes in CPHIV and CHEU may be confounded by differences in time related HIV/ART-exposure status, particularly there could be differences between white matter outcomes due to infection and exposure to during prenatal brain maturation and in infancy. No analysis was performed with neurocognitive data or rs-fMRI data, limiting the conclusions we can draw about functional consequences of the presented alterations. However, correlations with neuropsychological scores were reserved for subsequent tractographic analysis and graph theory measures where neuropsychological performance could be mapped to tracts connecting networks of known gray matter regions. Lastly, the clinical measures we studied are inadequate to paint a full picture of the pathophysiological means by which white matter microstructural changes associated with HIV CNS invasion occur. Additional associations with clinical outcomes such as inflammatory mechanisms that modulate a systemic response to HIV infection and their effect on the white matter health may offer new insight. Furthermore, the DTI method applied here cannot resolve the microstructural complexity of dendrites and axons in vivo. As such, we could not distinguish between effects due to direct viral action and indirect effects due to these secondary mechanisms. This, however, presents an opportunity to further investigate the underlying mechanisms of HIV-related white matter microstructural changes.

3.5. Conclusion

At 9 years we report evidence of alterations in similar regions to those found at ages 5 and 7. More specifically, these include two regions in the left CST that extend into the SCR. We also found clusters bilaterally in the IFOF, one cluster in the forceps minor, ATR and an additional cluster in the left SLF. A few of these alterations were associated with delayed viral load suppression because of deferred ART. Furthermore, we report an additional region of increased MD in the right F. Major at 9 years, pointing to progressive white matter insults with age. These results point to the early establishment of localized longstanding and continued HIV/ART related white matter alterations.

These localized white matter alterations were predominantly attributed to increased MD, AD and RD which may reflect HIV-related changes in structural connectivity driven by a combination of altered maturation events, dys- and or demyelination despite evidence of improved tract health. In addition, we report no significant ART exposure related differences between CHEU and CHUU. Regional white matter developmental delay in CHEU resolves at 9 years. Furthermore, differential white matter

growth patterns may dictate individual tract vulnerabilities with age. ART exposure and HIV disease progression.

IV: White matter connectivity and network measures related to working memory in 9-year-old children living with HIV.

4.1. Introduction

The persistence of neurodevelopmental delays and deficits suggests HIV continues to disrupt healthy brain maturation. Studies across modalities have consistently reported alterations involving subcortical, cortical, and white matter regions including but not limited to basal ganglia (Nwosu *et al.*, 2018; Randal *et al.*, 2017), IFOF, ILF, SLF, SCR (Ackermann *et al.*, 2016; Jankiewicz *et al.*, 2017; Madzime *et al.*, 2021) and the CC (Randal *et al.*, 2017). While imaging research provides evidence that HIV infection and exposure influence brain development in the treatment era, the consequences of these alterations are not well understood. In CPHIV, there is consistent evidence of deficit risks in working memory and executive function (Milligan & Cockcroft, 2017; Phillips *et al.*, 2016). Executive function includes many cognitive processes, including working memory. Adolescence is a critical period of development for executive function, which relies on brain integration. There is a need to study the contributions of HIV-related brain organization abnormalities with cognitive deficits in adolescence.

White matter is made up of neuronal axons insulated by oligodendrocytes to form myelin. HIV-1 viral trans-activator of transcription (Tat) protein is toxic to oligodendrocytes leading to myelin damage (Liu *et al.*, 2017). In addition, HIV-infection monocytes and T cells promotes the release of inflammatory cytokines, viral proteins, and excitotoxins which results in an activation and recruitment of macrophages, microglia and astrocytes to the CNS (Hong and Banks, 2015). These factors contribute significantly to the neuroinflammation observed in the CNS (Sarma *et al.*, 2021). Subtle ongoing inflammatory mechanisms are associated with white matter alterations and poorer cognitive outcomes in CPHIV, despite ART and viral suppression (Kapetanovic *et al.*, 2010; Hileman and Funderburg, 2017; Blokhuis *et al.*, 2019; Sarma *et al.*, 2021).

Studies in CPHIV and CHEU report an association between brain microstructural integrity and neurocognitive function (Hoare *et al.*, 2012; Tran *et al.*, 2016; Ackermann *et al.*, 2020; Yadav *et al.*, 2020b). Higher MD has been associated with lower IQ, lower digit span, and lower FA with lower digit span (S Cohen *et al.*, 2015b). The authors attribute these deficits to possible indolent viral replication, prolonged immunosuppression, and irreversible damage to brain tissue before ART administration and ART effects. Higher whole-brain MD was associated with poorer motivation and lower whole-brain FA was associated with increased anger and disruptive behavior (Hoare *et al.*, 2018). Among CPHIV at age 10 years, high-sensitive C-reactive protein (hs-CRP), a marker of systemic inflammation was associated with neurocognitive impairment in the general intelligence, visual spatial acuity and executive function domains. In addition, whole brain MD increased with

higher hs-CRP values (Hoare *et al.*, 2020). However, ART initiation in these cohorts was at the age of approximately 2 years and older. In our cohort where ART initiation was within the first year of life, we observed a negative correlation between visual perception and radial diffusion in the right SLF and left ILF. The authors posit that pivotal maturation outcomes in the SLF and ILF are disrupted in CPHIV at 5 years of age (Ackermann *et al.*, 2020). Taken together, these findings suggest that poor white matter integrity and inflammatory mechanisms underly poorer cognitive performance in CPHIV despite ART.

Among CHEU, significant positive correlations of MD from the right middle temporal with RAKIT exclusion and hidden figure scores was observed, while MD from the right cerebellum showed negative correlation with discs (Yadav *et al.*, 2020b). Exclusion and hidden figure tests measure perceptual reasoning in children while discs are a measure of visuospatial perception and awareness (Bleichrodt, Hoksbergen and Khire, 1999).

However, only a handful of studies have utilized DTI tractography in the context of perinatally acquired HIV. In a study examining the effects of HIV infection in youth, white matter properties of perinatally infected youth were characterized by reduced FA in the right IFOF and left uncinate tracts and increased MD in F minor; and increased streamlines in the left ILF. These diffusivity changes were associated to past disease severity. Lower FA in the right IFOF was associated with peak viral load and lower working memory performance (Uban *et al.*, 2016). Within our cohort of perinatally infected children who initiated ART in infancy, tractography analysis was performed at age 7 years. HIV-related white matter changes were characterized by reductions in FA and increases in MD, both attributed primarily to changes in RD, in the CST, forceps minor, SLF, ATR and cingulum. Interestingly, a few grey matter regions were implicated across functional networks, specifically, seeds in the putamen, superior temporal cortex, and superior frontal cortex were impacted (Madzime *et al.*, 2021). Alterations are reported in specific tracts but also alter brain networks, both locally and globally (Madzime *et al.*, 2021). Hence, it is imperative to employ methods to investigate the potential disruptions in global and local network properties that reflect HIV pathophysiology in CPHIV.

In network models, the brain may be conceptualized as a graph with GM regions as “nodes” of a network with white matter tracts as “edges” as connections and interactions between them. Altered white matter connections and grey matter (GM) regions in brain networks model the disruptive effects caused by trauma or disease (Griffa *et al.*, 2013; Fornito, Zalesky and Breakspear, 2015). Furthermore, white matter connections between gray matter regions vary in strength and edges can be weighted as a function of strength between a given pair of nodes to make weighted networks. Weighted networks enable the characterization of the brain network topology and properties like node strength, and clustering coefficient and small worldness are preserved (Colon-Perez *et al.*, 2016). A

handful of graph theoretical studies measuring functional connectivity and structural connectivity based topological properties in adults living with HIV with HAND have reported local and global aberrations associated with cognitive performance (Thomas *et al.*, 2015; Abidin *et al.*, 2018; Bell *et al.*, 2018). Another useful method to investigate structural reorganization in the brain involve the construction of structural covariance networks that describe an interdependence in morphological changes among brain regions that are structurally and functionally connected (Alexander-Bloch, Giedd and Bullmore, 2013). Changes in gray matter morphology often occur with changes in white matter integrity (Giorgio *et al.*, 2010). Studies have reported gray matter atrophy associated with injury to association fibers in multiple sclerosis (Han *et al.*, 2017; Lee *et al.*, 2020). As such, we can take advantage of the implied overlap between structural covariance networks and tractography based structural connectivity networks to draw common inferences about how they relate to cognitive function. In CPHIV, graph theoretical models have, so far, used covariance in maturation of connected GM regions to show disrupted GM maturation and regional connectivity in HIV infection. Though correlation analyses with cognitive scores were not performed, CPHIV presented with altered focal gray matter morphology, structural covariance networks and, scored significantly lower in neuropsychological tests which may suggest that these alterations they report may be related to cognitive decline in children living with perinatal HIV (Yadav *et al.*, 2017; Li *et al.*, 2018).

In this study, we use whole brain DTI tractography on a well characterized cohort of CPHIV, CHEU and CHU at 9 years. To investigate the possible influence of HIV infection on the organizational structure of the developing brain, we examine white matter fiber connections between grey matter regions from DTI data. We hypothesize HIV-related altered white matter connectivity in tracks that make up the IFOF, ILF and SLF (association tracts that connect the fronto-temporoparietal regions and occipital regions) CST/SCR (pyramidal fibers that project and fan out to motor and sensory areas), forceps minor and forceps major (interhemispheric fibers that link frontal and occipital areas, respectively). We hypothesize connections to/from the basal ganglia will be observed, as this is a highly vulnerable region implicated in previous studies in this cohort.

We expect changes in white matter connectivity will affect cognitive performances in CPHIV. We hypothesize aberrations in local and global network organization influenced by altered connectivity between gray matter regions in fronto-temporoparietal, occipital, brain stem, cerebellar, motor, and sensory areas in the brains of CPHIV compared to CHU. Furthermore, local and global alterations are likely to be associated with cognitive performance. Furthermore, as graph theoretical studies in pediatric HIV have reported nodal alterations and shifts in hub location, we posit CPHIV will have altered nodal profiles of structural wirings and demonstrate hub relocation compared to controls.

4.2. Methods

4.2.1. Tractography

An atlas was defined by modifying an existing Haskins pediatric atlas by removing all non-gray matter regions using 3dcalc. We dubbed the newly created atlas with a total of 87 gray matter regions, the “Haskins 87 pediatric atlas” (Table 3). We then used 3dROIMaker to create sets of ROIs labeled with corresponding integers from the newly generated atlas. We used the AFNI’s 3dDWUncert tool to compute fiber orientation uncertainties on FA maps using a jackknife resampling technique (Taylor and Biswal, 2011; Taylor and Saad, 2013). We performed whole brain probabilistic tractography in AFNI using the *3dTrackID* tool (Taylor *et al.*, 2016) found in the Functional and Tractographic Connectivity Analysis Toolbox (FATCAT) (Taylor and Saad, 2013). Probabilistic fiber tracking was performed with the Haskins 87 pediatric atlas with the fully probabilistic (PROB) option in accordance with the following stopping criteria: Valid FA values for each voxel had to satisfy a 0.2 threshold and tracts were to be a minimum of 20 mm in length and tracking propagation could not have a turning angle less than 60°. Monte-Carlo simulations were performed to a total of 5000 iterations. At each iteration, the voxel parameters were perturbed according to estimated parameter uncertainties. We modelled existing white matter tracts between pairwise GM connections. For our analysis we considered fractional the number of tracts (fNT) and FA, MD, AD, RD.

4.2.2. Network construction

We used fractional number of tracts– the probabilistic number of tracts between the nodes divided by the total number of probabilistic tracts in the whole brain, as edge weights [Equation 1.18]. We created an 87×87 weighted adjacency matrix for each subject based on the pairwise fNT values (Tinaz *et al.*, 2017). Thresholding was deemed not necessary for this analysis due to the use of scaled edge weights normalized white matter connectivity between nodes by implementing equation 1.18 (Tinaz *et al.*, 2017). Custom R scripts incorporating a combination of *brainGraph* and *igraph* libraries were used to obtain organizational properties for the fNT networks. We performed linear regression analyses for these metrics controlling for age and sex. Age-related sex differences in white matter maturation have been described which merits their inclusion as potential confounders (Tamnes *et al.*, 2018).

Global graph measures

The following global network measures were computed: global clustering coefficient (a measure of segregation defined as the fraction of triangles around a node), characteristic path length (a measure of integration defined as the average shortest path between all nodes). In addition, we calculated and modularity (Blondel *et al.*, 2008), global efficiency (the average of the inverse shortest path length) and global transitivity for each subject.

Nodal graph measures

We also examined five nodal network metrics: degree, strength (Rubinov and Sporns, 2010), local and nodal efficiency and transitivity.

4.2.3. Statistical analyses and visualization

FA, AD, MD, and RD values were extracted from every pairwise white matter connection between the GM regions of the Haskins Pediatric atlas in FATCAT. To examine the possible influence of HIV infection on white matter connectivity we performed linear regression analyses comparing FA, MD, AD and RD between CPHIV and CHU, CHEU and CHUU and, ART after 12 w and ART before 12 w groups correcting for sex and age. Statistical analyses were performed for tracts available in at least 95% of the subjects and subsequently corrected for multiple comparisons using the false discovery rate (FDR) method ($q < 0.05$) (Benjamini and Hochberg, 1995) due to the high number of comparisons. More specifically, a total of 508 tracts were tested. Outlier profiles were first examined and values less than $Q_L - 1.5(IQR)$ and over $Q_U + 1.5(IQR)$ were identified as outliers and were excluded case-wise. More specifically, if the significance in a specific test and measure changed from significant FDR q to not significant, these were significant outliers, otherwise the outliers were kept. Further, we present results in the form of chord diagrams (created using *circlize* package in R) representing implicated WM connections. For ease of interpretation, we employed the use of standardized variables in our regression analysis. Standardized coefficients are independent of the involved variables' units of measurement. A regression carried out on standardized variables produces standardized coefficients (β), a measure of effect size, quantifying the "magnitude" of the effect of one variable on another and, β se (a measure of spread). Using the *scale()* in R implements the following formula to compute scaled variables:

$$Scaled\ x = (x - \bar{x}) / s$$

where: x is the original value of x , while $\bar{x}$ and s are the sample mean and standard deviation, respectively.

In the graph analysis, we performed linear regression analyses for these metrics with age and sex as potential confounders (Tamnes *et al.*, 2018). P-values ($\alpha = 0.05$) were corrected for multiple comparisons using False Discovery Rate (FDR; q). All variables were checked for gaussian distribution using the Shapiro-Wilk test ($p < 0.05$) prior to statistical analysis and visually assessed using the histogram function and appropriate statistical tests were performed. For instance, for variables with a gaussian distribution, Pearson correlations were more appropriate, while Spearman's rank correlation tests were performed for variables with skewed distributions. Furthermore, we performed the Levene's test to assess the equality of variances for each variable before group

comparisons were made. Samples for which their distributions failed to meet the assumption of equal variances were subjected to variations of statistical tests for group comparisons that consider this information during computation. All statistical analyses were performed with R (<https://www.r-project.org>).

4.2.4. Tract identification

To improve the precision of our identification of superficially located white matter interleaved in the space between the subcortical network and the cortex, we warped the JHU White-Matter Tractography Atlas to the subject space using *3dQwarp* and *3dNwarpApply* using the MNI152_2009_template (Fonov *et al.*, 2009, 2011). JHU white matter probabilistic tracts have unique values for each voxel they are made up of. To ensure a uniform value across the whole track, we divided each voxel value by itself using FSL function *fslmaths* such that non-zero voxel values assumed the value of 1 thereby binarizing it. We then used *3dcalc* to identify overlaps between white matter probabilistic tracks and binarized JHU white matter masks:

$$\text{only } a : -\{x : x \in a \wedge x \notin (L/a)\}$$

$$a \text{ not in } b : -\{x : x \in a \wedge x \notin b\}$$

$$\text{not } a : -\{x : x \notin a \wedge x \notin L\}$$

Probabilistic tracks may intersect with multiple masks, so we calculated the number of voxels with non-zero values in each of these intersections using *3dROIstats* and the track identity was assigned to the masks with the most voxels as follows:

$$\text{if } a \text{ or } b : -\{x : x \in a \cup b\}$$

$$a : -\{x : y \in a; z \in b: y \geq x\}$$

$$\text{else: } b$$

where multiple masks provided equal number of voxels:

$$a \text{ and } b : -\{x : x \in a \cap b\}$$

To identify possible functionally impaired gray matter regions, we determined the termination points of tracked regions in the gray matter - white matter interface, whereafter partial correlations were performed with affected neurocognitive outcomes (discussed below in section 4.2.5).

4.2.5. Associations with clinical/treatment-related variables and neuropsychological outcomes

To explore potential linear relationships between DTI and graph metrics in regions where we observed HIV effects and clinical measures, we performed Pearson's correlation tests and Spearman's rank correlation tests in R. The following clinical and treatment related variables were chosen for their known prognostic potential in HIV disease: CD4 lymphocyte counts (CD4 count), CD8 lymphocyte

counts (CD8 count), CD4 lymphocyte percent (CD4%), CD4/CD8 ratio) at study enrolment, at scan, nadir values, age at first viral load (VL) suppression and time to VL suppression. Due to the significantly large number of tests (discussed later in section 4.2.6), we performed correction for multiple comparisons using the Benjamini–Hochberg false discovery rate method (Benjamini and Hochberg, 1995).

We also compared neuropsychological scores between the CPHIV and CHU groups. Neuropsychological scores showing significant differences were assessed for their potential associations with measures of white matter integrity and graph metrics in affected regions across the study group. We also performed correction for multiple comparisons using the Benjamini–Hochberg false discovery rate method. Children in our cohort participated in a comprehensive test neuropsychological assessments at nine years under professional instruction with quality control measures as detailed by van Wyhe *et al.* (van Wyhe *et al.*, 2021). The tests are robust for testing cognitive fitness in the South African demographic given its unique context (Laughton *et al.*, 2012; Van Wyhe *et al.*, 2017; Boivin *et al.*, 2018; Laughton, Cornell, Kidd, Springer, Dobbels, A. J. Van Rensburg, *et al.*, 2018). It included the Beery-Buktenika Developmental Test of Visual-Motor Integration (Beery-VMI), which is a test for visual perception and motor coordination; the Kaufman Assessment Battery for Children – Second Edition (KABC-II) (Kaufman and Kaufman, 2013). Different combinations of the test subtests can derive measures of sequential processing (an assessment of auditory working memory), simultaneous processing (visual-spatial processing and problem solving), learning (short-term memory) and planning (executive reasoning). We measured a child’s receptive language ability (Eigsti, 2021) using the Peabody Picture Vocabulary Test – fourth Edition (PPVT-IV) (Dunn and Dunn, 2007).

4.2.6. Multiple comparisons testing

Where some type I errors are acceptable, a less conservative method may be used. One may opt to control the False Discovery Rate (FDR) instead of the FWER using the Benjamini-Hochberg FDR methods. The FDR controls the expected rate of type 1 error in the rejected hypothesis list. It is less conservative. By performing the comparison procedure with a greater power compared to FWER control, the probability that a type I error will occur can be increased (Benjamini and Hochberg, 1995). Additionally, more liberal methods like FDR may be used if type II error (false negatives) should be avoided and possible effects should not be missed. Furthermore, when the number of tests is very large, like in ‘omics’ studies, it is preferable to control of the FDR for its notable gain in power compared to controlling for FWER (Glickman, Rao and Schultz, 2014). Particularly, it was important to pick out all the white matter that could be at risk in CPHIV, hence we found it more appropriate to decrease the number of null hypotheses wrongly rejected due to lack of statistical power (Pike, 2011).

4.3. Results

4.3.1. Tractography

After visual inspection, we excluded data from 25 subjects (14 CPHIV, 11 CHU) due to motion. We present data from 58 CPHIV (ART before 12 weeks (about 3 months) = 45, ART after 12 weeks = 13) and 42 CHU (CHEU = 20, CHUU = 22). CPHIV on ART show white matter regions of significantly higher MD, with corresponding increases in AD and/or RD. Results are shown in chord diagrams in Figures 1 -3 and summarized in appendix Tables 6.3. a-k. Structural connections involving the basal ganglia, insula, and temporal lobe are highly represented.

We found alterations in association fibers connecting the Insula to fronto-temporoparietal regions. More specifically, connections to sensorimotor area (precentral (PREC) and postcentral (PSTC) gyri), and prefrontal cortical areas – inferior frontal gyrus (parsopercularis (POPE) and parstriangularis (PTRI), lateral- and medial- orbitofrontal (L/MOF) gyri.

We also found alterations in projection fibers connecting the subcortical regions to occipital regions. Additional alterations in projection fibers connecting fronto-temporoparietal to subcortical regions were found with the putamen (PUT), hippocampus (HPC) and amygdala (AMG) heavily impacted. Changes in white matter microstructure were also observed in association and U-fiber connections between subcortical regions.

Tract identification

Tract identification revealed alterations in regions bilaterally in regions involving the IFOF, inferior longitudinal fasciculus (ILF), SLF, ATR, CST, forceps minor, forceps major, corona radiata, uncinate fasciculus, external capsule, internal capsule, fornix/stria terminalis, cingulum, inferior cerebellar peduncle, and middle cerebellar peduncle.

We did not find any group differences in DTI metrics in the CHUU vs. CHEU and ART before and after 12 weeks comparisons.

Table 4.1: Summary characteristics for neuropsychological performance for participants who provided usable data. The CHU group comprises both children perinatally HIV-exposed, but uninfected (CHEU) and children who are HIV-unexposed and uninfected (CHUU).

Neuropsychological tests	ALL		CHU		CPHIV		<i>p</i>
	Mean	SE	Mean	SE	Mean	SE	
Beery VMI Foreign Norms Std Median [IQR]	87	[83; 87.88]	87	[83;94]	87	[79;94]	0.541
KABC Index Scores:							
Sequential Processing Std Median [IQR]	81.5	[74.75; 88.00]	84	[74.75; 94]	80	[76.25;85.75]	0.0301*
Learning Std Median [IQR]	81	[73.00; 86.00]	84	[73;86]	76.5	[72.25;84]	0.0671
Simultaneous Processing Std Median [IQR]	81	[75.00; 92.25]	81	[69;90]	82.5	[75;94]	0.35
Planning Std Median [IQR]	75	[72.00; 80.00]	77	[72.75;81.5]	75	[71.25;80]	0.173
Nonverbal Index Std	78.07	1.154281	79.9	2.266	77.107	1.289	0.257
Mental Processing Index Std Median [IQR]	75	[68.00; 79.00]	75	[68;84]	74	[68.75; 79]	0.123
Delayed Recall Std	81.07	1.220941	83.14	2.57	80	1.2855	0.225
PPVT							
Raw			80.5	[68.25; 95.25]	72	[66; 89]	0.425
Foreign Norms Std			62	[54.25; 69.75]	57	[52; 67]	0.457
Neuropsychological tests			HUU		HEU		<i>p</i>
			Mean	SE	Mean	SE	
Beery VMI Foreign Norms Std Median [IQR]			87	[83;91]	89.5	[86; 95]	0.98
KABC Index Scores:							
Sequential Processing Std Median [IQR]			83	[71; 91]	83	[76.25; 94.95]	0.76
Learning Std Median [IQR]			81	[70; 86]	85	[76.75; 86]	0.87
Simultaneous Processing Std Median [IQR]			81	[69; 84]	87	[68.25; 90]	0.82
Planning Std Median [IQR]			77	[72; 80]	77	[76.5; 80.5]	0.87
Nonverbal Index Std			77.5	2.994	82	3.449	0.45
Mental Processing Index Std Median [IQR]			75	[68; 92]	76.5	[71; 81.25]	0.8
Delayed Recall Std			82.47	3.0776	82.1	3.77	0.74
PPVT							
Raw			80	[68; 92]	85	[67.25; 105.5]	0.37
Foreign Norms Std			62	[54; 69]	64	[53.75; 77]	0.42

Table 4.2. Regional Parcellation Coding Scheme.

Location	Grey matter region	Abbreviation*
Cerebellum	Cerebellum-cortex	CER
	Brainstem	BST
Paracentral	Paracentral	PARC
Frontal cortex	Caudalmiddlefrontal	CMF
	Frontalpole	FP
	Lateralorbitofrontal	LOF
	Medialorbitofrontal	MOF
	Parsopercularis	POPE
	Parsorbitalis	PORB
	Parstriangularis	PTRI
	Precentral	PREC
	Rostralanteriorcingulate	RAC
	Rostralmiddlefrontal	RMF
	Superiorfrontal	SF
Insula	Insula	INS
Limbic cortex	Caudalanteriorcingulate	CAC
	Isthmuscingulate	ISTH
	Posteriorcingulate	PC
Occipital cortex	Cuneus	CUN
	Fusiform	FUS
	Lateraloccipital	LOCC
	Lingual	LING
	Parahippocampal	PARH
	Precuneus	PCUN
Parietal lobe	Inferiorparietal	IP
	Pericalcarine	PCAL
	Postcentral	PSTC
	Superiorparietal	SP
	Supramarginal	SMAR
Basal Ganglia	Accumbens	ACC
	Amygdala	AMG
	Caudate	CAU
	Hippocampus	HPC
	Pallidum	PAL
	Putamen	PUT
	Thalamus	THAL
	Ventral diencephalon	VDC
Temporal lobe	Bank of the superior temporal sulcus	BSTS
	Entorhinal	ENT
	Inferiortemporal	IT
	Middletemporal	MT
	Superiortemporal	ST
	Temporalpole	TP
	Transversetemporal	TT

*Names and abbreviations of a subset of brain regions in the Haskins pediatric atlas considered in our analysis. Naming convention is consistent with Human Connectome Project nomenclature from Hagmann et al. (2008).

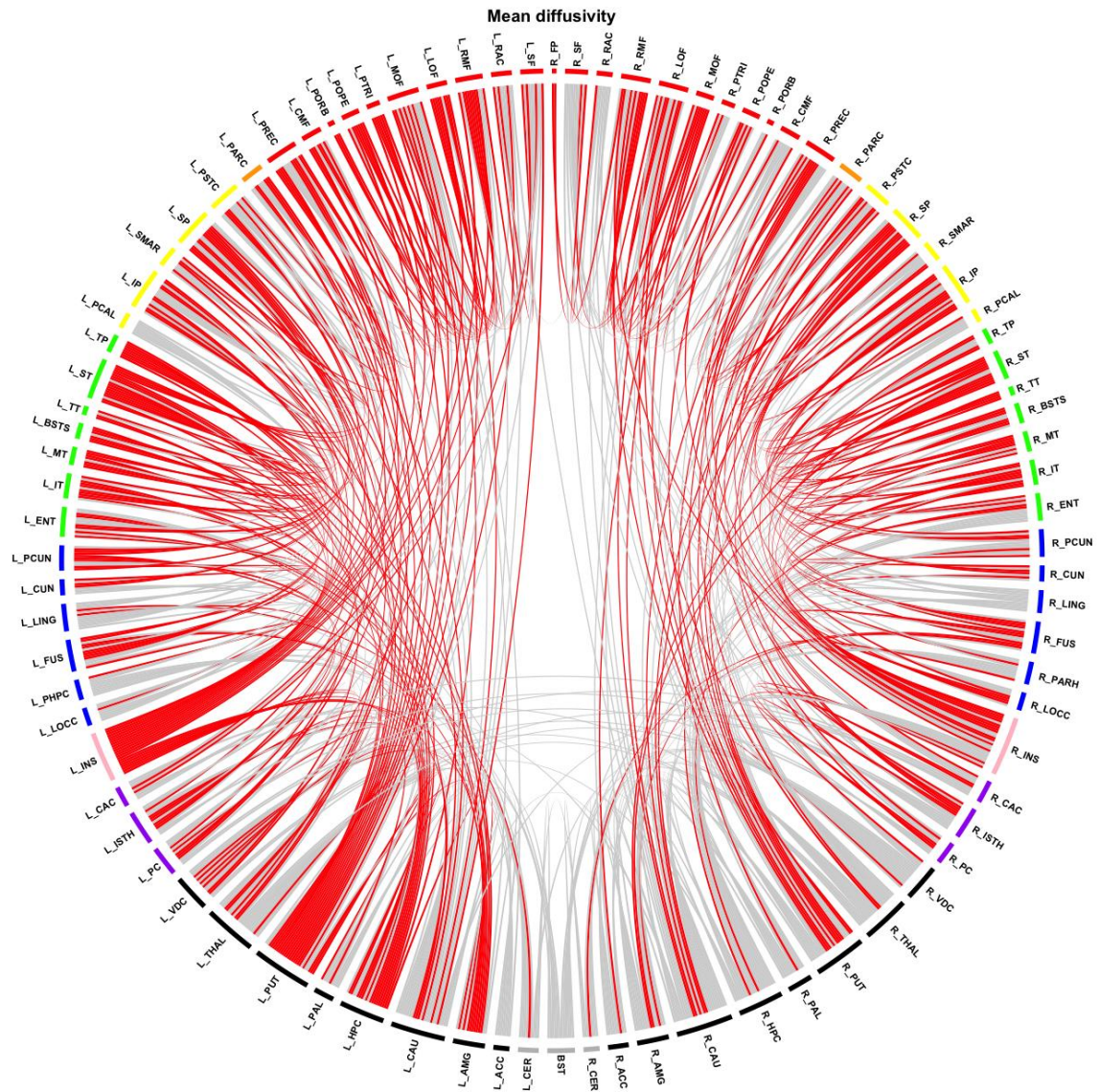


Fig. 4.1. A chord diagram showing MD-related structural connectivity differences between CHU vs. CPHIV groups. Haskins pediatric template parcellations as nodes color-coded by membership in cerebral lobes (Frontal – red, Parietal – yellow, Temporal – green, Occipital – blue, insular – peach, Limbic – purple, Subcortical – black, Brain stem and cerebellar cortices Gray) and edges (red = $q < 0.05$) and grey = $[0.05 \leq \text{FDR } q < 1]$ are color-coded by statistical significance in the group differences $[\text{CHU} < \text{CPHIV}]$. L left; R right.

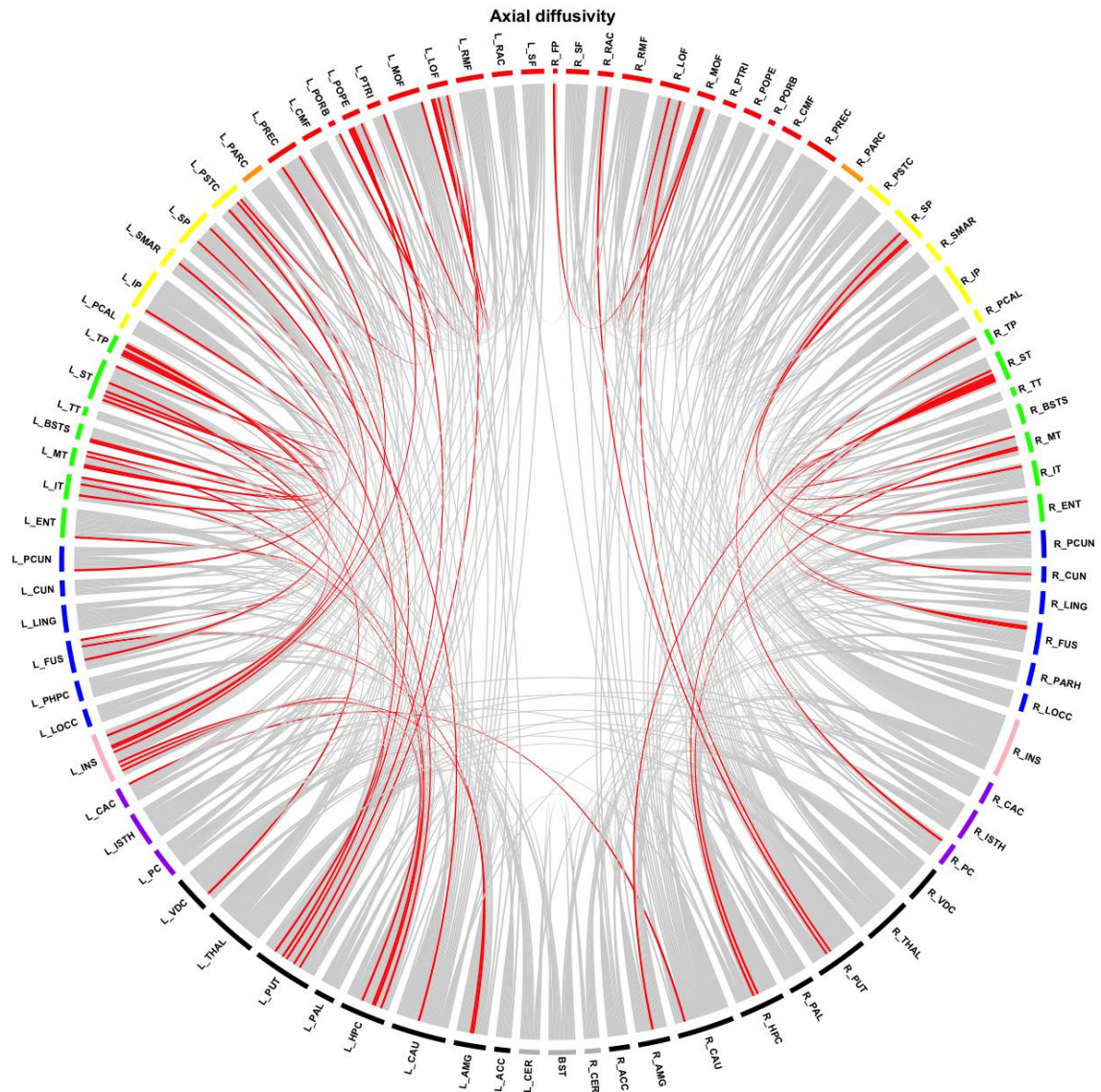


Fig. 4.2. A chord diagram showing AD-related structural connectivity differences between CHU vs. CPHIV groups. Haskins pediatric template parcellations as nodes color-coded by membership in cerebral lobes (Frontal – red, Parietal – yellow, Temporal – green, Occipital – blue, insular – peach, Limbic – purple, Subcortical – black, Brain stem and cerebellar cortices Gray) and edges (red = $q < 0.05$) and grey = $[0.05 \leq \text{FDR } q < 1]$ are color-coded by statistical significance in the group differences $[\text{CHU} < \text{CPHIV}]$. L left; R right.

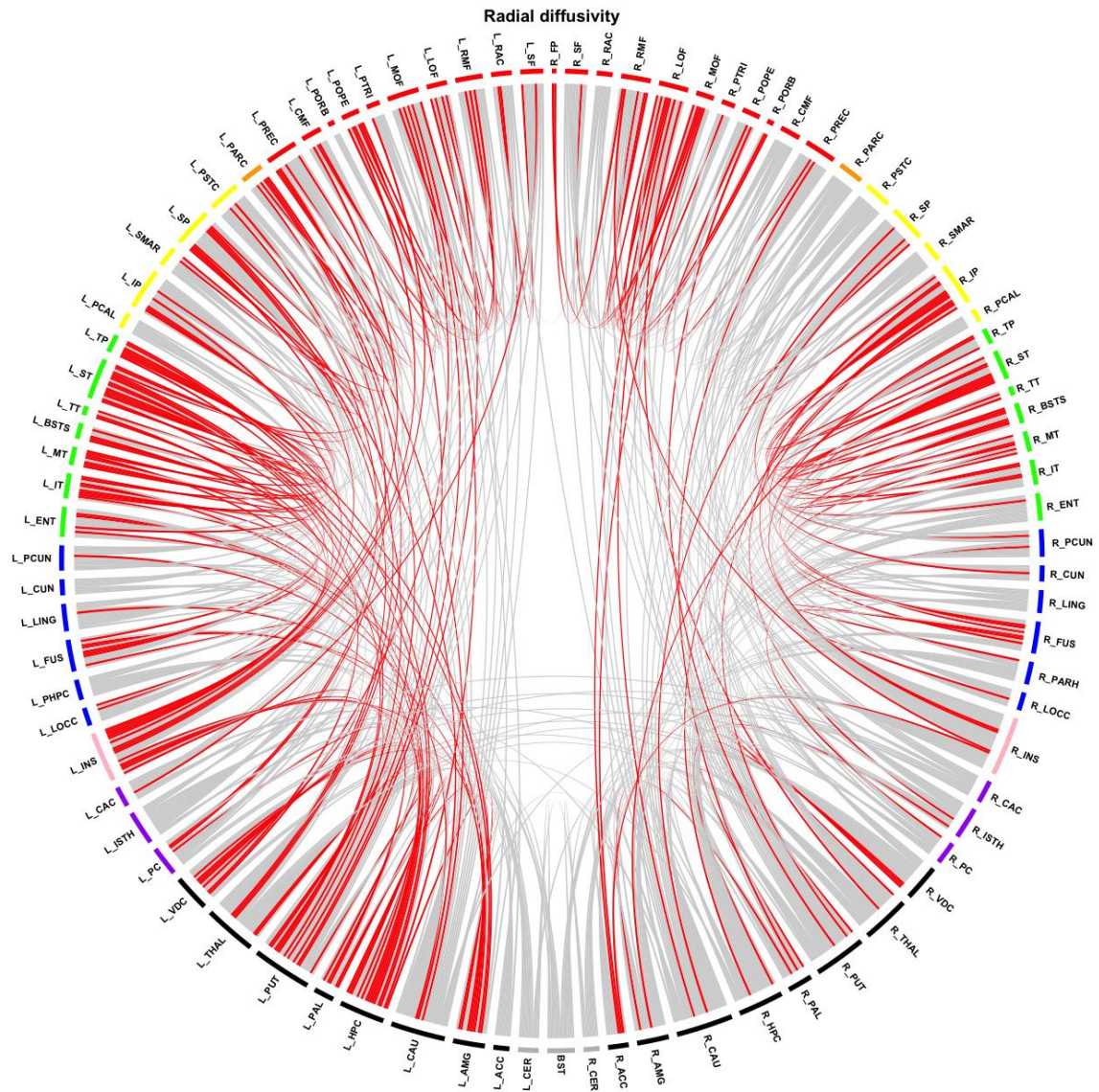


Fig. 4.3. A chord diagram showing RD-related structural connectivity differences between CHU vs. CPHIV groups. Haskins pediatric template parcellations as nodes color-coded by membership in cerebral lobes (Frontal – red, Parietal – yellow, Temporal – green, Occipital – blue, insular – peach, Limbic – purple, Subcortical – black, Brain stem and cerebellar cortices Gray) and edges (red = $q < 0.05$) and grey = $[0.05 \leq \text{FDR } q < 1]$ are color-coded by statistical significance in the group differences $[\text{CHU} < \text{CPHIV}]$. L left; R right.

4.3.2. Neuropsychological performance in CPHIV vs. CHU.

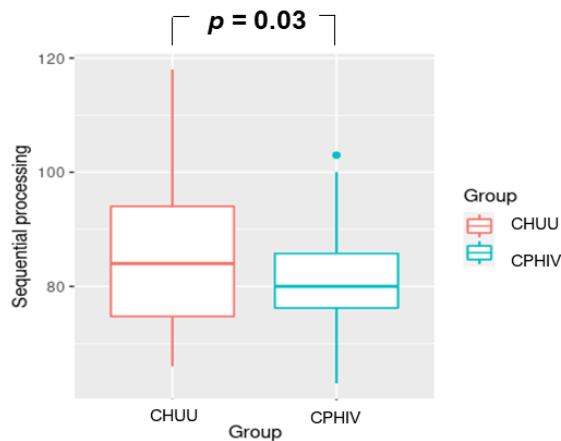


Fig. 4.4. Group comparisons showing differences in performances in sequential processing between CPHIV and CHU.

CPHIV scored significantly lower (80.27 ± 8.73) than CHU (85.43 ± 12.87) on only the KABC Index Scores: Sequential Processing Std ($p = 0.03$) out of a total of 10 neuropsychological measures tested. Neurocognitive measures were not significantly different between CHEU vs. CHUU and CPHIV who received ART before or after 12 weeks of age.

4.3.3. Associations with neuropsychological scores

Across participants, higher MD in fronto-temporoparietal connections was associated with lower performance in sequential processing (Table 4.4). It is important to note that neither of the results in this section survive multiple comparison correction.

Among CHU, we found significant negative correlations between sequential processing and MD in basal ganglia connections to insula and fronto-parietal regions. Particularly, left hemispheric connections between the caudate and superior temporal, putamen and inferior parietal, putamen and left rostral anterior cingulate and, pallidum and insula. In the right hemisphere, we found regions of poor sequential processing in connections between the caudate and precentral gyrus, putamen and right precentral gyrus, ventral diencephalon and insula, precentral gyrus and precuneus (see Fig. 4.6).

Among CPHIV, we found significant negative correlations between sequential processing and MD in a handful of tracts connecting regions in the insula and temporoparietal junction. More specifically, lower sequential processing was associated with higher MD in white matter in a local circuit involving the right insula, superior temporal (ST) lobule, right bank of superior temporal sulcus and right inferior parietal (IP) lobule. Additionally, higher MD was associated with poorer performance in sequential processing in tracts that connect: the left orbitofrontal gyrus to the left rostral anterior cingulate, the left fusiform gyrus to the superior parietal lobule and, the left putamen to the isthmus cingulate (see Fig 4.7).

4.3.4. Associations with clinical variables

We assessed the associations between clinical variables and DTI parameters MD, AD and RD. Among CPHIV, none of the clinical variables recorded with each visit (Baseline CD4 count and percent, CD4 count and percent at scan, CD4/CD8 ratio, nadir CD4 count and percent, age at first viral load suppression) were significantly associated before and after multiple comparison correction.

4.3.5. fNT weighted connectome

Global effects

Table 4.3: Global tractography based graph theory effects.

fNT	std B	se	<i>p</i>
global efficiency	-0.041	0.020	0.453
Modularity	0.174	0.007	0.094
Transitivity	-0.071	0.008	0.495

There were no differences between CPHIV and CHU groups in global graph measures (global efficiency, $p = 0.453$, modularity, $p = 0.094$ and transitivity, $p = 0.495$).

Nodal effects

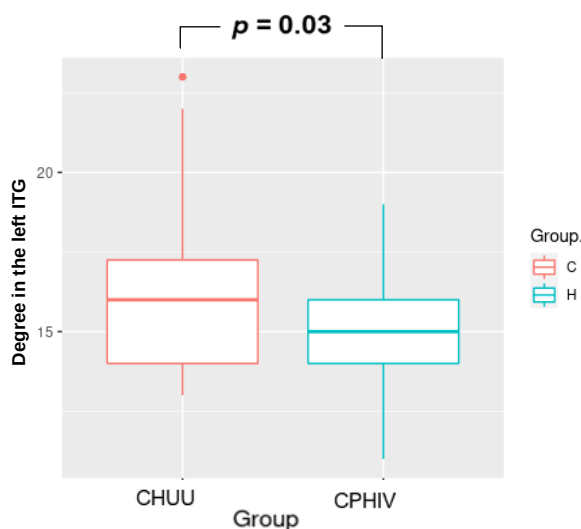


Fig. 4.5. Group comparisons were made for each one of the 87 regions that made up the nodes in our connectome between CPHIV and CHU. Among them, we found lower degree in L inferior temporal gyrus (ITG), (-0.39 , $p = 0.03$) in the CPHIV when compared to the CHU. We provide a plot labeled with the t-test p-value for significance, However, this test survived the threshold for significance when controlling for age and sex as covariates.

With the exception of nodal degree, there were no differences between CPHIV and CHU groups in nodal measures (strength, nodal efficiency, local efficiency and transitivity). The results are summarized in Tables 6.4. A-D.

Table 4.4: Associations among children with CPHIV and CHU of sequential processing with DTI parameters in regions where HIV-related white matter changes were found. Asterisks indicate associations that survive threshold for significance corrected for multiple comparisons (FDR (q) < 0.05).

ROI	Mean diffusivity								Radial diffusivity						Axial diffusivity					
	All		CHU			CPHIV			CHU			CPHIV			CHU			CPHIV		
	<i>r</i>	<i>p</i>	<i>r</i>	<i>p</i>	<i>q</i>	<i>r</i>	<i>p</i>	<i>q</i>	<i>r</i>	<i>p</i>	<i>q</i>	<i>r</i>	<i>p</i>	<i>q</i>	<i>r</i>	<i>p</i>	<i>q</i>	<i>r</i>	<i>p</i>	<i>q</i>
R_PUT - R_LOF	-0.143	0.205	-0.423	0.020*	0.636	0.018	0.900	0.983	-0.468	0.010*	0.805	-0.060	0.680	0.936	-0.186	0.333	0.942	-0.015	0.912	0.988
R_PUT - R_PREC	-0.218	0.045*	-0.372	0.047*	0.636	-0.063	0.643	0.983	-0.298	0.116	0.805	0.022	0.878	0.977	-0.365	0.052	0.942	-0.051	0.712	0.988
R_POPE - R_INS	-0.169	0.121	-0.391	0.036*	0.636	-0.047	0.734	0.983	-0.355	0.054	0.805	-0.012	0.932	0.977	-0.203	0.291	0.942	0.007	0.960	0.988
R_PSTC - R_PCUN	-0.221	0.045*	-0.468	0.010*	0.636	-0.091	0.511	0.983	-0.358	0.057	0.805	-0.089	0.516	0.906	-0.209	0.285	0.942	0.130	0.362	0.988
R_CAU - R_PSTC	-0.282	0.009*	-0.430	0.020*	0.636	-0.194	0.153	0.983	-0.124	0.514	0.833	-0.087	0.523	0.906	-0.325	0.085	0.942	-0.211	0.125	0.988
L_LOF - L_RAC	-0.239	0.033*	-0.305	0.114	0.636	-0.288	0.038*	0.983	-0.289	0.135	0.805	-0.134	0.360	0.906	-0.149	0.442	0.942	-0.167	0.228	0.988
L_CAU - L_SP	-0.265	0.018*	-0.486	0.010*	0.636	-0.134	0.342	0.983	-0.384	0.043*	0.805	-0.095	0.502	0.906	-0.266	0.164	0.942	-0.207	0.153	0.988
L_PUT - L_IP	-0.283	0.012*	-0.367	0.050	0.636	-0.101	0.488	0.983	-0.298	0.117	0.805	-0.229	0.117	0.906	-0.366	0.051	0.942	-0.125	0.367	0.988
L_PUT - L_ISTH	-0.282	0.010*	-0.205	0.287	0.640	-0.287	0.037*	0.983	-0.215	0.262	0.805	-0.259	0.058	0.906	-0.177	0.397	0.942	-0.173	0.234	0.988
L_PUT - L_PAC	-0.102	0.373	-0.389	0.037*	0.636	0.127	0.386	0.983	0.056	0.790	0.904	0.032	0.828	0.970	-0.200	0.290	0.942	0.126	0.400	0.988
L_PAL - L_INS	-0.213	0.055	-0.404	0.033*	0.636	-0.098	0.479	0.983	-0.391	0.039*	0.805	0.014	0.917	0.977	-0.150	0.436	0.942	-0.032	0.817	0.988
R_VDC - R_INS	-0.220	0.050	-0.382	0.045*	0.636	-0.073	0.608	0.983	-0.346	0.066	0.805	-0.070	0.611	0.929	0.002	0.991	0.991	-0.094	0.504	0.988
L_ENT - L_ST	-0.272	0.011*	-0.266	0.155	0.636	-0.257	0.055	0.983	-0.189	0.317	0.805	-0.290	0.030*	0.906	-0.314	0.098	0.942	-0.016	0.910	0.988
R_IP - R_ST	-0.286	0.009*	-0.215	0.253	0.636	-0.308	0.025*	0.983	-0.204	0.279	0.805	-0.315	0.022	0.906	-0.163	0.389	0.942	-0.120	0.381	0.988
R_ST - R_INS	-0.319	0.003*	-0.239	0.204	0.636	-0.315	0.023*	0.983	-0.169	0.373	0.807	-0.169	0.227	0.906	-0.281	0.133	0.942	-0.165	0.239	0.988
R_BSTS - R_ST	-0.291	0.008*	-0.196	0.299	0.640	-0.331	0.015*	0.983	-0.255	0.175	0.805	-0.208	0.151	0.906	-0.056	0.769	0.975	0.015	0.915	0.988

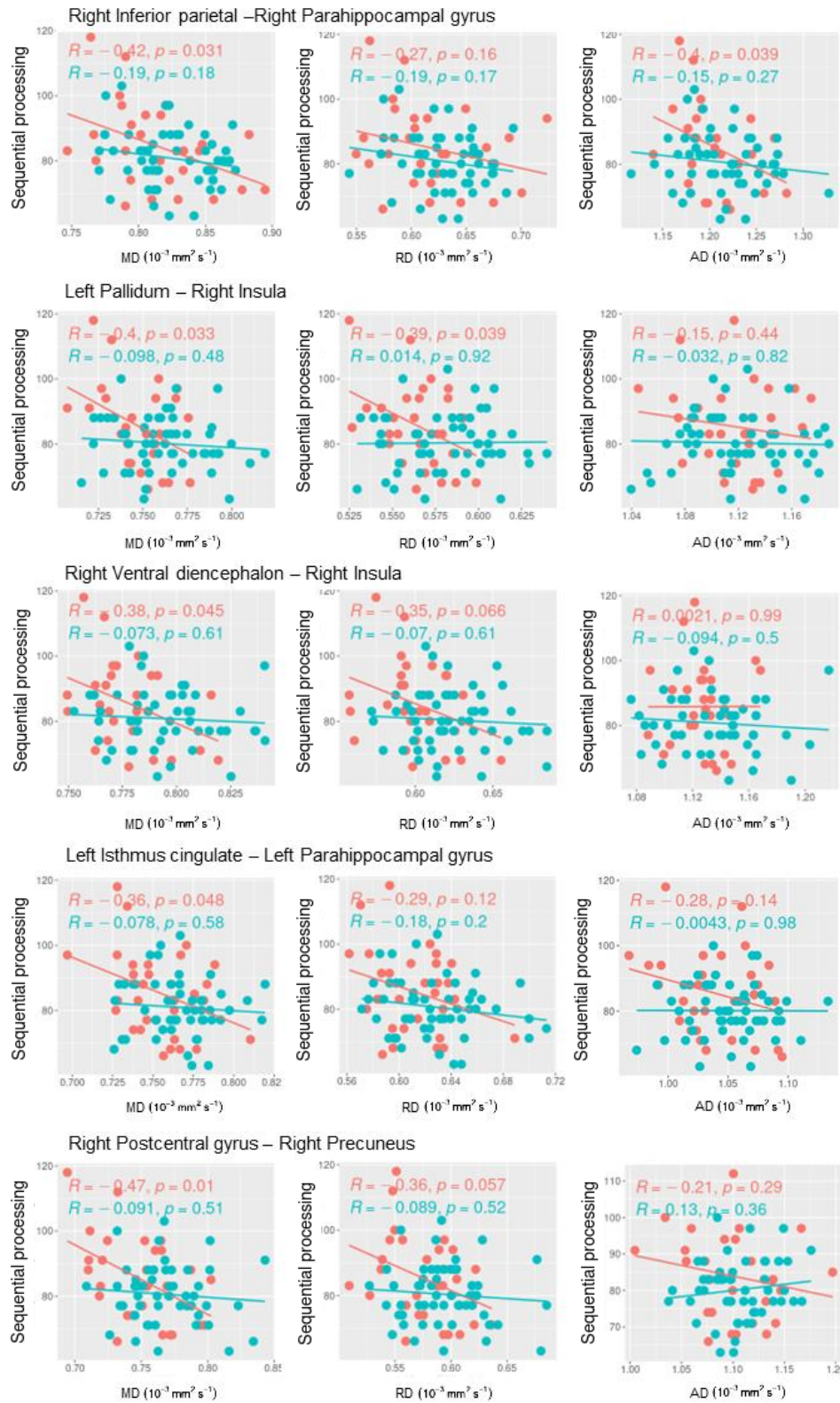


Fig. 4.6. Associations between DTI parameters and sequential processing in subcortical regions in CPHIV and CHU. Plots are provided for associations across the sample. Refer to Table 4.4 for summary of correlation analysis.

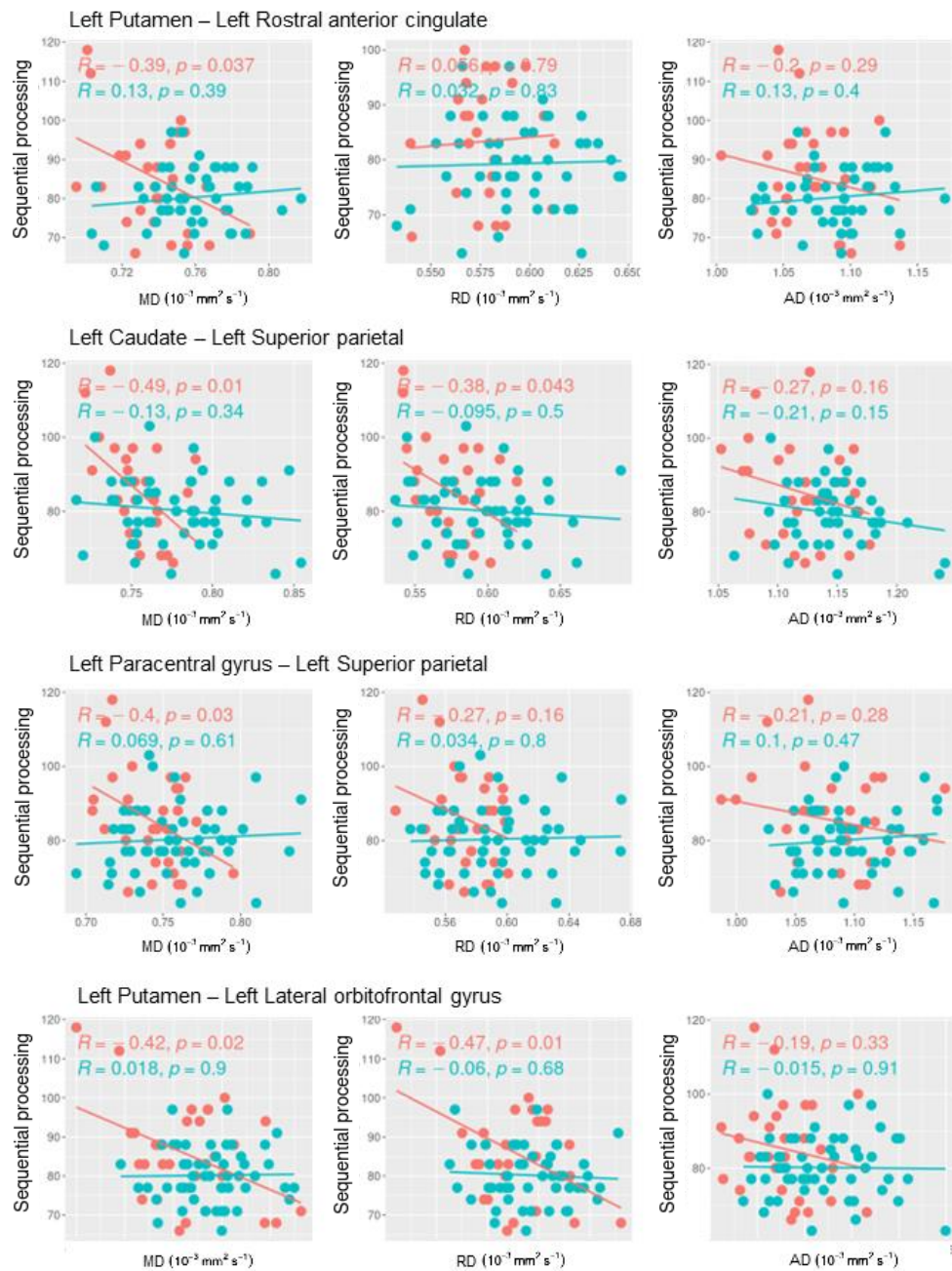


Fig. 4.7. Associations between DTI parameters and sequential processing in frontoparietal regions in CPHIV and CHU. Plots are provided for associations across the sample. Refer to Table 4.4 for summary of correlations analysis.

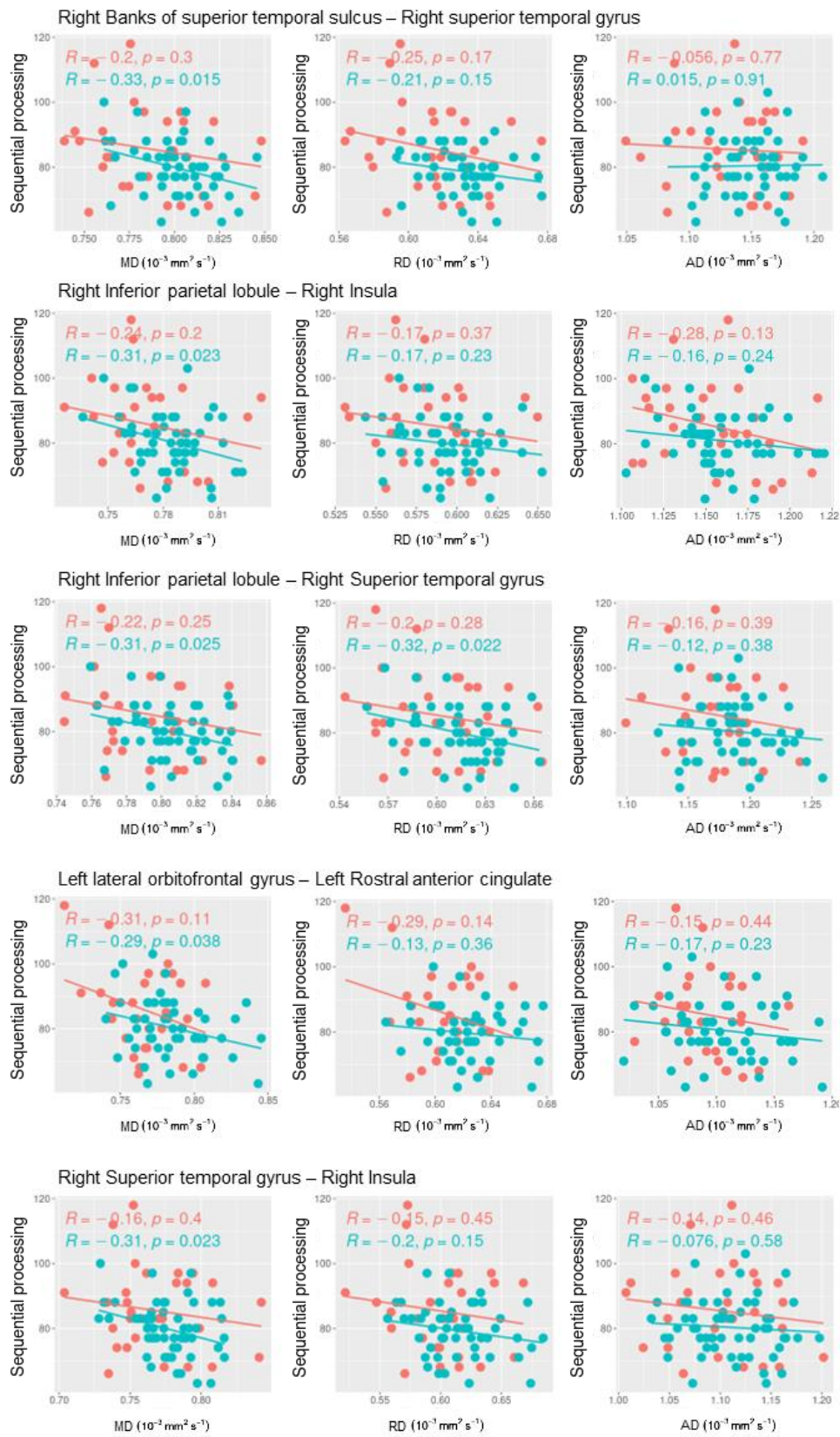


Fig. 4.8. Associations between DTI parameters and sequential processing in frontoparietal regions in CPHIV and CHU. Plots are provided for associations across the sample. Refer to Table 4.4 for summary of correlations analysis.

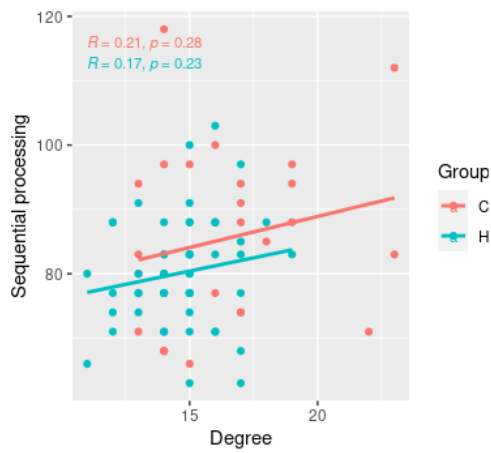


Fig. 4.9. Association between nodal degree of the inferior temporal gyrus and sequential processing in frontoparietal regions in CPHIV and CHU. Plot provided for an association across the sample.

In the correlation analysis, we report a positive association ($\rho = 0.246; p = 0.029$) between nodal degree of the left inferior temporal gyrus and scaled Sequential processing across the sample.

4.4. Discussion

We report several tracts with increased MD in CPHIV compared to CHU at 9 years, attributed mainly to higher RD. Structural connections involving the putamen and insula appear highly impacted by HIV infection. We observe alterations among association tracts, particularly in fronto-striatal and fronto-parietal pathways. Interestingly, many of these connections were associated with working memory function, primarily in CHU only. Nodal degree was significantly lower in the inferior temporal gyrus of CPHIV, and it was associated with working memory performance across all children. Together, these findings demonstrate white matter abnormalities contribute to reductions in localized nodal connections but do not influence global network properties. And select HIV-related white matter and structural nodal alterations relate to deficits in working memory in CPHIV at the beginning of adolescence.

4.4.1. White matter maturation in adolescence

White matter matures from infancy into adulthood to enable cognitive functioning (Giedd *et al.*, 1999; Lenroot and Giedd, 2006; Webster, Elashoff and Weickert, 2011). During this time, pruning of synaptic connections, increased myelination and changes in axonal diameter occur by region (Giedd *et al.*, 1999; Lebel *et al.*, 2008; Gong *et al.*, 2009; Lebel and Beaulieu, 2011). These functional modifications lead to a more efficient network (Hagmann *et al.*, 2010). White matter development is characterized by an age-related increase in regional FA with a corresponding increase in AD and a decrease in RD (Lebel, Caverhill-Godkewitsch and Beaulieu, 2010). In adolescents, regional age-related increases in white matter volumes occur simultaneously with FA and AD increases in association and projection tracts for the establishment of long-distance connections (Giorgio *et al.*, 2010).

4.4.2. Effects of HIV infection on white matter maturation in adolescence

We reported alterations characterized by increased MD, RD and/or AD bilaterally in the following tracts the IFOF, ILF, SLF, ATR, CST, forceps minor, forceps major and corona radiata. We also found additional alterations in the uncinate fasciculus, external capsule, internal capsule, fornix/stria terminalis, cingulum, inferior cerebellar peduncle, and middle cerebellar peduncle. At age 7 years, we found alterations in tracts connecting grey matter regions of the default mode, salience, and somatosensory networks (Madzime *et al.*, 2021). These include the left forceps minor, CST, SLF, left ATR, left cingulum.

Several tracts demonstrate both higher MD and RD, pointing to demyelination. In addition, some connections had higher MD along with above-normal AD and RD. This combination suggests

diffusivity increases due to an increased extra-axonal space which is likely due to axonal loss and demyelination. Both biological processes may be contributing to the abnormalities reported.

At age 5 years, we reported significantly larger nuclear accumbens and putamen volumes bilaterally and left pallidum volumes compared to CHU (Randall *et al.*, 2017). And, at age 7 years we found reduced gyrification in the parietal cortex, as well as reduced volumes in the putamen and hippocampus in CPHIV (Nwosu *et al.*, 2017). Similarly, we report alterations in white matter tracts connecting the putamen bilaterally to parietal, frontal, subcortical, temporal, and left limbic regions. Additional structural connections involving regions within the parietal lobe and the left hippocampus, and left amygdala appear impacted at age 9. Taken together, these results suggest gray matter regions previously affected by HIV in this cohort are vulnerable to white matter developmental disruptions.

White matter alterations within the somatosensory and motor networks, particularly in tracts connecting superior temporal cortex and the putamen in both hemispheres were reported in previous tractography work in CPHIV of our cohort (Madzime *et al.*, 2021). Here, we found altered white matter connectivity between the left putamen and left superior temporal cortex only. White matter damage reported in the right hemisphere may reflect developmental delay in the limbic connections at 7 years that resolves at age 9 years.

Within our cohort we observe a high occurrence of alterations among association fibers. Association tracts, such as the IFOF and SLF connecting to the prefrontal cortex, have the slowest developmental trajectory (Sedmak *et al.*, 2018). The affected tracts involve connections to gray matter regions associated with higher order cognitive functioning (Lewis-de los Angeles *et al.*, 2017). More specifically, left and right hemisphere postcentral gyrus, rostral middle frontal gyrus, superior frontal gyrus, and superior parietal cortex. This is consistent with findings in previous gray matter morphometric work in our cohort in CPHIV where HIV infection was associated with regional brain volume reduction in the left postcentral gyrus, right precentral gyrus, left rostral middle frontal gyrus and right superior parietal cortex (Nwosu *et al.*, 2017). These findings are consistent with work done in perinatally youth living with HIV, where regional brain volume reduction in the left postcentral gyrus, right precentral gyrus, left rostral middle frontal gyrus and right superior parietal cortex were observed (Lewis-de los Angeles *et al.*, 2017).

Our study of CPHIV identifies alterations in white matter connections including and between gray matter regions of the prefrontal cortex. Importantly, prefrontal regions undergo tremendous development during adolescence (Colby, Van Horn and Sowell, 2011; Krogsrud *et al.*, 2016). In addition, we found altered white matter connectivity within the frontal, temporal, and parietal brain regions of the language circuit. Interestingly, in our tractographic analysis we find alterations in white matter connections to the transverse temporal gyrus of the superior temporal gyrus. The superior temporal is paramount in language and auditory processing in normally developing individuals and, in

individuals with atypical development and disease (Bigler *et al.*, 2007). Five tracts course through the transverse temporal junction of the language circuit. These include the anterior segment of the arcuate fasciculus, the middle longitudinal fasciculus, the acoustic radiation, the IFOF, and the optic radiation (Fernández *et al.*, 2020). Similarly, our analysis implicates the same tracts in the reduced connectivity between the TT and ST to other regions of the language circuit. Namely, the IFOF, SLF.

We also found predominant MD related changes in the white matter structures connecting left insula cortex to subcortical regions, frontal, temporal, and parietal lobes. In humans, diffusion weighted imaging studies have demonstrated that the anterior insular connects to the anterior cingulate, frontal, orbitofrontal, and anterior temporal areas while the posterior insula primarily has connections with posterior temporal, parietal, and sensorimotor areas (Cerliani *et al.*, 2012; Cloutman *et al.*, 2012; Ghaziri *et al.*, 2017; Uddin *et al.*, 2017). Connections to grey matter structures in these regions is associated with insula involvement in sensorimotor, central-olfactogustatory, socio-emotional and cognitive processes (Kurth *et al.*, 2010; Uddin *et al.*, 2017).

Interhemispheric connectivity

Interestingly, contrary to previous VWA results at ages 5 and 7 years (C. Ackermann *et al.*, 2016; Jankiewicz *et al.*, 2017), we observe alterations within commissural fibers. More specifically, we find RD related changes in an interhemispheric connection between the left caudal anterior cingulate and the right caudate in CPHIV. These results are consistent with the previous tractography study in our cohort at 7 years (Madzime *et al.*, 2021). Spatiotemporal white matter maturation is generally characterized by a proximal to distal pattern where interhemispheric tracts develop earlier than the association tracts (Yu *et al.*, 2020), and projection before association (Volpe, 2000). Early maturation in interhemispheric tracts and ART administration may mitigate HIV-associated dysmyelination effects. We acknowledge this result represents one out of many interhemispheric connections which show typical microstructure and do not want to overinterpret the finding.

4.4.3. Graph analysis

Age related changes in the structural brain connectome

We sought to investigate the potential effects of HIV infection on the structural organization of CPHIV at 9 years. Studies investigating age-related changes in structural organization report significant increases in node strength and global efficiency, with a decrease in clustering coefficient from childhood to adulthood (Hagmann *et al.*, 2010; Huang *et al.*, 2015). Increased node strength reflects greater signal transduction, particularly of long pathways (Hagmann *et al.*, 2010; Rubinov and Sporns, 2010). Increased global efficiency along with a decrease in clustering coefficient suggests increased functional integration (Rubinov and Sporns, 2010). White matter connectivity profiles among adjacent regions decrease in favor of long-range connections between more sparsely located

regions, consequently functional segregation between these regions decreases with age. Removal of nodes (e.g., cortical, or subcortical areas) and edges (e.g., white matter pathways) from such a network are computational constructs that model the disruptive effects of lesions or degeneration caused by trauma or disease (Farooq, Lenglet and Nelson, 2020). Network robustness refers to a network's ability to display elasticity to grey and white matter insults such as the removal of nodes or edges (Bullmore and Sporns, 2012). Network robustness increases with age, with younger brains more vulnerable to node and edge altering pathologies. In summary, regional white matter maturation follows a defined age-dependent growth trajectory while structural networks display dynamic topological properties that reflect these growth patterns. Individual white matter tracts and structural networks may display age-related vulnerabilities to HIV-related disruptions.

Global effects

We found no significant differences in modularity, global transitivity, and global efficiency between CPHIV and CHU. At the global network level, efficiency increases, and modularity and characteristic path length decrease over time (Cao et al., 2014; Dennis et al., 2013; Hagmann et al., 2010; Wierenga et al., 2016). A lack of changes in the brain modular structure in the CPHIV group suggests a typical structural network.

Nodal effects

We found a significantly lower degree on the left inferior temporal gyrus node in CPHIV after FDR correction. Nodal degree is a centrality measure which is the number of edges connecting a node to the rest of the network of brain regions (Rubinov and Sporns 2010). Decreased nodal degree in the inferior temporal gyrus could have functional and structural implications related to temporoparietal area, where it is located. This densely connected local network is where we also find predominant alterations in white matter integrity using DTI tractography. Further, the inferior temporal gyrus (Brodmann area 20) is an area of the neocortex that plays an important role in mediation of verbal fluency. This cortical region is important for semantic language and has important neural interconnections with medial temporal cortex structures, especially the parahippocampal gyrus (Scheff *et al.*, 2011). Connections between inferior temporal gyrus and other gyri in the fronto-temporoparietal lobes via association fibers point to its function in language (Lin *et al.*, 2020a). In our tractographic analysis, we demonstrated white matter alterations in connections between the inferior temporal gyrus and other regions in the temporal and parietal lobe. In addition, the temporal lobe was heavily impacted in CPHIV compared to CHU with interconnectivity between regions within this lobe characterized by demyelination and possible axonal loss. The identified nodal effects represent an aggregate of decreased connectivity strengths in later-developing fronto-temporal regions,

consistent with research showing increased vulnerability to disruption in brain regions undergoing rapid development (Babikian et al., 2015).

4.4.4. Associations with clinical measures and neuropsychological scores

Long-term reductions in gray and white matter volumes in adolescents living with perinatal HIV are associated with cognitive impairments (S Cohen et al., 2015; Lewis-de los Angeles et al., 2017; Yu et al., 2019). The subgroup of CPHIV represented in this thesis with imaging data, as well as the entire cohort tested, underperformed on KABC Index Scores: sequential processing as compared to CHU (Fig. 3.5) (van Wyhe *et al.*, 2022). Poor performance on sequential processing is indicative of auditory working memory deficits. Working memory has been reported to show a strong association with academic achievement (Milligan and Cockcroft, 2017).

In our investigation looking at neuropsychological scores and DTI measures within HIV-affected tracts, we found negative associations between MD and sequential processing across the study participants in tracks connecting the right putamen to the right precentral gyrus. Among CHU only, we found negative correlations between sequential processing and MD in basal ganglia connections to limbic and fronto-parietal regions. Consistent with the finding of associations between regional grey matter volume reductions in the left and right PREC with poorer working memory, processing speed, and left RMF with cognitive proficiency and working memory and cognitive proficiency (Lewis-de los Angeles *et al.*, 2017). These significant associations where increased MD, AD and/or RD was correlated with lower auditory working memory were found in basal ganglia connections to limbic and fronto-parietal regions. Further these associations hold when tested across the sample, suggesting ongoing development in fronto-striatal pathways at 9 years.

Among CPHIV, we found negative associations between MD, AD and/or RD in tracks connecting the insula temporoparietal junction where higher MD was associated with poorer sequential processing. Particularly, lower sequential processing was associated with higher MD in the right banks of superior temporal sulcus and right superior temporal gyrus, while higher MD and RD were associated with lower sequential processing in the fibers connecting the right inferior parietal gyrus and right superior temporal gyrus. Additionally, lower sequential processing was associated with higher MD and RD in the tract connecting the left fusiform and the left superior temporal gyrus. Neuronal atrophy of temporoparietal regions is associated with language impairment in advanced Alzheimer's (Harasty *et al.*, 1999). These associations were found in the CPHIV group only, suggesting that the tracts of the language area and associated with HIV disease specific auditory working memory deficits. Studies have shown that language impairment in children often occurs alongside deficient working memory capacity (Haresabadi, no date). Similarly, children with deficits in auditory working memory have been shown to have difficulty learning a second language (Ardila, 2003).

In our graph analysis reduced connectivity to the inferior temporal gyrus was associated with sequential processing across the cohort. The inferior temporal gyrus displays altered interconnectivity with fronto-temporoparietal gyri which suggests impairment in language function in CPHIV (Lin *et al.*, 2020a). However, the inferior temporal gyrus has also been implicated in reading function (Lin *et al.*, 2020a). Particularly, lesions to the posterior section of the inferior temporal gyrus are associated reading impairment (Sakurai, 2004). This suggests inferior temporal gyrus involvement in reading function through storing the visual word (Lin *et al.*, 2020b). Working memory predicts performance in reading function in children (Cain, Oakhill and Bryant, 2004). Poor working memory may adversely affect the reading function in CPHIV. Studies looking at the growth trajectory of working memory capacity report a curvilinear, increasing yet decelerating growth pattern (Tulsky *et al.*, 2013; Stipek and Valentino, 2015; Lensing and Elsner, 2018; Reynolds *et al.*, 2022). The finding of altered interconnectivity between inferior temporal gyrus and fronto-temporoparietal brain regions suggests delays in language and working memory development associated with a delay in maturation of white matter in these areas in CPHIV.

Temporal evolution of general working memory and associated white matter changes is well documented. White matter pathways in the temporal, parietal and frontal cortices were associated with working memory in aging adults (Charlton *et al.*, 2010). Studies report significant association between FA and AD of the left superior longitudinal fasciculus and the Perceptual Organization Index, a measure of visual-spatial organization and visual-motor skills within a defined period (Rosenblum-Fishman and Forbes, 2013), and a significant correlation between FA of the left SLF and the Working Memory Index in healthy human adults (Koshiyama *et al.*, 2020). Longitudinal analysis of white matter changes and functional connectivity in children and young adults (6 – 25 years) revealed FA and white matter volume in fronto-parietal and fronto-striatal white matter tracts and, BOLD activity in caudate are predictive of working memory capacity. In a cross-sectional analysis, working memory capacity correlated with BOLD activity in frontal and parietal regions, cortical thickness in parietal cortex, and both FA and white matter volume of fronto-parietal and fronto-striatal tracts (Darki and Klingberg, 2015). Similarly, in adolescents (8 – 21 years), FA of the bilateral SLF showed a positive association with verbal working memory performance and partially mediated increases in verbal fluency as a function of increasing age (Peters *et al.*, 2012). In a cohort of 8 – 19 typically developing participants, verbal working memory was related to structural properties of cortical regions within the fronto-parietal network and connecting pathways during childhood and adolescence. More specifically, storage capacity was linked to the supramarginal gyrus and rostral middle frontal cortex, while RD in the SLF was associated with working memory performance. (Østby *et al.*, 2011). Further evidence supporting arcuate fasciculus/superior longitudinal fasciculus (AF/SLF) involvement in speech processing and verbal working memory have been presented in single patient imaging studies where damage to the AF/SLF and aphasia is reported

(Yamada *et al.*, 2007; Meyer *et al.*, 2014). A significant association between higher FA in the left fronto-parietal network and better spatial working memory skills was reported in typically developing children of ages 7 to 13 years (Vestergaard *et al.*, 2011).

4.4.5. Effects of ART initiation in CPHIV on white matter maturation

As at 7 years, we continue to find no ART initiation differences among CPHIV.

4.4.6. CHUU vs. CHEU

In a VWA at 7 years, we reported clusters of higher FA in the posterior corona radiata and corticospinal tract in CHEU children (Jankiewicz *et al.*, 2017). In addition, we found higher FA in CHEU compared with CHUU for connections within the cingulum bundle, the forceps major and the SLF using tractography at 7 years (Madzime *et al.*, 2021). Contrary to our findings at age 7, we find no significant FA and MD differences within our population of CHEU children at 9 years. These results suggest the exposure related findings in VWA and tractography at age 7 in our cohort likely represented delayed white matter maturation that has resolved by age 9 years.

Further, these results add the small body of literature focused on white matter development in CHEU. Our findings are similar to a 2015 study in 10-year-old CHEU which also reported no exposure differences in FA or MD (Jahanshad *et al.*, 2015). The study also reported associations between DTI metrics and neuropsychological scores that also seems to be present even where there are no group differences between CHEU and CHUU (Jahanshad *et al.*, 2015), suggesting continued white matter maturation within associated cognitive domains.

4.5. Conclusion

Using DTI Tractography, we found HIV-related alterations in white matter connectivity in fronto-temporoparietal and limbic regions in a cohort of 9- to 10-year-old children. When investigating the influence of HIV infection on the structural organization CPHIV, we found nodal dysconnectivity in the inferior temporal gyrus. The extensive involvement of the inferior temporal gyrus in connections of the fronto-temporoparietal areas, which are in active maturation, makes the white matter connecting to it particularly vulnerable to disease. In addition, these alterations were associated with auditory working memory primarily among CHU, suggesting these abnormalities disrupt typical white matter connections participating in this domain. In CPHIV, we observe typical networks that are robust to the effects of altered connectivity among regions of the temporoparietal cortex, limbic and subcortical areas. In addition, we observe a robust global network despite dysconnectivity tracts connecting the inferior temporal gyrus of CPHIV. Lastly, we observe no HIV exposure effects on

white matter integrity and network measures suggesting differences reported at 7 years in this cohort have resolved.

V. Discussion

Within our cohort, this thesis aimed to determine if regional HIV-related white matter abnormalities observed at 5 and 7 years continued into early adolescence as well as if HIV infection and exposure influence structural connections and organization and contribute to neuropsychological deficits. Using VWA analyses, we identified persistent HIV-related white matter alterations as well as affected tracts to fronto-temporoparietal areas that relate to auditory working memory deficits in a cohort of 9 to 10-year-old CPHIV who initiated ART in infancy. Further, this work determined specific grey matter regions, such as the putamen and insula, linked to abnormal white matter tracts.

This thesis used two different methods to analyze diffusion data. The goal of the first study was to compare DTI outcomes at age 9 years with previous work done at 5 and 7 years. Since previous work used a VWA approach, this study followed the same pipeline in order to provide a consistent picture of age-related changes in the cohort. By analyzing the movement of water in each voxel of a DTI image, VWA DTI provides information about the microstructural properties of brain tissue and can evaluate local perturbations diffuse throughout the brain due to injury or disease. The study indeed found clusters in similar regions as previous studies, showing that there is persistent white matter damage in this cohort with age.

Furthermore, this thesis uncovered newer effects that were not reported consistently from age 5 through 9. Particularly, we report a cluster of increased MD in the left-SLF in 5 year old and 9 year old CPHIV that were not present at 7 years. We also report new clusters in the forceps major at age 9 suggesting WM vulnerabilities to HIV continue between scanning sessions as the cohort matures. Additionally, contrary to our earlier findings at age 7 years, CHUU present with no statistically significant white matter alterations. Further, we speculate that due to these studies being of a cross-sectional nature, alterations found at each time point may represent delay at one age that resolve by the next age.

By conducting a cross-sectional analysis at multiple time points, we can identify trends over time. This can help with understanding how white matter outcomes are changing over time in both infection and exposure groups. Sometimes, cross-sectional studies detect effects that are not detected by longitudinal analysis. This may be because the effect is present in the short term and may dissipate over time. In our case, there may be effects associated with early adolescence that may influence white matter susceptibility to HIV-associated insults. A cross-sectional study may capture this effect because it measures the population at a single point in time, while a longitudinal study may miss it because it measures the same population over an extended period. However, it is important to note that the variability in sample participants and size with age introduced by newly enrolled participants

and dropouts in our cohort limit our interpretation of the difference in microstructural outcomes between groups. It is still interesting to see persevering damage as some children were studied across all ages.

The second work presented in this thesis uses DTI tractography. This analysis allowed for the inclusion of grey matter regions into our interpretation of white matter changes, which is not possible using the VWA approach. DTI tractography can generate three-dimensional fiber-tract reconstructions of pathways between brain ROIs through a propagation algorithm that seeks the path of principal diffusion. From this a connectivity profile between sparsely distributed brain ROIs can be developed. This was particularly of interest considering previous studies in the cohort have identified grey matter regions affected by HIV at ages 5 and 7 years. As this analysis was more focused on trying to understand the relationship with grey matter, we also explored associations with neuropsychological outcomes. An assessment of the relationship between diffusion metrics and neuropsychological outcomes revealed associations between DTI tractography derived MD, AD and/or RD and auditory working memory in CPHIV. The associations we found in the CHU group suggest that this relationship is not specific to HIV infection. Instead, the relationship found in the CHU between MD, AD and/or RD with auditory working memory in basal ganglia connections to frontal, parietal and limbic may reflect continued white maturation and associated working memory development. Thus, in this thesis, we identified white matter diffusivity associations with auditory working memory in fronto-striatal and temporoparietal areas. Protracted maturational trajectories lead to an increased vulnerability to disruption in these tracts and subsequent working memory function.

Another advantage of the tractography approach is the possibility of constructing network measures. We included this analysis with our group wise comparisons, allowing us to identify if the white matter abnormalities reported impact the overall architecture of white matter. Surprisingly, we identified many connections disrupted by HIV however the global properties of white matter networks remain intact. We did however identify a regional organizational disruption, which was related to a cognitive domain in which CPHIV demonstrated a cognitive deficit. The graph analysis provided a focal point - alterations in fronto-temporoparietal areas and the broken associations with auditory working memory - for the effects of HIV at the beginning of adolescence in this cohort.

Performing tractography also provided an opportunity to compare results between the two methods. To date, most published DTI studies use a VWA approach. In our cohort from age 5 to 9 we revealed impaired white matter microstructure characterized by persistent regions of lower FA, higher MD, AD and RD using the same VWA pipeline. Particularly, HIV-related effects in the tracts connecting the fronto-temporoparietal regions such as IFOF, ILF, SLF, ATR and CST/SCR detected at ages 7 and 9, while intensities in the forceps minor were seen from age 5 through 9 (Table 6.1 and Fig. 6.1 in

the appendix). The tractographic analysis identified white matter alterations consistent with in our VWA, thereby validating their involvement in HIV-related white matter assault in 9-year-old CPHIV. Figure 5 shows voxel-wise effects wholly intersect with tractographic analysis results. This suggests that VWA effects are subsets of the full extent of the damage demonstrated by our tractographic analysis.

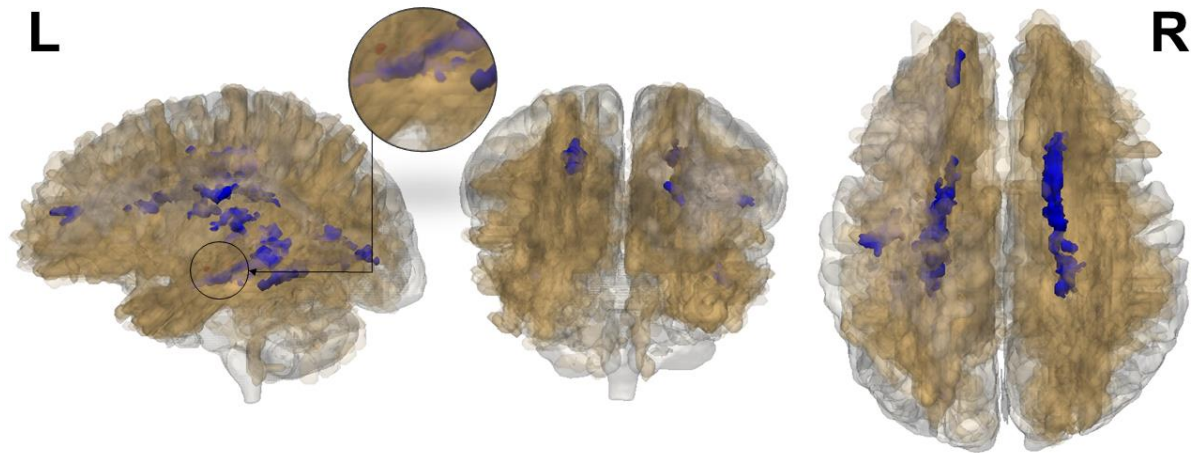


Fig 5. Voxel-wise clusters showing either lower FA (in red) or higher MD (in blue) in CPHIV compared to CHU. The clusters are shown overlaid on masks of DTI tractography results (in brown) from the same comparison.

Using DTI tractography, we also reported additional HIV-related alterations which were not identified using VWA. A potential reason for the difference in methodical outcomes could be that VWA analysis loses statistical power due to stringent multiple comparison corrections at the voxel level. Moreover, our VWA method is prone to type II error as it limits the analysis of voxelwise intensities to an intersection of white matter voxels. Consequently, some disease related intensities outside of this intersection are not detected. These findings are not unexpected as VWA only allows for the detection of clusters of reduced volume due to stringent thresholding and registration steps that are characteristic of this method. Consequently, clusters of diffusivity differences that do not meet a specific cluster size threshold were not considered for cluster-tract identification. This clustering method limits the occurrence of type 1 error at the cost of reduced sensitivity in VWA. Alternatively, tractography based DTI analysis averages intensities over the full length of pairwise wise white matter connections and hence can detect more pronounced effects.

Strengths and limitations and future work

Strengths of this work include the presentation of two different methods that yield similar outcomes. Neuroimaging studies can be biased due to software choices and pipelines used, and it is comforting to observe similar results when using different methodological approaches on the same data set. The

cohort explored in this thesis includes a rich dataset, with clinical and neuropsychological data as well as previous imaging analyses at early ages. This data allows for a better interpretation and context of the current results.

In addition, a strength of the work done in the thesis is that sociodemographic variables of interest such as age and sex were well matched across groups. Moreover, these children are of a similar socioeconomic status as they were drawn from the same community. However, group sizes in the CHEU vs. CHUU and ART before 12 weeks vs. ART after 12 weeks subgroups were small and unequal, respectively. An unequal number of participants (n) could potentially bias the results. Particularly, ART before 12 weeks group (n = 45) was significantly larger than the ART after 12 weeks (n=13) group and thus may have had more statistical power to detect differences, even if those differences are small or not meaningful.

While the inclusion of clinical data in the thesis is a strength, there were limitations in the data available. While VL in CPHIV was suppressed at the time of scan, spikes in viral load were observed at varied time points in the first 8 years of follow up in this cohort. This time series of variable viral loads was not considered when modelling effects in CPHIV vs CHU comparison, potentially confounding our results. Additionally, treatment related outcomes were largely dependent on the age at ART initiation, with CPHIV who initiated ART after-12w reaching Nadir CD4 counts and percentages when much younger than their early treated counterparts. Furthermore, ART interruption was only introduced in the ART before-12w group. Age at ART initiation was thus identified as a potential confounding factor and is the basis for conducting an independent analysis for these CPHIV subgroups.

Every neuroimaging modality has limitations that need to be taken into consideration when interpreting study data. Diffusion weighted imaging typically has low spatial resolution. Diffusion weighted imaging relies on certain biological assumptions, such as the single tensor model in DTI that works with the assumption that water diffusion is Gaussian and can only infer a single dominant fiber orientation within each voxel. Consequently, the ability to resolve fine details of white matter pathways is impacted, particularly in regions with complex fiber crossings. Diffusion data is sensitive to noise, and even small amounts of noise can lead to errors in estimating diffusion parameters and fiber tractography. In addition, there is significant variability in the diffusion properties of white matter tracts between individuals, which can make it challenging to draw general conclusions or make group comparisons. A more detailed discussion about these effects is provided in sections 2.2.6-8.

There are limitations due to the differences between the approaches used. Using a tract identification algorithm, we identified the tracts through which the affected tracts traverse. Cluster tract

classifications in VWA were identified by a combination of peak and center-of-gravity coordinates of the cluster relative to the JHU probabilistic white matter atlas in FSLeyes. Consequently, clusters were attributed to the probabilistic tract in which it occupies the most space, limiting the comparative potential between tractography and VWA results.

We performed our analysis on a population of 9–10-year-olds. The inferences we may make are thus restricted to children of that age. Therefore, longitudinal analysis may provide insight into influence of HIV on white matter development. Based on our findings, future work to consider would include longitudinal analysis using a tractographic approach. This approach would allow for the inclusion of grey matter regions into the analysis, providing a better understanding of white matter maturation. Moreover, no quantitative comparisons of outcomes were conducted between the different age groups. As such we lack an understanding of how outcomes vary across different age cohorts. In addition, future work combining tractography with resting state functional MRI (RS-fMRI) would allow for a better understanding of the functional consequences of the abnormalities presented.

5.2. Conclusions

Using DTI VWA, tractography and graph theory analyses along with neuropsychological test, this work describes the breadth of HIV related WM alterations in CPHIV and CHEU approaching adolescence. This thesis adds to the body of knowledge that demonstrates the persistent nature of HIV-related white matter abnormalities as well as the role this damage plays in cognitive deficits. The predominant alterations in fronto-temporoparietal areas, the links with auditory working memory and delayed viral suppression and treatment interruption present a pattern of HIV related WM pathology in this cohort at the beginning of adolescence.

VI. Appendix

Table 6.1 | Peak and/or center of gravity (COG) coordinates (in MNI space) of significant clusters showing lower FA or higher MD in CPHIV than CHU at ages 5, 7 and 9. Table only showing overlapping regions and matching sets are indicated by a representative number.

5 Years	7 Years		9 Years	
Cluster Location	Cluster Location		Cluster Location	
Coordinates (mm)	Peak (mm)	COG (mm)	Peak (mm)	COG (mm)
Association tracts				
L IFOF	L Inferior longitudinal fasciculus		L Inferior longitudinal fasciculus	
(-37; -10; -17) ¹	(-34.0; -29.5; 3.5) ¹	(-34.0; -29.5; 3.5) ¹	(-36; -17; -8) ¹	(-34.4; -16.3; -5.41) ¹
			L Inferior fronto-occipital fasciculus	
			(-41; -7; -15) ¹	(-34; -31.4; 3.28) ¹
	R Inferior fronto-occipital fasciculus		R Inferior fronto-occipital fasciculus	
	(36.0; -29.5; 1.5) ²	(33.4; -31.2; 7.3) ²	(39; -27; -6) ²	(5.9; -24.1; -0.145)
	L Anterior thalamic radiations		L Anterior thalamic radiations	
	(-24.0; 10.5; 11.5) ³	(-22.4; 14.6; 12.5)	(-25; 8; 17) ³	(-24; 1.52; 23.8)
Projection tracts				
	L Superior corona radiata		L Superior corona radiata	
	(-18.0; -28.5; 25.5) ⁴	(-16.9; 27.4; 25.8)	(-23; -26; 31) ⁴	(-21.4; -15.5; 37.6) ⁵
	L Superior corona radiata			
	(-18.0; -27.5; 41.5) ⁴	(-19.8; -17.4; 39.3) ⁵		
R SCR/CST	R Superior corona radiata		R Superior corona radiata	
(19; -24; 42) ⁷	(18.0; 24.5; 29.5) ⁷	(16.1; 23.6; 31.9) ⁶	(17; 19; 27) ⁶	(19; -7.71; 36.7) ⁷
Interhemispheric tracts				
L Forceps minor			L Forceps minor	
(-19; 43; 14) ⁸			(-18; 49; 4) ⁸	(-16.7; 50.9; 3.22)
L Forceps minor				
(-17 ;42; -1) ⁸				
	R Forceps minor		R Forceps minor	
	(16.0; 40.5; -0.5) ⁹	(16.0; 40.5; -0.5)	(16; 45; 15) ⁹	(15.5; 47.2; 16.7)

¹ Overlapping regions in the temporal area of the left inferior fronto-occipital fasciculus. ²Overlapping regions in the temporal area of the right inferior fronto-occipital fasciculus. ³ In the left anterior thalamic radiations two regions occupied similar spatial locations. ^{4,5}Across all ages, alterations were found in the anterior (4) and superior (5) portion of the left corona radiata. ^{6,7}We also found overlapping regions of altered white matter integrity in the right superior corona radiata. ⁸CPHIV related effects at 5 years and 9 years were found in similar spatial coordinates in the left forceps minor. ⁹Right forceps minor.

Inferior fronto-occipital fasciculus



Forceps minor



Anterior thalamic radiations



Corticospinal tract/Corona radiata

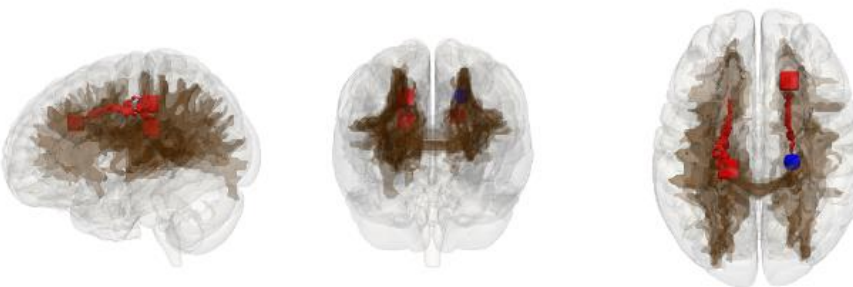


Figure 6.1. Clusters showing either lower FA (in blue) or higher MD (in red) in CPHIV compared to CHU in CPHIV compared to CHU across ages 5 (spheres), 7 (cubes) and 9 (complete voxel-wise intensity mask) years that overlap in space. The clusters were overlaid on masks of the corresponding probabilistic tracts (JHU White-Matter Tractography Atlas and JHU ICBM-DTI-81 White Matter Labels).

Table 6.2. | Associations among CPHIV of clinical and treatment-related variables with DTI parameters in regions where HIV-related white matter changes were found. Asterisks indicate associations that survive threshold for significance uncorrected for multiple comparisons ($p < 0.05$).

Cluster location	Size (mm ³)	Age at ART initiation		Age at 1st VL suppression		Baseline CD4%		Scan CD4%		Nadir CD4%		Age at Nadir CD4%	
		Spearman p	p	Spearman p	p	Pearson r	p	Pearson r	p	Pearson r	p	Spearman p	p
L IFOF	212	0.01	0.924	0.02	0.898	0.12	0.368	-0.04	0.786	-0.04	0.753	0.12	0.371
L IFOF		-0.09	0.5	0.19	0.148	0.1	0.47	-0.1	0.483	-0.1	0.464	-0.01	0.946
L IFOF		-0.08	0.554	-0.01	0.927	-0.09	0.514	-0.01	0.915	-0.04	0.791	-0.08	0.542
L IFOF	2076	-0.14	0.281	0.17	0.21	-0.06	0.642	-0.11	0.443	-0.13	0.349	-0.11	0.414
L IFOF		-0.21	0.116	0	0.993	0.01	0.918	-0.19	0.167	-0.14	0.306	0.11	0.393
L IFOF		-0.09	0.524	0.27	0.044*	-0.09	0.516	-0.02	0.878	-0.08	0.554	-0.22	0.094
R IFOF	422	-0.07	0.61	0.19	0.159	-0.2	0.142	-0.18	0.194	-0.22	0.1	-0.07	0.624
R IFOF		-0.2	0.126	0.09	0.5	-0.03	0.82	-0.12	0.388	-0.1	0.442	0.21	0.108
R IFOF		0.06	0.666	0.19	0.148	-0.23	0.081	-0.16	0.241	-0.22	0.102	-0.16	0.239
L SCR	911	-0.05	0.694	0.23	0.079	-0.19	0.152	-0.13	0.355	-0.18	0.177	-0.17	0.212
L SCR		-0.04	0.791	0.18	0.179	-0.1	0.467	-0.05	0.696	-0.2	0.135	-0.12	0.378
L SCR		-0.09	0.502	0.13	0.339	-0.17	0.211	-0.12	0.395	-0.09	0.525	-0.03	0.804
R SCR	644	0.06	0.645	0.25	0.063	-0.13	0.318	-0.19	0.164	-0.16	0.227	-0.18	0.181
R SCR		0	0.981	0.14	0.303	-0.13	0.319	0.05	0.708	-0.13	0.347	-0.17	0.193
R SCR		0.06	0.655	0.19	0.153	-0.07	0.583	-0.25	0.063	-0.11	0.408	-0.07	0.601
R F. Major	624	-0.12	0.354	0.26	0.051	-0.12	0.364	-0.09	0.536	-0.07	0.586	-0.25	0.061
R F. Major		-0.05	0.695	0.15	0.255	-0.09	0.48	-0.24	0.074	-0.18	0.188	0.01	0.931
R F. Major		-0.06	0.66	0.23	0.087	-0.08	0.56	0.05	0.723	0.02	0.86	-0.25	0.058
L F. Minor	204	0.14	0.303	0.11	0.399	-0.05	0.685	-0.04	0.775	0	0.998	0.14	0.288
L F. Minor		0.15	0.274	-0.01	0.965	-0.21	0.122	-0.07	0.607	-0.07	0.581	0.17	0.214
L F. Minor		0.03	0.835	0.13	0.345	0.09	0.494	0.01	0.927	0.05	0.706	-0.04	0.764
R F. Minor	195	0.13	0.313	0.14	0.291	0.02	0.864	-0.12	0.366	0.02	0.858	-0.01	0.934
R F. Minor		0.12	0.371	-0.06	0.66	-0.18	0.183	-0.1	0.459	-0.12	0.387	-0.12	0.373
R F. Minor		0.09	0.5	0.23	0.086	0.14	0.293	-0.06	0.659	0.1	0.45	0.06	0.663
L ATR	293	-0.14	0.301	0.14	0.294	-0.14	0.308	-0.16	0.233	-0.23	0.088	-0.01	0.962
L ATR		-0.06	0.646	0.03	0.83	-0.22	0.093	-0.19	0.161	-0.25	0.057	-0.07	0.624
L ATR		-0.11	0.432	0.12	0.354	0.03	0.847	-0.03	0.831	-0.05	0.691	0.07	0.581
L SLF	227	0.06	0.637	0.27	0.041*	0.11	0.427	0.05	0.718	0.01	0.92	-0.06	0.681
L SLF		-0.23	0.077	0.03	0.803	-0.16	0.241	0.01	0.96	-0.16	0.223	0.09	0.497
L SLF		0.19	0.145	0.28	0.035*	0.2	0.135	0.05	0.709	0.1	0.465	-0.1	0.474

Table 6.3.A: FDR corrected results from comparisons of fractional anisotropy, mean diffusivity, axial diffusivity, radial diffusivity, and fractional Number of Tracks in CPHIV compared to CHU. Asterisks indicate associations that survive threshold for significance corrected for multiple comparisons (FDR $q < 0.05$).

ROI X	ROI Y	Area X	Area Y	Fractional anisotropy				Mean diffusivity				Axial diffusivity				Radial diffusivity				fractional Number of tracks			
				stdB	se	p	FDR q	stdB	se	p	FDR q	stdB	se	p	FDR q	stdB	se	p	FDR q	stdB	se	p	FDR q
L_CER	L_THAL	L-BST-CER	L-Subcortical	-0.680	0.209	0.002	0.069	0.396	0.209	0.062	0.094	0.235	0.212	0.271	0.412	0.437	0.208	0.038	0.075	0.028	0.209	0.894	0.986
L_CER	BST	L-BST-CER	B-BST-CER	-0.447	0.207	0.034	0.201	0.247	0.212	0.246	0.300	0.155	0.212	0.468	0.600	0.472	0.212	0.029	0.067	0.023	0.214	0.915	0.986
L_CER	L_VDC	L-BST-CER	L-Subcortical	-0.176	0.210	0.404	0.602	0.360	0.210	0.090	0.127	0.322	0.211	0.131	0.250	0.470	0.213	0.030	0.068	-0.483	0.212	0.025	0.302
L_CER	R_CER	L-BST-CER	R-BST-CER	-0.011	0.214	0.958	0.973	0.335	0.209	0.113	0.153	0.197	0.209	0.349	0.499	0.370	0.210	0.082	0.124	0.170	0.210	0.422	0.931
L_CER	R_VDC	L-BST-CER	R-Subcortical	-0.489	0.213	0.024	0.188	0.403	0.216	0.066	0.099	0.478	0.216	0.029	0.092	0.376	0.217	0.087	0.127	0.661	0.225	0.004	0.183
L_CER	L_ENT	L-BST-CER	L-Temporal	-0.257	0.213	0.232	0.469	-0.091	0.214	0.672	0.716	-0.209	0.214	0.332	0.482	0.032	0.214	0.882	0.891	0.074	0.214	0.730	0.979
L_CER	L_FUS	L-BST-CER	L-Occipital	0.102	0.211	0.629	0.757	0.169	0.212	0.427	0.492	0.213	0.211	0.317	0.467	0.079	0.211	0.710	0.745	-0.050	0.209	0.812	0.986
L_CER	L_LING	L-BST-CER	L-Occipital	0.101	0.210	0.631	0.757	0.505	0.210	0.018	0.044*	0.422	0.211	0.048	0.121	0.392	0.210	0.065	0.104	0.534	0.227	0.021	0.286
L_CER	L_PHPC	L-BST-CER	L-Occipital	-0.359	0.208	0.088	0.288	0.120	0.213	0.574	0.632	-0.086	0.213	0.688	0.770	0.266	0.211	0.210	0.263	0.174	0.207	0.403	0.930
L_THAL	L_CAU	L-Subcortical	L-Subcortical	-0.053	0.213	0.806	0.869	0.250	0.212	0.240	0.294	0.316	0.210	0.136	0.257	0.168	0.212	0.431	0.485	0.019	0.212	0.927	0.986
L_THAL	L_PUT	L-Subcortical	L-Subcortical	-0.364	0.214	0.093	0.295	0.407	0.209	0.055	0.086	0.155	0.210	0.462	0.597	0.429	0.208	0.042	0.078	-0.167	0.205	0.417	0.930
L_THAL	L_PAL	L-Subcortical	L-Subcortical	-0.417	0.207	0.047	0.217	0.197	0.211	0.354	0.419	-0.130	0.208	0.534	0.651	0.543	0.211	0.012	0.044*	-0.167	0.210	0.426	0.934
L_THAL	BST	L-Subcortical	B-BST-CER	-0.641	0.212	0.003	0.080	0.341	0.210	0.109	0.149	0.124	0.211	0.557	0.665	0.464	0.207	0.028	0.066	-0.192	0.212	0.367	0.914
L_THAL	L_HPC	L-Subcortical	L-Subcortical	-0.433	0.209	0.041	0.217	0.479	0.204	0.021	0.046*	0.097	0.211	0.647	0.743	0.611	0.201	0.003	0.027*	-0.460	0.214	0.034	0.354
L_THAL	L_AMG	L-Subcortical	L-Subcortical	-0.416	0.205	0.045	0.217	0.146	0.212	0.493	0.555	-0.108	0.209	0.607	0.707	0.310	0.210	0.143	0.190	-0.069	0.207	0.742	0.979
L_THAL	L_ACC	L-Subcortical	L-Subcortical	-0.589	0.210	0.006	0.101	0.031	0.213	0.885	0.892	-0.046	0.214	0.832	0.873	0.100	0.212	0.640	0.681	-0.068	0.214	0.752	0.979
L_THAL	L_VDC	L-Subcortical	R-Subcortical	-0.586	0.212	0.007	0.101	0.356	0.211	0.094	0.132	0.062	0.212	0.770	0.837	0.449	0.208	0.034	0.071	-0.437	0.208	0.038	0.373
L_THAL	R_THAL	L-Subcortical	R-Subcortical	-0.258	0.208	0.217	0.461	0.165	0.210	0.434	0.498	0.048	0.209	0.819	0.868	0.266	0.211	0.210	0.263	-0.232	0.210	0.271	0.850
L_THAL	R_HPC	L-Subcortical	R-Subcortical	0.089	0.210	0.673	0.786	0.159	0.215	0.462	0.524	0.150	0.213	0.484	0.614	0.140	0.216	0.521	0.570	-0.412	0.217	0.061	0.484
L_THAL	R_VDC	L-Subcortical	L-Frontal	-0.600	0.203	0.004	0.082	-0.063	0.214	0.769	0.793	-0.338	0.210	0.111	0.224	0.167	0.214	0.438	0.492	0.074	0.212	0.727	0.979
L_THAL	L_ISTH	L-Subcortical	L-Occipital	-0.135	0.212	0.527	0.684	0.487	0.207	0.021	0.046*	0.359	0.210	0.090	0.189	0.471	0.207	0.025	0.063	-0.528	0.208	0.013	0.245
L_THAL	L_MOF	L-Subcortical	L-Parietal	-0.571	0.214	0.009	0.114	0.086	0.214	0.689	0.729	-0.014	0.213	0.948	0.967	0.144	0.214	0.501	0.555	0.113	0.207	0.587	0.974
L_THAL	L_PHPC	L-Subcortical	L-Limbic	-0.610	0.204	0.004	0.080	0.196	0.210	0.355	0.419	-0.283	0.210	0.181	0.310	0.472	0.207	0.025	0.063	0.112	0.209	0.594	0.974
L_THAL	L_PARC	L-Subcortical	L-Temporal	-0.227	0.213	0.289	0.514	0.695	0.204	0.001	0.010*	0.268	0.212	0.210	0.340	0.561	0.211	0.009	0.040*	-0.119	0.216	0.585	0.974
L_THAL	L_PSTC	L-Subcortical	R-Limbic	-0.448	0.212	0.037	0.205	0.335	0.214	0.121	0.162	0.103	0.215	0.632	0.733	0.567	0.215	0.010	0.041*	0.180	0.216	0.406	0.930
L_THAL	L_PC	L-Subcortical	L-Limbic	-0.185	0.212	0.385	0.593	0.117	0.213	0.584	0.638	0.060	0.211	0.777	0.837	0.147	0.213	0.492	0.545	-0.173	0.214	0.419	0.930
L_THAL	L_PREC	L-Subcortical	L-Frontal	-0.056	0.215	0.796	0.869	0.512	0.209	0.016	0.040*	0.406	0.211	0.057	0.137	0.344	0.212	0.108	0.150	0.031	0.213	0.883	0.986
L_THAL	L_SP	L-Subcortical	L-Insula	-0.290	0.223	0.196	0.442	0.631	0.208	0.003	0.016*	0.321	0.217	0.142	0.265	0.643	0.207	0.003	0.026*	-0.235	0.217	0.283	0.865
L_THAL	L_ST	L-Subcortical	L-Subcortical	0.037	0.217	0.865	0.903	0.296	0.220	0.183	0.230	0.352	0.214	0.103	0.210	0.400	0.215	0.065	0.104	-0.342	0.213	0.112	0.682
L_THAL	L_INS	L-Subcortical	L-Central sulcus	-0.181	0.208	0.387	0.593	0.528	0.205	0.012	0.034*	0.309	0.204	0.133	0.252	0.486	0.208	0.021	0.059	-0.013	0.198	0.946	0.986
L_THAL	R_ISTH	L-Subcortical	L-Parietal	0.350	0.207	0.095	0.297	0.063	0.214	0.769	0.793	0.240	0.210	0.257	0.399	-0.133	0.215	0.536	0.584	-0.091	0.214	0.671	0.976
L_CAU	L_PUT	L-Subcortical	L-Subcortical	-0.309	0.209	0.142	0.378	0.457	0.208	0.030	0.058	0.236	0.210	0.263	0.406	0.459	0.207	0.029	0.068	0.150	0.209	0.476	0.960
L_CAU	L_PAL	L-Subcortical	L-Subcortical	-0.564	0.211	0.009	0.114	0.256	0.211	0.229	0.282	0.041	0.209	0.847	0.885	0.441	0.211	0.039	0.075	-0.109	0.213	0.610	0.974
L_CAU	L_HPC	L-Subcortical	L-Subcortical	-0.262	0.210	0.216	0.460	0.476	0.207	0.024	0.051	0.440	0.213	0.042	0.112	0.443	0.208	0.036	0.072	-0.045	0.209	0.831	0.986
L_CAU	L_AMG	L-Subcortical	L-Subcortical	-0.376	0.207	0.073	0.253	0.250	0.211	0.240	0.294	0.003	0.210	0.988	0.994	0.341	0.211	0.109	0.150	-0.020	0.214	0.926	0.986
L_CAU	L_ACC	L-Subcortical	L-Subcortical	0.048	0.212	0.821	0.876	0.466	0.216	0.034	0.063	0.090	0.212	0.673	0.761	0.447	0.213	0.039	0.075	-0.165	0.211	0.435	0.938
L_CAU	L_VDC	L-Subcortical	L-Subcortical	-0.641	0.215	0.004	0.080	0.363	0.204	0.078	0.114	0.097	0.205	0.638	0.737	0.405	0.207	0.053	0.092	-0.030	0.212	0.888	0.986
L_CAU	R_CAU	L-Subcortical	R-Subcortical	-0.268	0.211	0.206	0.457	-0.093	0.213	0.662	0.712	-0.282	0.212	0.186	0.312	0.061	0.213	0.776	0.801	0.087	0.211	0.682	0.976
L_CAU	L_CAC	L-Subcortical	L-Limbic	-0.133	0.209	0.524	0.684	0.197	0.213	0.357	0.419	0.110	0.214	0.607	0.707	0.219	0.212	0.303	0.358	0.255	0.213	0.235	0.846
L_CAU	L_CMF	L-Subcortical	L-Frontal	-0.040	0.218	0.854	0.897	0.297	0.216	0.171	0.218	0.327	0.215	0.132	0.252	0.174	0.217	0.425	0.482	0.074	0.217	0.733	0.979
L_CAU	L_ISTH	L-Subcortical	L-Limbic	-0.471	0.215	0.031	0.201	0.435	0.215	0.046	0.076	0.077	0.214	0.718	0.795	0.517	0.211	0.016	0.051	0.227	0.212	0.288	0.865
L_CAU	L_LOF	L-Subcortical	L-Frontal	-0.112	0.210	0.595	0.727	0.542	0.207	0.010	0.031*	0.374	0.212	0.081	0.176	0.430	0.209	0.042	0.078	0.153	0.211	0.469	0.954
L_CAU	L_MOF	L-Subcortical	L-Parietal	-0.278	0.210	0.189	0.432	0.444	0.208	0.035	0.065	0.318	0.209	0.131	0.250	0.447	0.208	0.034	0.071	-0.080	0.206	0.698	0.979
L_CAU	L_PARC	L-Subcortical	L-Limbic	-0.447	0.210	0.036	0.204	0.583	0.207	0.006	0.024*	0.538	0.212	0.013	0.066	0.567	0.207	0.007	0.035*	-0.010	0.212	0.962	0.986
L_CAU	L_PSTC	L-Subcortical	L-Frontal	-0.185	0.216	0.393	0.593	0.298	0.215	0.169	0.215	0.440	0.219	0.048	0.121	0.285	0.214	0.186	0.236	0.232	0.212	0.278	0.854
L_CAU	L_PC	L-Subcortical	L-Frontal	-0.419	0.208	0.047	0.217	0.068	0.209	0.748	0.783	-0.197	0.208	0.348	0.499	0.285	0.211	0.180	0.230	0.213	0.209	0.312	0.871

Table 6.3.B: FDR corrected results from comparisons of fractional anisotropy, mean diffusivity, axial diffusivity, radial diffusivity, and fractional Number of Tracks in CPHIV compared to CHU. Asterisks indicate associations that survive threshold for significance corrected for multiple comparisons (FDR $q < 0.05$).

ROI X	ROI Y	Area X	Area Y	Fractional anisotropy				Mean diffusivity				Axial diffusivity				Radial diffusivity				fractional Number of tracks			
				stdB	se	p	FDR q	stdB	se	p	FDR q	stdB	se	p	FDR q	stdB	se	p	FDR q	stdB	se	p	FDR q
L_CAU	L_PREC	L-Subcortical	L-Frontal	-0.060	0.214	0.781	0.861	0.474	0.209	0.025	0.052	0.470	0.208	0.026	0.088	0.329	0.212	0.123	0.166	0.256	0.209	0.222	0.828
L_CAU	L_PCUN	L-Subcortical	R-Limbic	-0.527	0.201	0.010	0.121	0.578	0.209	0.007	0.026*	0.290	0.216	0.183	0.310	0.658	0.203	0.002	0.021*	0.242	0.217	0.268	0.850
L_CAU	L_RAC	L-Subcortical	L-Frontal	-0.272	0.210	0.198	0.445	0.298	0.211	0.162	0.209	0.114	0.213	0.596	0.700	0.336	0.210	0.113	0.155	0.440	0.204	0.033	0.354
L_CAU	L_RMF	L-Subcortical	L-Frontal	-0.197	0.211	0.354	0.577	0.388	0.210	0.067	0.099	0.363	0.210	0.087	0.185	0.336	0.210	0.113	0.155	-0.011	0.214	0.958	0.986
L_CAU	L_SF	L-Subcortical	L-Insula	-0.214	0.210	0.309	0.540	0.488	0.206	0.020	0.046*	0.434	0.207	0.038	0.105	0.431	0.207	0.040	0.077	0.356	0.209	0.091	0.619
L_CAU	L_SP	L-Subcortical	L-Central sulcus	-0.400	0.216	0.067	0.243	0.761	0.205	0.000	0.008	0.641	0.209	0.003	0.044*	0.670	0.208	0.002	0.021*	-0.085	0.218	0.696	0.979
L_CAU	L_INS	L-Subcortical	L-Occipital	-0.381	0.208	0.070	0.246	0.511	0.206	0.015	0.039*	0.215	0.205	0.298	0.444	0.498	0.207	0.018	0.054	-0.415	0.201	0.042	0.387
L_CAU	R_CAC	L-Subcortical	L-Parietal	-0.107	0.214	0.617	0.752	-0.097	0.209	0.643	0.697	-0.140	0.212	0.512	0.634	-0.041	0.210	0.844	0.861	-0.023	0.217	0.915	0.986
L_PUT	L_PAL	L-Subcortical	L-Subcortical	-0.304	0.211	0.153	0.393	0.497	0.207	0.018	0.044*	0.097	0.213	0.648	0.743	0.511	0.207	0.015	0.051	-0.244	0.211	0.249	0.849
L_PUT	L_HPC	L-Subcortical	L-Frontal	-0.569	0.206	0.007	0.101	0.634	0.204	0.002	0.014*	0.396	0.210	0.062	0.145	0.666	0.203	0.001	0.021*	-0.369	0.208	0.079	0.571
L_PUT	L_AMG	L-Subcortical	L-Frontal	-0.313	0.209	0.138	0.374	0.514	0.207	0.015	0.038*	0.362	0.208	0.085	0.182	0.486	0.208	0.021	0.059	-0.136	0.211	0.520	0.966
L_PUT	L_ACC	L-Subcortical	L-Subcortical	-0.534	0.207	0.011	0.121	0.013	0.214	0.951	0.951	-0.535	0.211	0.013	0.066	0.277	0.212	0.194	0.246	-0.182	0.212	0.392	0.930
L_PUT	L_VDC	L-Subcortical	L-Subcortical	-0.436	0.215	0.046	0.217	0.562	0.204	0.007	0.026*	0.353	0.207	0.090	0.189	0.564	0.205	0.007	0.035*	-0.246	0.209	0.243	0.849
L_PUT	L_CMF	L-Subcortical	L-Frontal	-0.190	0.211	0.369	0.581	0.643	0.203	0.002	0.013*	0.571	0.201	0.006	0.051	0.508	0.207	0.016	0.051	-0.073	0.211	0.729	0.979
L_PUT	L_IP	L-Subcortical	L-Parietal	-0.245	0.213	0.254	0.489	0.545	0.210	0.011	0.033*	0.541	0.210	0.011	0.065	0.466	0.211	0.030	0.068	-0.268	0.207	0.198	0.823
L_PUT	L_ISTH	L-Subcortical	L-Limbic	-0.031	0.212	0.883	0.918	0.554	0.208	0.009	0.031*	0.579	0.205	0.006	0.052	0.364	0.211	0.088	0.128	-0.479	0.211	0.026	0.302
L_PUT	L_LOF	L-Subcortical	L-Frontal	-0.311	0.209	0.140	0.376	0.708	0.201	0.001	0.010*	0.600	0.204	0.004	0.049*	0.612	0.204	0.003	0.027*	0.367	0.208	0.080	0.576
L_PUT	L_MOF	L-Subcortical	L-Frontal	-0.229	0.210	0.278	0.505	0.607	0.204	0.004	0.017*	0.526	0.204	0.012	0.065	0.523	0.207	0.013	0.048*	0.110	0.209	0.599	0.974
L_PUT	L_PARC	L-Subcortical	L-Frontal	-0.369	0.214	0.088	0.288	0.805	0.198	0.000	0.006*	0.347	0.213	0.106	0.215	0.895	0.194	0.000	0.003*	0.060	0.216	0.781	0.986
L_PUT	L_POPE	L-Subcortical	L-Subcortical	-0.399	0.206	0.055	0.230	0.931	0.191	0.000	0.001*	0.756	0.195	0.000	0.019*	0.829	0.196	0.000	0.006*	-0.393	0.208	0.062	0.485
L_PUT	L_PTRI	L-Subcortical	L-Subcortical	-0.192	0.211	0.365	0.580	0.566	0.205	0.007	0.026*	0.446	0.206	0.033	0.098	0.349	0.213	0.104	0.146	0.066	0.208	0.752	0.979
L_PUT	L_PSTC	L-Subcortical	L-Frontal	-0.124	0.213	0.562	0.705	0.655	0.203	0.002	0.012*	0.597	0.203	0.004	0.049*	0.486	0.208	0.021	0.059	0.020	0.214	0.925	0.986
L_PUT	L_PC	L-Subcortical	L-Central sulcus	-0.416	0.223	0.066	0.243	0.631	0.207	0.003	0.016*	0.215	0.217	0.325	0.475	0.714	0.208	0.001	0.020*	0.147	0.220	0.506	0.966
L_PUT	L_PREC	L-Subcortical	L-Limbic	-0.170	0.212	0.426	0.618	0.641	0.203	0.002	0.013*	0.547	0.205	0.009	0.057	0.510	0.207	0.016	0.051	0.100	0.212	0.639	0.974
L_PUT	L_RAC	L-Subcortical	L-Parietal	-0.161	0.211	0.446	0.631	0.693	0.209	0.001	0.010*	0.584	0.211	0.007	0.056	0.484	0.213	0.025	0.063	0.505	0.206	0.016	0.267
L_PUT	L_RMF	L-Subcortical	L-Temporal	-0.281	0.210	0.183	0.426	0.367	0.217	0.094	0.132	0.473	0.206	0.024	0.084	0.377	0.216	0.084	0.125	0.099	0.208	0.634	0.974
L_PUT	L_SF	L-Subcortical	L-Temporal	-0.219	0.205	0.289	0.514	0.425	0.210	0.046	0.076	0.389	0.206	0.062	0.145	0.451	0.208	0.033	0.070	0.145	0.211	0.493	0.966
L_PUT	L_SP	L-Subcortical	L-Frontal	-0.427	0.207	0.042	0.217	0.700	0.200	0.001	0.010*	0.476	0.205	0.022	0.080	0.684	0.201	0.001	0.021*	-0.114	0.212	0.594	0.974
L_PUT	L_ST	L-Subcortical	L-Frontal	-0.363	0.210	0.087	0.287	0.742	0.200	0.000	0.008*	0.525	0.206	0.012	0.066	0.653	0.203	0.002	0.021*	-0.143	0.211	0.501	0.966
L_PUT	L_SMAR	L-Subcortical	L-Insula	-0.131	0.209	0.531	0.684	0.672	0.202	0.001	0.010*	0.601	0.202	0.004	0.049*	0.506	0.207	0.016	0.051	-0.416	0.209	0.049	0.417
L_PUT	L_TT	L-Subcortical	L-Parietal	-0.412	0.209	0.052	0.225	0.758	0.199	0.000	0.008*	0.477	0.208	0.024	0.084	0.665	0.202	0.001	0.021*	-0.100	0.211	0.635	0.974
L_PUT	L_INS	L-Subcortical	L-Parietal	-0.394	0.211	0.065	0.243	0.853	0.195	0.000	0.004*	0.712	0.196	0.000	0.026*	0.729	0.200	0.000	0.016*	-0.066	0.213	0.757	0.979
L_PAL	L_HPC	L-Subcortical	L-Subcortical	-0.705	0.201	0.001	0.055	0.316	0.211	0.137	0.180	-0.252	0.212	0.236	0.373	0.603	0.204	0.004	0.028*	-0.278	0.212	0.193	0.823
L_PAL	L_AMG	L-Subcortical	L-Subcortical	-0.420	0.208	0.047	0.217	0.371	0.212	0.083	0.119	0.035	0.213	0.868	0.902	0.537	0.205	0.010	0.042*	-0.071	0.211	0.738	0.979
L_PAL	L_ACC	L-Subcortical	L-Subcortical	-0.467	0.209	0.028	0.193	0.023	0.210	0.913	0.916	-0.545	0.202	0.008	0.056	0.158	0.213	0.459	0.512	-0.069	0.210	0.744	0.979
L_PAL	L_VDC	L-Subcortical	L-Subcortical	-0.534	0.206	0.011	0.121	0.300	0.212	0.160	0.207	-0.051	0.211	0.810	0.866	0.583	0.204	0.005	0.030*	-0.214	0.212	0.315	0.871
L_PAL	L_MOF	L-Subcortical	L-Frontal	-0.395	0.210	0.063	0.243	0.398	0.209	0.060	0.092	0.072	0.212	0.736	0.808	0.422	0.211	0.048	0.087	0.055	0.210	0.793	0.986
L_PAL	L_INS	L-Subcortical	L-Insula	-0.435	0.204	0.036	0.204	0.602	0.203	0.004	0.017*	0.276	0.203	0.176	0.305	0.630	0.203	0.003	0.026*	0.080	0.209	0.702	0.979
BST	L_HPC	B-BST-CER	L-Subcortical	-0.336	0.218	0.127	0.362	0.359	0.209	0.089	0.126	0.183	0.213	0.391	0.529	0.412	0.206	0.049	0.087	-0.207	0.212	0.333	0.881
BST	L_VDC	B-BST-CER	L-Subcortical	-0.654	0.207	0.002	0.069	0.324	0.210	0.127	0.168	0.151	0.209	0.473	0.606	0.418	0.212	0.052	0.090	-0.306	0.210	0.149	0.767
BST	R_CER	B-BST-CER	R-BST-CER	-0.162	0.210	0.442	0.631	0.322	0.210	0.129	0.170	0.162	0.211	0.444	0.578	0.387	0.212	0.071	0.111	-0.069	0.212	0.745	0.979
BST	R_THAL	B-BST-CER	R-Subcortical	-0.460	0.214	0.034	0.201	0.207	0.213	0.333	0.397	0.049	0.212	0.817	0.868	0.395	0.208	0.061	0.102	-0.254	0.208	0.227	0.828
BST	R_HPC	B-BST-CER	R-Subcortical	-0.297	0.211	0.163	0.404	0.067	0.211	0.750	0.784	-0.093	0.209	0.657	0.746	0.164	0.212	0.443	0.495	-0.259	0.210	0.222	0.828
BST	R_VDC	B-BST-CER	R-Subcortical	-0.627	0.204	0.003	0.080	0.169	0.213	0.431	0.495	-0.004	0.211	0.985	0.992	0.256	0.211	0.229	0.281	-0.544	0.209	0.011	0.227
BST	L_ENT	B-BST-CER	L-Temporal	-0.438	0.214	0.044	0.217	0.088	0.217	0.686	0.727	-0.049	0.214	0.820	0.868	0.154	0.217	0.481	0.534	-0.444	0.214	0.041	0.387
BST	L_PHPC	B-BST-CER	L-Occipital	-0.680	0.210	0.002	0.069	0.315	0.210	0.137	0.180	0.130	0.213	0.542	0.657	0.364	0.210	0.087	0.127	0.021	0.203	0.916	0.986
BST	R_ENT	B-BST-CER	R-Temporal	-0.121	0.215	0.573	0.714	-0.068	0.215	0.752	0.785	-0.147	0.214	0.493	0.620	0.016	0.215	0.939	0.945	-0.091	0.215	0.673	0.976
BST	R_PARH	B-BST-CER	R-Occipital	-0.330	0.213	0.125	0.361	-0.105	0.213	0.624	0.678	-0.265	0.211	0.211	0.341	0.054	0.213	0.801	0.823	0.043	0.214	0.841	0.986

Table 6.3.C: FDR corrected results from comparisons of fractional anisotropy, mean diffusivity, axial diffusivity, radial diffusivity, and fractional Number of Tracks in CPHIV compared to CHU. Asterisks indicate associations that survive threshold for significance corrected for multiple comparisons (FDR $q < 0.05$).

ROI X	ROI Y	Area X	Area Y	Fractional anisotropy				Mean diffusivity				Axial diffusivity				Radial diffusivity				fractional Number of tracks			
				stdB	se	p	FDR q	stdB	se	p	FDR q	stdB	se	p	FDR q	stdB	se	p	FDR q	stdB	se	p	FDR q
L_HPC	L_AMG	L-Subcortical	L-Occipital	-0.731	0.200	0.000	0.055	0.680	0.202	0.001	0.010*	0.358	0.210	0.091	0.191	0.764	0.199	0.000	0.016	-0.166	0.212	0.435	0.938
L_HPC	L_VDC	L-Subcortical	L-Occipital	-0.523	0.207	0.013	0.128	0.580	0.203	0.005	0.022*	0.228	0.212	0.285	0.430	0.661	0.200	0.001	0.021*	-0.611	0.204	0.004	0.163
L_HPC	L_BSTs	L-Subcortical	L-Temporal	-0.317	0.211	0.136	0.372	0.512	0.215	0.019	0.044*	0.302	0.212	0.157	0.286	0.365	0.211	0.086	0.127	0.133	0.212	0.531	0.966
L_HPC	L_ENT	L-Subcortical	L-Parietal	-0.614	0.205	0.003	0.080	0.613	0.206	0.004	0.017*	0.376	0.213	0.080	0.176	0.694	0.202	0.001	0.020*	0.359	0.211	0.091	0.619
L_HPC	L_FUS	L-Subcortical	L-Limbic	-0.694	0.201	0.001	0.055	0.691	0.202	0.001	0.010*	0.453	0.210	0.034	0.098	0.746	0.200	0.000	0.016*	0.369	0.208	0.079	0.571
L_HPC	L_IP	L-Subcortical	L-Subcortical	-0.317	0.211	0.135	0.372	0.500	0.208	0.018	0.043*	0.489	0.206	0.019	0.076	0.449	0.209	0.034	0.071	0.258	0.210	0.222	0.828
L_HPC	L_IT	L-Subcortical	L-Subcortical	-0.409	0.211	0.056	0.230	0.706	0.199	0.001	0.010*	0.668	0.203	0.001	0.037*	0.686	0.200	0.001	0.020*	0.001	0.212	0.997	0.997
L_HPC	L_ISTH	L-Subcortical	L-Temporal	-0.237	0.211	0.264	0.500	0.687	0.205	0.001	0.010*	0.095	0.208	0.651	0.744	0.395	0.209	0.062	0.102	0.122	0.211	0.565	0.974
L_HPC	L_LING	L-Subcortical	L-Occipital	-0.198	0.206	0.339	0.571	0.322	0.209	0.127	0.168	0.178	0.208	0.392	0.529	0.548	0.210	0.010	0.042*	0.048	0.208	0.819	0.986
L_HPC	L_MOF	L-Subcortical	L-Frontal	-0.506	0.207	0.016	0.147	0.518	0.206	0.014	0.037	0.165	0.211	0.437	0.571	0.600	0.204	0.004	0.028*	-0.446	0.222	0.047	0.407
L_HPC	L_MT	L-Subcortical	L-Temporal	-0.396	0.210	0.063	0.243	0.682	0.203	0.001	0.010*	0.637	0.203	0.002	0.039*	0.615	0.205	0.004	0.027*	-0.032	0.211	0.879	0.986
L_HPC	L_PHPC	L-Subcortical	L-Temporal	-0.692	0.208	0.001	0.069	0.331	0.210	0.119	0.160	0.143	0.211	0.501	0.629	0.305	0.213	0.155	0.203	0.106	0.208	0.611	0.974
L_HPC	L_ST	L-Subcortical	L-Temporal	-0.399	0.209	0.059	0.241	0.622	0.203	0.003	0.016*	0.521	0.207	0.013	0.066	0.590	0.204	0.005	0.030*	-0.365	0.208	0.082	0.581
L_HPC	L_TP	L-Subcortical	L-Temporal	-0.709	0.203	0.001	0.055	0.109	0.189	0.000	0.000*	0.739	0.202	0.000	0.026*	0.986	0.190	0.000	0.001*	0.112	0.216	0.606	0.974
L_HPC	L_INS	L-Subcortical	L-Insula	-0.539	0.206	0.010	0.121	0.864	0.194	0.000	0.004*	0.638	0.203	0.002	0.039*	0.824	0.196	0.000	0.006*	-0.132	0.209	0.530	0.966
L_AMG	L_ACC	L-Subcortical	L-Subcortical	-0.359	0.211	0.092	0.295	0.093	0.213	0.664	0.712	-0.173	0.210	0.414	0.550	0.240	0.213	0.262	0.315	-0.096	0.211	0.649	0.974
L_AMG	L_VDC	L-Subcortical	L-Frontal	-0.788	0.197	0.000	0.055	0.519	0.204	0.013	0.035	0.050	0.208	0.812	0.866	0.712	0.200	0.001	0.018*	-0.198	0.207	0.342	0.887
L_AMG	L_ENT	L-Subcortical	L-Temporal	-0.231	0.209	0.272	0.503	0.619	0.202	0.003	0.016*	0.429	0.209	0.043	0.115	0.605	0.201	0.003	0.027*	0.333	0.212	0.119	0.705
L_AMG	L_FUS	L-Subcortical	L-Subcortical	-0.104	0.214	0.630	0.757	0.698	0.203	0.001	0.010*	0.597	0.205	0.004	0.049	0.551	0.208	0.009	0.040*	0.090	0.211	0.669	0.976
L_AMG	L_IT	L-Subcortical	L-Temporal	0.055	0.215	0.800	0.869	0.562	0.209	0.008	0.030*	0.558	0.208	0.009	0.057	0.342	0.213	0.112	0.154	-0.074	0.215	0.731	0.979
L_AMG	L_MOF	L-Subcortical	L-Temporal	-0.261	0.212	0.221	0.462	0.308	0.211	0.149	0.193	0.158	0.213	0.458	0.594	0.343	0.211	0.107	0.150	-0.112	0.209	0.594	0.974
L_AMG	L_ST	L-Subcortical	L-Temporal	-0.260	0.207	0.213	0.459	0.684	0.200	0.001	0.010*	0.583	0.205	0.005	0.051	0.598	0.200	0.003	0.027*	-0.030	0.211	0.888	0.986
L_AMG	L_TP	L-Subcortical	L-Occipital	-0.472	0.219	0.034	0.201	0.606	0.206	0.004	0.019*	0.498	0.210	0.019	0.076	0.596	0.205	0.005	0.030*	0.271	0.210	0.199	0.823
L_AMG	L_INS	L-Subcortical	L-Insula	-0.246	0.209	0.243	0.477	0.680	0.201	0.001	0.010*	0.613	0.197	0.002	0.039*	0.578	0.205	0.006	0.031*	-0.058	0.207	0.779	0.986
L_ACC	L_VDC	L-Subcortical	L-Subcortical	-0.322	0.210	0.128	0.362	0.453	0.221	0.043	0.073	-0.025	0.211	0.905	0.928	0.223	0.212	0.294	0.350	-0.459	0.215	0.036	0.354
L_ACC	L_MOF	L-Subcortical	L-Frontal	-0.240	0.211	0.259	0.494	0.310	0.211	0.146	0.190	0.187	0.212	0.380	0.523	0.336	0.211	0.115	0.156	-0.291	0.211	0.171	0.800
L_VDC	R_THAL	L-Subcortical	R-Subcortical	-0.246	0.208	0.241	0.475	-0.121	0.214	0.572	0.631	-0.195	0.214	0.364	0.507	-0.047	0.213	0.826	0.845	-0.006	0.214	0.978	0.990
L_VDC	R_VDC	L-Subcortical	R-Subcortical	-0.712	0.207	0.001	0.055	0.061	0.207	0.769	0.793	-0.145	0.204	0.480	0.611	0.176	0.208	0.399	0.457	0.035	0.212	0.868	0.986
L_VDC	L_ENT	L-Subcortical	L-Temporal	-0.065	0.217	0.766	0.850	-0.197	0.217	0.367	0.430	-0.285	0.216	0.189	0.315	-0.118	0.217	0.589	0.632	-0.185	0.216	0.393	0.930
L_VDC	L_MOF	L-Subcortical	L-Occipital	-0.640	0.203	0.002	0.069	0.535	0.206	0.011	0.033*	0.169	0.211	0.426	0.559	0.663	0.203	0.001	0.021*	-0.006	0.209	0.978	0.990
L_VDC	L_PHPC	L-Subcortical	L-Frontal	-0.416	0.209	0.050	0.221	0.076	0.213	0.721	0.757	-0.141	0.212	0.507	0.632	0.245	0.212	0.251	0.304	-0.509	0.217	0.021	0.286
L_VDC	L_ST	L-Subcortical	L-Insula	-0.194	0.213	0.365	0.580	0.665	0.203	0.001	0.011*	0.603	0.204	0.004	0.049	0.562	0.206	0.008	0.035*	-0.286	0.211	0.178	0.814
L_VDC	L_INS	L-Subcortical	L-Temporal	-0.321	0.213	0.134	0.372	0.687	0.200	0.001	0.010*	0.513	0.198	0.011	0.064	0.658	0.203	0.002	0.021*	-0.040	0.204	0.845	0.986
R_CER	R_THAL	R-BST-CER	R-Subcortical	-0.253	0.211	0.234	0.469	0.145	0.213	0.497	0.559	0.050	0.214	0.815	0.868	0.183	0.212	0.390	0.448	0.098	0.213	0.646	0.974
R_CER	R_VDC	R-BST-CER	R-Subcortical	-0.146	0.210	0.488	0.659	0.161	0.213	0.452	0.515	0.083	0.211	0.696	0.777	0.186	0.212	0.384	0.442	-0.049	0.213	0.817	0.986
R_CER	R_ENT	R-BST-CER	R-Temporal	-0.042	0.211	0.842	0.890	-0.095	0.210	0.651	0.702	-0.111	0.210	0.598	0.700	-0.077	0.210	0.715	0.749	0.103	0.215	0.631	0.974
R_CER	R_FUS	R-BST-CER	R-Occipital	-0.295	0.211	0.166	0.404	0.534	0.210	0.013	0.035	0.137	0.212	0.520	0.641	0.479	0.208	0.024	0.062	-0.139	0.212	0.512	0.966
R_CER	R_PARH	R-BST-CER	R-Occipital	-0.371	0.213	0.084	0.284	0.157	0.215	0.466	0.527	-0.040	0.216	0.852	0.889	0.295	0.213	0.170	0.219	0.182	0.215	0.401	0.930
R_THAL	R_CAU	R-Subcortical	R-Subcortical	-0.414	0.210	0.052	0.225	0.257	0.208	0.220	0.273	0.245	0.210	0.247	0.387	0.165	0.209	0.430	0.485	0.004	0.211	0.985	0.992
R_THAL	R_PUT	R-Subcortical	R-Subcortical	-0.636	0.199	0.002	0.069	0.137	0.212	0.519	0.582	-0.086	0.209	0.680	0.768	0.498	0.208	0.018	0.055	-0.468	0.191	0.016	0.267
R_THAL	R_PAL	R-Subcortical	R-Subcortical	-0.445	0.200	0.028	0.193	0.035	0.213	0.869	0.881	-0.514	0.207	0.015	0.066	0.267	0.207	0.200	0.252	-0.232	0.212	0.276	0.854
R_THAL	R_HPC	R-Subcortical	R-Subcortical	-0.516	0.197	0.010	0.121	0.190	0.213	0.375	0.436	-0.136	0.211	0.521	0.641	0.463	0.205	0.026	0.064	-0.209	0.205	0.312	0.871
R_THAL	R_AMG	R-Subcortical	R-Subcortical	-0.498	0.194	0.012	0.122	0.119	0.213	0.578	0.634	-0.152	0.206	0.464	0.598	0.357	0.208	0.090	0.130	-0.138	0.208	0.509	0.966
R_THAL	R_ACC	R-Subcortical	R-Subcortical	-0.054	0.214	0.800	0.869	0.273	0.212	0.201	0.251	0.271	0.212	0.205	0.335	0.263	0.213	0.220	0.271	-0.144	0.214	0.504	0.966
R_THAL	R_VDC	R-Subcortical	R-Subcortical	-0.791	0.206	0.000	0.055	0.294	0.211	0.166	0.212	0.007	0.209	0.973	0.985	0.585	0.205	0.005	0.030*	-0.446	0.205	0.032	0.354
R_THAL	L_ISTH	R-Subcortical	L-Limbic	0.143	0.210	0.497	0.665	-0.165	0.216	0.447	0.510	-0.079	0.214	0.712	0.790	-0.196	0.215	0.364	0.422	0.160	0.212	0.454	0.943
R_THAL	R_ISTH	R-Subcortical	R-Limbic	-0.174	0.210	0.409	0.608	0.063	0.213	0.768	0.793	-0.033	0.213	0.878	0.908	0.129	0.212	0.545	0.590	-0.062	0.210	0.768	0.982

Table 6.3.D: FDR corrected results from comparisons of fractional anisotropy, mean diffusivity, axial diffusivity, radial diffusivity, and fractional Number of Tracks in CPHIV compared to CHU. Asterisks indicate associations that survive threshold for significance corrected for multiple comparisons (FDR $q < 0.05$).

ROI X	ROI Y	Area X	Area Y	Fractional anisotropy				Mean diffusivity				Axial diffusivity				Radial diffusivity				fractional Number of tracks			
				stdB	se	p	FDR q	stdB	se	p	FDR q	stdB	se	p	FDR q	stdB	se	p	FDR q	stdB	se	p	FDR q
R_THAL	R_LOF	R-Subcortical	R-Occipital	-0.050	0.210	0.811	0.869	0.608	0.211	0.005	0.021*	0.570	0.216	0.010	0.060	0.558	0.211	0.010	0.041*	-0.176	0.203	0.390	0.930
R_THAL	R_PARH	R-Subcortical	R-Central sulcus	-0.253	0.203	0.216	0.460	0.044	0.213	0.835	0.854	-0.116	0.210	0.582	0.687	0.178	0.209	0.396	0.454	0.021	0.214	0.923	0.986
R_THAL	R_PARC	R-Subcortical	R-Parietal	-0.131	0.208	0.531	0.684	0.461	0.213	0.033	0.062	0.183	0.210	0.387	0.527	0.209	0.213	0.329	0.385	-0.204	0.214	0.344	0.887
R_THAL	R_PSTC	R-Subcortical	R-Limbic	0.012	0.215	0.955	0.972	0.415	0.212	0.053	0.084	0.375	0.211	0.080	0.176	0.309	0.213	0.150	0.197	-0.229	0.213	0.286	0.865
R_THAL	R_PC	R-Subcortical	R-Parietal	-0.192	0.217	0.379	0.587	0.020	0.217	0.927	0.929	-0.049	0.216	0.823	0.868	0.078	0.217	0.721	0.752	-0.175	0.216	0.419	0.930
R_THAL	R_PREC	R-Subcortical	R-Insula	-0.101	0.210	0.632	0.757	0.498	0.208	0.018	0.044*	0.323	0.209	0.126	0.243	0.365	0.209	0.084	0.125	-0.232	0.207	0.265	0.849
R_THAL	R_SP	R-Subcortical	R-Frontal	-0.225	0.215	0.298	0.527	0.464	0.210	0.030	0.058	0.379	0.212	0.077	0.174	0.352	0.214	0.103	0.145	0.177	0.214	0.410	0.930
R_THAL	R_INS	R-Subcortical	R-Frontal	-0.510	0.211	0.018	0.152	0.385	0.214	0.074	0.109	0.046	0.213	0.830	0.873	0.480	0.210	0.025	0.063	-0.046	0.210	0.829	0.986
R_CAU	R_PUT	R-Subcortical	R-Subcortical	-0.406	0.204	0.050	0.221	0.459	0.208	0.030	0.058	0.271	0.208	0.197	0.325	0.450	0.206	0.031	0.069	0.181	0.213	0.398	0.930
R_CAU	R_PAL	R-Subcortical	R-Subcortical	-0.519	0.205	0.013	0.128	0.209	0.212	0.327	0.391	0.074	0.212	0.726	0.799	0.229	0.209	0.275	0.329	-0.003	0.209	0.990	0.994
R_CAU	R_HPC	R-Subcortical	R-Subcortical	-0.122	0.212	0.568	0.710	0.202	0.216	0.352	0.418	0.102	0.215	0.636	0.736	0.189	0.214	0.380	0.439	-0.081	0.205	0.692	0.979
R_CAU	R_AMG	R-Subcortical	R-Subcortical	-0.378	0.204	0.067	0.243	0.171	0.213	0.424	0.490	-0.086	0.211	0.687	0.770	0.293	0.209	0.165	0.215	0.009	0.213	0.968	0.987
R_CAU	R_ACC	R-Subcortical	R-Subcortical	-0.191	0.212	0.368	0.581	0.047	0.213	0.824	0.846	-0.085	0.212	0.688	0.770	0.137	0.213	0.523	0.572	-0.110	0.213	0.605	0.974
R_CAU	R_VDC	R-Subcortical	R-Subcortical	-0.504	0.210	0.018	0.153	0.244	0.212	0.252	0.307	0.145	0.209	0.490	0.617	0.400	0.210	0.060	0.100	-0.138	0.206	0.503	0.966
R_CAU	L_CAC	R-Subcortical	L-Limbic	-0.002	0.213	0.992	0.994	-0.313	0.211	0.141	0.184	-0.614	0.211	0.005	0.049*	-0.255	0.210	0.229	0.281	0.041	0.214	0.849	0.986
R_CAU	L_RAC	R-Subcortical	L-Frontal	-0.074	0.213	0.727	0.830	-0.289	0.207	0.165	0.212	-0.299	0.209	0.155	0.284	-0.175	0.209	0.406	0.463	-0.012	0.214	0.955	0.986
R_CAU	R_CAC	R-Subcortical	R-Limbic	0.007	0.213	0.975	0.982	0.045	0.211	0.832	0.852	0.071	0.213	0.741	0.811	0.005	0.211	0.981	0.983	0.193	0.213	0.366	0.914
R_CAU	R_CMF	R-Subcortical	R-Frontal	-0.049	0.210	0.816	0.872	0.407	0.212	0.057	0.089	0.349	0.211	0.102	0.210	0.291	0.210	0.170	0.219	0.161	0.214	0.454	0.943
R_CAU	R_ISTH	R-Subcortical	R-Limbic	-0.001	0.214	0.997	0.997	0.199	0.214	0.355	0.419	0.186	0.212	0.382	0.524	0.144	0.216	0.507	0.560	0.011	0.214	0.959	0.986
R_CAU	R_LOF	R-Subcortical	R-Central sulcus	-0.194	0.211	0.361	0.580	0.634	0.204	0.002	0.014*	0.521	0.207	0.013	0.066	0.559	0.205	0.008	0.036*	0.295	0.208	0.159	0.784
R_CAU	R_MOF	R-Subcortical	R-Limbic	-0.171	0.212	0.423	0.616	0.494	0.206	0.019	0.044*	0.368	0.209	0.082	0.178	0.475	0.209	0.025	0.063	-0.007	0.212	0.975	0.990
R_CAU	R_PARC	R-Subcortical	R-Occipital	-0.255	0.208	0.223	0.463	0.415	0.208	0.049	0.079	0.294	0.211	0.167	0.297	0.379	0.207	0.070	0.109	0.040	0.212	0.850	0.986
R_CAU	R_PSTC	R-Subcortical	R-Frontal	-0.105	0.213	0.624	0.756	0.499	0.209	0.019	0.044*	0.284	0.211	0.182	0.310	0.325	0.211	0.127	0.171	0.006	0.213	0.979	0.990
R_CAU	R_PC	R-Subcortical	R-Frontal	-0.072	0.213	0.737	0.835	-0.044	0.213	0.839	0.855	-0.051	0.213	0.811	0.866	-0.022	0.213	0.916	0.924	0.176	0.212	0.408	0.930
R_CAU	R_PREC	R-Subcortical	R-Frontal	-0.171	0.211	0.419	0.614	0.549	0.206	0.009	0.031*	0.372	0.210	0.079	0.176	0.340	0.210	0.109	0.150	0.094	0.213	0.658	0.974
R_CAU	R_PCUN	R-Subcortical	R-Insula	-0.161	0.215	0.457	0.636	0.468	0.217	0.034	0.063	0.199	0.214	0.354	0.500	0.421	0.217	0.056	0.095	0.261	0.213	0.224	0.828
R_CAU	R_RAC	R-Subcortical	R-Frontal	-0.053	0.213	0.805	0.869	0.176	0.210	0.403	0.469	0.151	0.212	0.476	0.607	0.122	0.211	0.564	0.608	0.088	0.212	0.677	0.976
R_CAU	R_RMF	R-Subcortical	R-Parietal	-0.251	0.209	0.233	0.469	0.394	0.212	0.066	0.099	0.385	0.210	0.070	0.162	0.442	0.209	0.037	0.073	-0.430	0.209	0.043	0.387
R_CAU	R_SF	R-Subcortical	R-Frontal	-0.275	0.209	0.192	0.435	0.463	0.207	0.028	0.055	0.373	0.210	0.079	0.176	0.412	0.207	0.050	0.088	0.263	0.210	0.214	0.823
R_CAU	R_SP	R-Subcortical	R-Frontal	-0.292	0.215	0.178	0.426	0.711	0.206	0.001	0.010*	0.595	0.209	0.006	0.051	0.651	0.207	0.002	0.026*	0.573	0.209	0.007	0.183
R_CAU	R_INS	R-Subcortical	R-Parietal	-0.263	0.213	0.220	0.462	0.364	0.212	0.089	0.126	0.012	0.214	0.957	0.970	0.329	0.214	0.128	0.171	0.093	0.211	0.661	0.974
R_PUT	R_PAL	R-Subcortical	R-Subcortical	-0.457	0.206	0.029	0.193	0.414	0.209	0.050	0.080	0.037	0.212	0.862	0.897	0.480	0.207	0.023	0.061	-0.197	0.213	0.357	0.901
R_PUT	R_HPC	R-Subcortical	R-Subcortical	-0.459	0.207	0.029	0.193	0.230	0.212	0.281	0.339	0.005	0.210	0.980	0.989	0.307	0.211	0.150	0.197	-0.225	0.211	0.288	0.865
R_PUT	R_AMG	R-Subcortical	R-Subcortical	-0.570	0.212	0.008	0.112	0.291	0.209	0.168	0.214	0.027	0.211	0.899	0.924	0.334	0.209	0.114	0.156	-0.097	0.206	0.639	0.974
R_PUT	R_ACC	R-Subcortical	R-Subcortical	-0.271	0.211	0.204	0.453	0.138	0.214	0.522	0.582	-0.076	0.212	0.722	0.797	0.224	0.214	0.298	0.353	-0.222	0.212	0.298	0.866
R_PUT	R_VDC	R-Subcortical	R-Frontal	-0.736	0.211	0.001	0.055	0.615	0.206	0.004	0.017*	0.299	0.205	0.148	0.273	0.659	0.204	0.002	0.021*	-0.241	0.208	0.250	0.849
R_PUT	R_CMF	R-Subcortical	R-Parietal	-0.160	0.207	0.443	0.631	0.451	0.209	0.033	0.062	0.271	0.209	0.199	0.326	0.435	0.207	0.038	0.075	-0.005	0.212	0.982	0.992
R_PUT	R_IP	R-Subcortical	R-Frontal	-0.560	0.203	0.007	0.101	0.406	0.211	0.058	0.089	0.207	0.210	0.327	0.476	0.587	0.206	0.005	0.030*	0.684	0.209	0.002	0.130
R_PUT	R_LOF	R-Subcortical	R-Frontal	-0.057	0.211	0.789	0.866	0.685	0.202	0.001	0.010*	0.676	0.201	0.001	0.036*	0.515	0.206	0.014	0.050	0.267	0.212	0.211	0.823
R_PUT	R_MOF	R-Subcortical	R-Frontal	-0.006	0.214	0.978	0.982	0.530	0.206	0.012	0.034*	0.519	0.207	0.014	0.066	0.481	0.215	0.028	0.066	0.271	0.212	0.204	0.823
R_PUT	R_PARC	R-Subcortical	R-Temporal	-0.197	0.217	0.366	0.580	0.659	0.207	0.002	0.013*	0.413	0.212	0.055	0.134	0.486	0.212	0.024	0.063	-0.096	0.218	0.661	0.974
R_PUT	R_POPE	R-Subcortical	R-Parietal	-0.141	0.214	0.512	0.679	0.637	0.204	0.002	0.014*	0.552	0.207	0.009	0.058	0.533	0.207	0.012	0.044*	-0.356	0.212	0.096	0.632
R_PUT	R_PTRI	R-Subcortical	R-Frontal	-0.163	0.211	0.441	0.631	0.327	0.210	0.123	0.164	0.308	0.211	0.148	0.273	0.403	0.207	0.054	0.093	-0.186	0.211	0.380	0.930
R_PUT	R_PSTC	R-Subcortical	R-Central sulcus	-0.392	0.212	0.068	0.244	0.488	0.208	0.021	0.046*	0.332	0.209	0.116	0.226	0.427	0.209	0.044	0.081	0.128	0.213	0.550	0.974
R_PUT	R_PREC	R-Subcortical	R-Parietal	-0.433	0.213	0.045	0.217	0.530	0.207	0.012	0.034*	0.461	0.212	0.032	0.097	0.472	0.208	0.025	0.063	0.019	0.213	0.930	0.986
R_PUT	R_RAC	R-Subcortical	R-Frontal	0.201	0.218	0.360	0.580	0.218	0.218	0.319	0.382	0.763	0.217	0.001	0.027*	0.068	0.218	0.757	0.787	0.611	0.220	0.007	0.183

Table 6.3.E: FDR corrected results from comparisons of fractional anisotropy, mean diffusivity, axial diffusivity, radial diffusivity, and fractional Number of Tracks in CPHIV compared to CHU. Asterisks indicate associations that survive threshold for significance corrected for multiple comparisons (FDR $q < 0.05$).

ROI X	ROI Y	Area X	Area Y	Fractional anisotropy				Mean diffusivity				Axial diffusivity				Radial diffusivity				fractional Number of tracks			
				stdB	se	p	FDR q	stdB	se	p	FDR q	stdB	se	p	FDR q	stdB	se	p	FDR q	stdB	se	p	FDR q
R_PUT	R_RMF	R-Subcortical	R-Frontal	-0.252	0.209	0.230	0.469	0.537	0.206	0.011	0.033*	0.425	0.208	0.044	0.115	0.395	0.213	0.066	0.105	-0.062	0.211	0.771	0.982
R_PUT	R_SF	R-Subcortical	R-Parietal	-0.169	0.210	0.422	0.615	0.433	0.211	0.043	0.072	0.419	0.208	0.047	0.121	0.414	0.209	0.051	0.088	0.108	0.212	0.612	0.974
R_PUT	R_SP	R-Subcortical	R-Insula	-0.368	0.211	0.085	0.286	0.531	0.207	0.012	0.034*	0.465	0.208	0.028	0.089	0.440	0.208	0.037	0.073	0.269	0.212	0.207	0.823
R_PUT	R_ST	R-Subcortical	R-Subcortical	-0.483	0.204	0.020	0.165	0.235	0.212	0.271	0.328	-0.091	0.211	0.665	0.754	0.372	0.210	0.080	0.121	0.604	0.215	0.006	0.183
R_PUT	R_SMAR	R-Subcortical	R-Frontal	-0.340	0.208	0.106	0.319	0.333	0.211	0.118	0.159	0.196	0.209	0.351	0.500	0.346	0.210	0.103	0.145	0.245	0.208	0.240	0.849
R_PUT	R_INS	R-Subcortical	R-Frontal	-0.454	0.210	0.034	0.201	0.507	0.207	0.016	0.040*	0.542	0.206	0.010	0.060	0.474	0.208	0.025	0.063	0.126	0.212	0.554	0.974
R_PAL	R_HPC	R-Subcortical	R-Subcortical	-0.594	0.205	0.005	0.083	0.051	0.210	0.810	0.833	-0.250	0.210	0.237	0.373	0.390	0.208	0.064	0.104	-0.290	0.200	0.151	0.767
R_PAL	R_AMG	R-Subcortical	R-Subcortical	-0.571	0.203	0.006	0.101	0.336	0.209	0.111	0.151	-0.178	0.207	0.391	0.529	0.530	0.206	0.012	0.044	-0.085	0.213	0.692	0.979
R_PAL	R_ACC	R-Subcortical	R-Subcortical	-0.116	0.210	0.581	0.720	-0.128	0.213	0.551	0.612	-0.125	0.210	0.554	0.665	-0.066	0.214	0.757	0.787	0.041	0.212	0.848	0.986
R_PAL	R_VDC	R-Subcortical	R-Subcortical	-0.609	0.201	0.003	0.080	0.242	0.211	0.254	0.308	-0.223	0.209	0.288	0.431	0.571	0.205	0.007	0.032*	-0.253	0.209	0.230	0.833
R_PAL	R_LOF	R-Subcortical	R-Frontal	-0.354	0.211	0.096	0.299	0.121	0.215	0.575	0.632	-0.101	0.215	0.641	0.738	0.261	0.214	0.225	0.278	-0.012	0.210	0.955	0.986
R_PAL	R_PARC	R-Subcortical	R-Central sulcus	-0.246	0.219	0.265	0.500	0.437	0.218	0.048	0.078	0.200	0.219	0.364	0.507	0.386	0.220	0.082	0.124	-0.175	0.223	0.436	0.938
R_PAL	R_PREC	R-Subcortical	R-Insula	-0.372	0.212	0.083	0.284	0.677	0.205	0.001	0.010*	0.388	0.212	0.070	0.162	0.661	0.204	0.002	0.021*	0.063	0.213	0.769	0.982
R_PAL	R_INS	R-Subcortical	R-Frontal	-0.318	0.211	0.136	0.372	0.372	0.211	0.080	0.116	0.125	0.212	0.555	0.665	0.416	0.211	0.051	0.089	0.082	0.215	0.703	0.979
R_HPC	R_AMG	R-Subcortical	R-Subcortical	-0.425	0.212	0.048	0.221	0.264	0.211	0.213	0.264	0.044	0.213	0.836	0.876	0.334	0.210	0.115	0.156	-0.150	0.213	0.483	0.966
R_HPC	R_VDC	R-Subcortical	R-Subcortical	-0.609	0.202	0.003	0.080	0.158	0.213	0.460	0.523	-0.175	0.211	0.409	0.545	0.352	0.211	0.098	0.140	-0.235	0.203	0.249	0.849
R_HPC	R_BSTS	R-Subcortical	R-Temporal	-0.438	0.217	0.046	0.217	0.447	0.210	0.036	0.065	0.276	0.210	0.191	0.318	0.372	0.214	0.085	0.126	-0.123	0.211	0.561	0.974
R_HPC	R_ENT	R-Subcortical	R-Temporal	-0.163	0.211	0.442	0.631	0.392	0.209	0.064	0.097	0.280	0.209	0.183	0.310	0.476	0.207	0.024	0.062	-0.306	0.211	0.150	0.767
R_HPC	R_FUS	R-Subcortical	R-Occipital	-0.143	0.213	0.502	0.669	0.473	0.207	0.025	0.051	0.561	0.212	0.010	0.060	0.453	0.211	0.034	0.071	-0.300	0.204	0.145	0.767
R_HPC	R_IP	R-Subcortical	R-Limbic	-0.606	0.208	0.004	0.083	0.569	0.209	0.008	0.028*	0.503	0.217	0.023	0.081	0.619	0.208	0.004	0.027*	0.290	0.212	0.175	0.808
R_HPC	R_IT	R-Subcortical	R-Occipital	-0.180	0.213	0.400	0.599	0.659	0.206	0.002	0.013*	0.463	0.215	0.034	0.098	0.442	0.213	0.040	0.077	-0.029	0.214	0.894	0.986
R_HPC	R_ISTH	R-Subcortical	R-Temporal	-0.116	0.213	0.588	0.725	0.164	0.213	0.445	0.509	0.061	0.214	0.777	0.837	0.573	0.211	0.008	0.037*	0.171	0.214	0.427	0.934
R_HPC	R_LING	R-Subcortical	R-Occipital	-0.229	0.212	0.283	0.506	0.037	0.212	0.863	0.877	-0.127	0.213	0.551	0.665	0.177	0.212	0.407	0.464	-0.237	0.211	0.264	0.849
R_HPC	R_MT	R-Subcortical	R-Occipital	-0.148	0.213	0.489	0.659	0.455	0.209	0.032	0.061	1.038	0.189	0.000	0.000*	0.401	0.210	0.059	0.098	-0.031	0.212	0.883	0.986
R_HPC	R_PARH	R-Subcortical	R-Temporal	-0.029	0.214	0.892	0.923	0.341	0.209	0.106	0.146	0.338	0.209	0.110	0.221	0.263	0.211	0.217	0.269	-0.108	0.213	0.613	0.974
R_HPC	R_PCUN	R-Subcortical	R-Insula	-0.267	0.210	0.207	0.458	0.125	0.213	0.560	0.620	-0.067	0.212	0.752	0.820	0.253	0.213	0.238	0.290	0.761	0.213	0.001	0.130
R_HPC	R_ST	R-Subcortical	R-Temporal	-0.251	0.212	0.239	0.474	0.472	0.208	0.026	0.052	0.675	0.207	0.002	0.037	0.420	0.209	0.047	0.086	0.029	0.206	0.888	0.986
R_HPC	R_INS	R-Subcortical	R-Parietal	-0.493	0.205	0.018	0.152	0.476	0.208	0.024	0.051	0.127	0.211	0.550	0.665	0.377	0.212	0.078	0.120	-0.196	0.211	0.355	0.901
R_AMG	R_ACC	R-Subcortical	R-Subcortical	-0.125	0.213	0.560	0.704	-0.360	0.212	0.094	0.132	-0.457	0.208	0.031	0.094	-0.155	0.214	0.470	0.523	-0.293	0.211	0.169	0.800
R_AMG	R_VDC	R-Subcortical	R-Temporal	-0.643	0.202	0.002	0.069	0.284	0.204	0.167	0.213	-0.056	0.201	0.779	0.837	0.457	0.205	0.028	0.067	-0.200	0.203	0.328	0.879
R_AMG	R_ENT	R-Subcortical	R-Occipital	-0.414	0.212	0.054	0.230	0.367	0.207	0.079	0.115	0.563	0.207	0.008	0.056	0.402	0.208	0.056	0.095	-0.145	0.214	0.498	0.966
R_AMG	R_FUS	R-Subcortical	R-Temporal	0.307	0.212	0.151	0.392	0.487	0.209	0.022	0.046*	0.464	0.204	0.025	0.086	0.345	0.211	0.106	0.149	-0.450	0.210	0.035	0.354
R_AMG	R_IT	R-Subcortical	R-Frontal	0.025	0.213	0.907	0.934	0.401	0.211	0.061	0.093	0.376	0.210	0.077	0.174	0.284	0.212	0.183	0.233	-0.093	0.215	0.665	0.976
R_AMG	R_LOF	R-Subcortical	R-Insula	-0.132	0.213	0.538	0.685	0.079	0.211	0.708	0.745	0.025	0.210	0.906	0.928	0.101	0.212	0.634	0.678	-0.179	0.194	0.358	0.901
R_AMG	R_ST	R-Subcortical	R-Subcortical	-0.264	0.210	0.212	0.458	0.552	0.207	0.009	0.031*	0.429	0.209	0.043	0.115	0.491	0.207	0.020	0.057	0.031	0.211	0.883	0.986
R_AMG	R_TP	R-Subcortical	R-Temporal	-0.061	0.215	0.776	0.857	0.704	0.209	0.001	0.010*	0.677	0.208	0.002	0.037*	0.634	0.211	0.003	0.027	-0.213	0.215	0.326	0.879
R_AMG	R_INS	R-Subcortical	R-Temporal	-0.198	0.209	0.345	0.571	0.445	0.209	0.036	0.065	0.405	0.206	0.052	0.128	0.434	0.210	0.041	0.078	-0.247	0.202	0.226	0.828
R_ACC	R_VDC	R-Subcortical	R-Subcortical	-0.466	0.201	0.022	0.180	0.101	0.215	0.640	0.695	-0.380	0.210	0.074	0.168	0.270	0.213	0.206	0.259	-0.114	0.214	0.594	0.974
R_ACC	R_LOF	R-Subcortical	R-Frontal	-0.221	0.212	0.302	0.533	0.435	0.209	0.040	0.070	0.299	0.213	0.163	0.292	0.532	0.208	0.012	0.045*	-0.577	0.209	0.007	0.183
R_ACC	R_MOF	R-Subcortical	R-Insula	-0.419	0.206	0.044	0.217	0.804	0.197	0.000	0.006*	0.358	0.209	0.089	0.189	0.728	0.199	0.000	0.016*	-0.019	0.211	0.930	0.986
R_ACC	R_INS	R-Subcortical	R-Frontal	-0.522	0.213	0.016	0.147	0.295	0.215	0.174	0.220	-0.069	0.216	0.749	0.818	0.540	0.214	0.013	0.049*	-0.224	0.216	0.304	0.867
R_VDC	R_ENT	R-Subcortical	R-Temporal	-0.246	0.213	0.251	0.488	0.092	0.211	0.665	0.712	-0.093	0.209	0.656	0.746	0.169	0.212	0.428	0.485	-0.194	0.208	0.355	0.901
R_VDC	R_LOF	R-Subcortical	R-Frontal	-0.329	0.211	0.123	0.356	0.286	0.212	0.181	0.228	0.097	0.213	0.651	0.744	0.356	0.212	0.096	0.137	-0.070	0.202	0.731	0.979
R_VDC	R_PARH	R-Subcortical	R-Occipital	-0.191	0.200	0.343	0.571	0.033	0.213	0.877	0.886	-0.048	0.212	0.823	0.868	0.097	0.206	0.638	0.681	-0.055	0.213	0.799	0.986
R_VDC	R_INS	R-Subcortical	R-Insula	-0.290	0.208	0.167	0.404	0.547	0.206	0.009	0.031*	0.417	0.205	0.044	0.116	0.487	0.207	0.021	0.059	0.052	0.205	0.802	0.986
L_BSTS	L_FUS	L-Temporal	L-Parietal	-0.387	0.209	0.067	0.243	0.679	0.203	0.001	0.010*	0.493	0.206	0.018	0.074	0.637	0.205	0.002	0.026*	0.344	0.211	0.106	0.663
L_BSTS	L_IP	L-Temporal	L-Parietal	-0.291	0.208	0.165	0.404	0.486	0.206	0.020	0.046*	0.288	0.204	0.163	0.292	0.473	0.208	0.025	0.063	-0.043	0.213	0.841	0.986
L_BSTS	L_IT	L-Temporal	L-Occipital	-0.235	0.204	0.252	0.488	0.697	0.202	0.001	0.010*	0.666	0.199	0.001	0.036*	0.614	0.204	0.003	0.027*	0.159	0.212	0.455	0.943

Table 6.3.F: FDR corrected results from comparisons of fractional anisotropy, mean diffusivity, axial diffusivity, radial diffusivity, and fractional Number of Tracks in CPHIV compared to CHU. Asterisks indicate associations that survive threshold for significance corrected for multiple comparisons (FDR $q < 0.05$).

ROI X	ROI Y	Area X	Area Y	Fractional anisotropy				Mean diffusivity				Axial diffusivity				Radial diffusivity				fractional Number of tracks			
				stdB	se	p	FDR q	stdB	se	p	FDR q	stdB	se	p	FDR q	stdB	se	p	FDR q	stdB	se	p	FDR q
L_BSTS	L_MT	L-Temporal	L-Temporal	-0.153	0.207	0.460	0.637	0.671	0.202	0.001	0.010*	0.697	0.200	0.001	0.027*	0.553	0.205	0.008	0.037*	0.330	0.206	0.113	0.682
L_BSTS	L_ST	L-Temporal	L-Temporal	-0.461	0.206	0.028	0.193	0.713	0.201	0.001	0.010*	0.548	0.204	0.009	0.057	0.712	0.201	0.001	0.018*	-0.029	0.207	0.888	0.986
L_BSTS	L_SMAR	L-Temporal	L-Temporal	-0.291	0.208	0.166	0.404	0.461	0.210	0.030	0.058	0.136	0.210	0.518	0.640	0.486	0.209	0.022	0.059	-0.669	0.216	0.003	0.163
L_CAC	L_CMF	L-Limbic	L-Frontal	0.036	0.214	0.865	0.903	0.453	0.218	0.041	0.070	0.144	0.217	0.507	0.632	0.082	0.217	0.706	0.743	-0.556	0.211	0.010	0.217
L_CAC	L_ISTH	L-Limbic	L-Limbic	0.182	0.212	0.391	0.593	0.331	0.213	0.123	0.164	0.483	0.213	0.026	0.086	0.050	0.211	0.812	0.833	-0.033	0.218	0.879	0.986
L_CAC	L_PC	L-Limbic	L-Limbic	0.022	0.206	0.915	0.940	0.348	0.209	0.100	0.139	0.364	0.208	0.083	0.179	0.171	0.207	0.410	0.466	0.203	0.206	0.327	0.879
L_CAC	L_RAC	L-Limbic	L-Frontal	-0.146	0.208	0.484	0.659	0.439	0.209	0.038	0.067	0.254	0.209	0.227	0.361	0.357	0.208	0.090	0.130	0.046	0.209	0.825	0.986
L_CAC	L_RMF	L-Limbic	R-Limbic	-0.099	0.211	0.642	0.760	0.543	0.214	0.013	0.035*	0.271	0.215	0.210	0.340	0.473	0.213	0.029	0.067	-0.272	0.215	0.209	0.823
L_CAC	L_SF	L-Limbic	L-Frontal	-0.316	0.209	0.133	0.372	0.532	0.206	0.011	0.034*	0.354	0.211	0.096	0.199	0.554	0.204	0.008	0.036*	-0.023	0.212	0.916	0.986
L_CAC	R_CAC	L-Limbic	L-Frontal	0.081	0.206	0.696	0.805	-0.062	0.209	0.767	0.793	-0.003	0.213	0.990	0.994	-0.083	0.206	0.687	0.727	0.153	0.211	0.471	0.954
L_CMF	L_POPE	L-Frontal	L-Frontal	-0.342	0.211	0.107	0.323	0.660	0.202	0.002	0.011*	0.550	0.205	0.009	0.057	0.630	0.203	0.003	0.026*	-0.042	0.212	0.845	0.986
L_CMF	L_PSTC	L-Frontal	L-Parietal	-0.474	0.210	0.026	0.193	0.510	0.207	0.016	0.039*	0.335	0.211	0.115	0.226	0.486	0.208	0.021	0.059	0.041	0.213	0.846	0.986
L_CMF	L_PREC	L-Frontal	L-Frontal	-0.198	0.213	0.355	0.577	0.516	0.207	0.014	0.038*	0.441	0.209	0.037	0.103	0.462	0.209	0.029	0.068	-0.131	0.210	0.533	0.966
L_CMF	L_RMF	L-Frontal	L-Frontal	-0.528	0.206	0.012	0.122	0.514	0.207	0.015	0.038*	0.453	0.211	0.034	0.099	0.581	0.205	0.006	0.031*	0.085	0.213	0.691	0.979
L_CMF	L_SF	L-Frontal	L-Frontal	-0.129	0.209	0.538	0.685	0.408	0.210	0.055	0.086	0.424	0.209	0.045	0.118	0.363	0.209	0.085	0.126	-0.146	0.209	0.487	0.966
L_CMF	L_INS	L-Frontal	L-Insula	-0.530	0.205	0.011	0.121	0.731	0.200	0.000	0.009*	0.577	0.207	0.006	0.054	0.752	0.199	0.000	0.016*	0.098	0.208	0.639	0.974
L_CUN	L_IP	L-Occipital	L-Limbic	-0.043	0.215	0.843	0.890	0.496	0.209	0.020	0.045*	0.519	0.207	0.014	0.066	0.448	0.209	0.035	0.071	0.425	0.207	0.043	0.387
L_CUN	L_ISTH	L-Occipital	L-Occipital	-0.144	0.210	0.495	0.663	0.465	0.208	0.028	0.054	0.189	0.206	0.361	0.507	0.262	0.211	0.216	0.268	0.350	0.209	0.098	0.632
L_CUN	L_LOCC	L-Occipital	L-Occipital	0.069	0.213	0.746	0.840	0.422	0.212	0.050	0.080	0.525	0.206	0.013	0.066	0.268	0.215	0.215	0.268	0.261	0.209	0.214	0.823
L_CUN	L_LING	L-Occipital	L-Parietal	0.101	0.213	0.636	0.757	0.388	0.208	0.065	0.098	0.354	0.208	0.092	0.192	0.241	0.212	0.260	0.314	0.292	0.211	0.169	0.800
L_CUN	L_PCAL	L-Occipital	L-Parietal	0.169	0.212	0.427	0.618	0.173	0.212	0.415	0.481	0.288	0.209	0.170	0.299	0.041	0.214	0.849	0.862	0.260	0.212	0.223	0.828
L_CUN	L_PCUN	L-Occipital	L-Occipital	0.072	0.209	0.730	0.832	0.468	0.200	0.022	0.046*	0.513	0.199	0.012	0.065	0.453	0.206	0.030	0.069	0.475	0.202	0.021	0.286
L_CUN	L_SP	L-Occipital	L-Parietal	0.093	0.212	0.661	0.777	0.516	0.206	0.014	0.037*	0.579	0.202	0.005	0.051	0.309	0.211	0.148	0.195	0.303	0.207	0.146	0.767
L_ENT	L_FUS	L-Temporal	L-Temporal	-0.011	0.214	0.961	0.974	0.598	0.213	0.006	0.024*	0.786	0.202	0.000	0.019*	0.315	0.212	0.141	0.188	0.295	0.210	0.164	0.797
L_ENT	L_IT	L-Temporal	L-Frontal	-0.079	0.216	0.714	0.821	0.438	0.211	0.041	0.070	0.459	0.212	0.034	0.098	0.342	0.213	0.112	0.154	0.021	0.215	0.921	0.986
L_ENT	L_MOF	L-Temporal	L-Temporal	-0.392	0.209	0.063	0.243	0.129	0.213	0.547	0.610	-0.214	0.213	0.317	0.467	0.293	0.210	0.167	0.215	0.028	0.214	0.895	0.986
L_ENT	L_MT	L-Temporal	L-Occipital	0.095	0.220	0.668	0.782	0.486	0.214	0.026	0.052	0.523	0.213	0.016	0.068	0.282	0.218	0.200	0.252	0.547	0.213	0.012	0.241
L_ENT	L_PHPC	L-Temporal	L-Temporal	-0.607	0.209	0.005	0.083	0.334	0.209	0.114	0.154	0.198	0.212	0.353	0.500	0.370	0.208	0.079	0.120	-0.032	0.213	0.882	0.986
L_ENT	L_ST	L-Temporal	L-Temporal	-0.138	0.213	0.519	0.683	0.611	0.204	0.003	0.017*	0.578	0.205	0.006	0.052	0.484	0.207	0.022	0.059	0.333	0.211	0.118	0.704
L_ENT	L_TP	L-Temporal	L-Insula	-0.189	0.211	0.371	0.582	0.544	0.206	0.010	0.031*	0.474	0.210	0.026	0.088	0.520	0.205	0.013	0.047*	0.361	0.210	0.089	0.619
L_ENT	L_INS	L-Temporal	L-Occipital	-0.231	0.210	0.275	0.503	0.696	0.201	0.001	0.010*	0.533	0.204	0.011	0.062	0.612	0.204	0.003	0.027*	0.020	0.213	0.927	0.986
L_FUS	L_IP	L-Occipital	L-Parietal	-0.411	0.210	0.053	0.227	0.467	0.205	0.025	0.051	0.565	0.209	0.008	0.056	0.494	0.205	0.018	0.054	0.326	0.211	0.125	0.715
L_FUS	L_IT	L-Occipital	L-Occipital	-0.194	0.212	0.362	0.580	0.629	0.201	0.002	0.014*	0.573	0.202	0.006	0.051	0.575	0.204	0.006	0.031*	0.160	0.213	0.454	0.943
L_FUS	L_LOCC	L-Occipital	L-Occipital	-0.056	0.213	0.792	0.867	0.419	0.206	0.044	0.074	0.371	0.207	0.076	0.173	0.643	0.207	0.003	0.026*	0.004	0.210	0.986	0.992
L_FUS	L_LING	L-Occipital	L-Parietal	-0.253	0.212	0.234	0.469	0.188	0.208	0.369	0.431	0.061	0.210	0.772	0.837	0.236	0.209	0.262	0.315	0.058	0.212	0.784	0.986
L_FUS	L_MT	L-Occipital	L-Occipital	-0.464	0.207	0.028	0.193	0.687	0.200	0.001	0.010*	0.501	0.204	0.016	0.068	0.698	0.201	0.001	0.020*	0.461	0.200	0.024	0.299
L_FUS	L_PHPC	L-Occipital	L-Temporal	-0.114	0.212	0.591	0.727	0.565	0.213	0.010	0.031*	0.190	0.208	0.364	0.507	0.499	0.208	0.019	0.055	0.196	0.209	0.351	0.901
L_FUS	L_PCAL	L-Occipital	L-Temporal	0.013	0.216	0.951	0.970	0.117	0.212	0.581	0.636	0.135	0.213	0.528	0.646	0.084	0.212	0.693	0.730	-0.697	0.211	0.001	0.130
L_FUS	L_ST	L-Occipital	L-Temporal	-0.365	0.210	0.085	0.286	0.681	0.202	0.001	0.010*	0.518	0.207	0.014	0.066	0.635	0.203	0.002	0.026*	0.101	0.212	0.635	0.974
L_FUS	L_TP	L-Occipital	L-Temporal	-0.281	0.211	0.185	0.428	0.551	0.207	0.009	0.031*	0.616	0.205	0.003	0.049	0.499	0.208	0.018	0.055	0.271	0.210	0.200	0.823
L_IP	L_IT	L-Parietal	L-Temporal	-0.572	0.209	0.007	0.102	0.480	0.212	0.026	0.052	0.233	0.209	0.270	0.412	0.528	0.205	0.011	0.044*	-0.012	0.212	0.954	0.986
L_IP	L_ISTH	L-Parietal	L-Occipital	-0.046	0.218	0.834	0.887	0.581	0.208	0.006	0.025*	0.565	0.208	0.008	0.056	0.394	0.214	0.069	0.109	-0.026	0.218	0.907	0.986
L_IP	L_LOCC	L-Parietal	L-Occipital	-0.139	0.213	0.514	0.680	0.277	0.209	0.188	0.237	0.238	0.207	0.254	0.396	0.461	0.211	0.031	0.069	0.278	0.209	0.188	0.823
L_IP	L_LING	L-Parietal	L-Parietal	-0.058	0.216	0.788	0.866	0.456	0.215	0.036	0.066	0.484	0.212	0.025	0.086	0.132	0.215	0.539	0.586	0.489	0.210	0.022	0.291
L_IP	L_MT	L-Parietal	L-Parietal	-0.295	0.207	0.157	0.400	0.681	0.202	0.001	0.010*	0.541	0.213	0.013	0.066	0.616	0.204	0.003	0.027*	-0.116	0.213	0.588	0.974

Table 6.3.G: FDR corrected results from comparisons of fractional anisotropy, mean diffusivity, axial diffusivity, radial diffusivity, and fractional Number of Tracks in CPHIV compared to CHU. Asterisks indicate associations that survive threshold for significance corrected for multiple comparisons (FDR $q < 0.05$).

ROI X	ROI Y	Area X	Area Y	Fractional anisotropy				Mean diffusivity				Axial diffusivity				Radial diffusivity				fractional Number of tracks			
				stdB	se	p	FDR q	stdB	se	p	FDR q	stdB	se	p	FDR q	stdB	se	p	FDR q	stdB	se	p	FDR q
L_IP	L_PCAL	L-Parietal	L-Frontal	0.102	0.213	0.635	0.757	0.219	0.209	0.296	0.355	0.394	0.206	0.058	0.139	0.077	0.211	0.716	0.749	0.219	0.210	0.300	0.866
L_IP	L_PSTC	L-Parietal	L-Parietal	-0.275	0.209	0.192	0.435	0.434	0.207	0.039	0.069	0.362	0.205	0.080	0.176	0.404	0.209	0.056	0.095	-0.164	0.211	0.439	0.938
L_IP	L_PREC	L-Parietal	L-Parietal	-0.292	0.213	0.173	0.416	0.413	0.209	0.051	0.080	0.182	0.208	0.383	0.524	0.466	0.208	0.027	0.066	0.104	0.212	0.624	0.974
L_IP	L_PCUN	L-Parietal	L-Limbic	-0.252	0.212	0.237	0.471	0.539	0.204	0.010	0.031*	0.508	0.204	0.015	0.066	0.455	0.207	0.030	0.069	0.718	0.207	0.001	0.130
L_IP	L_SP	L-Parietal	L-Occipital	-0.227	0.210	0.282	0.506	0.443	0.208	0.036	0.065	0.589	0.208	0.006	0.051	0.576	0.207	0.007	0.032*	-0.106	0.210	0.614	0.974
L_IP	L_ST	L-Parietal	L-Temporal	-0.252	0.211	0.235	0.469	0.698	0.201	0.001	0.010*	0.653	0.202	0.002	0.037*	0.598	0.204	0.004	0.029*	0.043	0.212	0.841	0.986
L_IP	L_SMAR	L-Parietal	L-Insula	-0.303	0.209	0.151	0.392	0.439	0.208	0.037	0.067	0.448	0.209	0.035	0.099	0.443	0.208	0.036	0.073	-0.466	0.206	0.026	0.302
L_IP	L_INS	L-Parietal	L-Temporal	-0.293	0.210	0.167	0.404	0.572	0.206	0.006	0.025*	0.458	0.208	0.030	0.094	0.517	0.207	0.014	0.049*	-0.012	0.211	0.955	0.986
L_IT	L_LOCC	L-Temporal	L-Occipital	-0.146	0.207	0.483	0.659	0.751	0.199	0.000	0.008*	0.260	0.201	0.198	0.326	0.631	0.207	0.003	0.027*	-0.787	0.202	0.000	0.094
L_IT	L_LING	L-Temporal	L-Occipital	-0.065	0.214	0.763	0.849	0.275	0.211	0.196	0.245	0.236	0.210	0.264	0.406	0.225	0.214	0.295	0.350	-0.068	0.213	0.750	0.979
L_IT	L_MT	L-Temporal	L-Temporal	-0.230	0.210	0.275	0.503	0.704	0.201	0.001	0.010*	0.573	0.204	0.006	0.052	0.673	0.202	0.001	0.021*	0.046	0.205	0.822	0.986
L_IT	L_ST	L-Temporal	L-Temporal	-0.433	0.207	0.039	0.213	0.753	0.199	0.000	0.008*	0.565	0.205	0.007	0.056	0.699	0.201	0.001	0.020*	-0.208	0.207	0.317	0.871
L_IT	L_TP	L-Temporal	L-Temporal	0.020	0.210	0.924	0.948	0.823	0.200	0.000	0.006*	0.608	0.202	0.003	0.049*	0.624	0.203	0.003	0.026*	-0.024	0.211	0.909	0.986
L_ISTH	L_LING	L-Limbic	L-Occipital	-0.046	0.212	0.831	0.885	0.528	0.215	0.016	0.040*	0.184	0.210	0.385	0.526	0.211	0.212	0.321	0.377	0.160	0.212	0.452	0.943
L_ISTH	L_PHPC	L-Limbic	L-Central sulcus	-0.263	0.212	0.218	0.461	0.434	0.207	0.039	0.068	0.263	0.210	0.213	0.341	0.394	0.209	0.062	0.102	-0.094	0.212	0.658	0.974
L_ISTH	L_PC	L-Limbic	L-Limbic	-0.037	0.212	0.862	0.903	0.421	0.209	0.047	0.076	0.306	0.210	0.149	0.274	0.347	0.210	0.101	0.143	0.270	0.213	0.208	0.823
L_ISTH	L_PC	L-Limbic	R-Limbic	-0.120	0.204	0.557	0.702	0.370	0.208	0.078	0.114	0.296	0.206	0.154	0.283	0.377	0.208	0.073	0.113	0.265	0.210	0.210	0.823
L_ISTH	L_PCUN	L-Limbic	L-Occipital	-0.133	0.212	0.531	0.684	0.537	0.205	0.010	0.032	0.544	0.207	0.010	0.061	0.455	0.208	0.031	0.069	0.584	0.211	0.007	0.183
L_ISTH	L_SP	L-Limbic	L-Occipital	-0.161	0.211	0.446	0.631	0.654	0.203	0.002	0.012*	0.441	0.206	0.035	0.099	0.511	0.207	0.015	0.051	-0.016	0.209	0.940	0.986
L_ISTH	R_ISTH	L-Limbic	L-Parietal	0.234	0.210	0.267	0.500	0.090	0.213	0.673	0.716	0.231	0.211	0.278	0.421	-0.050	0.212	0.816	0.835	0.210	0.208	0.316	0.871
L_LOCC	L_LING	L-Occipital	L-Occipital	0.066	0.213	0.758	0.848	0.421	0.208	0.046	0.076	0.207	0.210	0.327	0.476	0.302	0.211	0.156	0.203	0.299	0.205	0.147	0.767
L_LOCC	L_PCAL	L-Occipital	L-Parietal	0.142	0.212	0.504	0.670	0.343	0.210	0.106	0.146	0.403	0.208	0.056	0.134	0.186	0.213	0.383	0.442	0.302	0.211	0.155	0.774
L_LOCC	L_PCUN	L-Occipital	L-Occipital	0.069	0.215	0.750	0.843	0.403	0.212	0.061	0.094	0.505	0.203	0.015	0.066	0.230	0.215	0.287	0.343	0.454	0.213	0.035	0.354
L_LOCC	L_SP	L-Occipital	L-Parietal	0.150	0.213	0.482	0.659	0.474	0.207	0.024	0.051	0.530	0.206	0.012	0.065	0.222	0.211	0.294	0.350	0.261	0.205	0.206	0.823
L_LOF	L_MOF	L-Frontal	L-Frontal	-0.150	0.211	0.479	0.657	0.648	0.203	0.002	0.013*	0.610	0.204	0.004	0.049*	0.541	0.206	0.010	0.041*	0.079	0.208	0.704	0.979
L_LOF	L_POPE	L-Frontal	L-Frontal	-0.238	0.214	0.269	0.503	0.634	0.206	0.003	0.015*	0.501	0.207	0.017	0.071	0.559	0.208	0.009	0.038*	0.527	0.217	0.017	0.268
L_LOF	L_PORB	L-Frontal	L-Insula	0.080	0.213	0.710	0.818	0.551	0.206	0.009	0.031*	0.706	0.200	0.001	0.027*	0.368	0.210	0.084	0.125	-0.172	0.211	0.418	0.930
L_LOF	L_PTRI	L-Frontal	L-Frontal	-0.100	0.212	0.637	0.757	0.547	0.206	0.009	0.031*	0.633	0.203	0.002	0.039*	0.476	0.209	0.025	0.063	0.021	0.212	0.923	0.986
L_LOF	L_RAC	L-Frontal	L-Frontal	-0.064	0.207	0.757	0.848	0.453	0.209	0.033	0.062	0.413	0.206	0.048	0.122	0.532	0.206	0.011	0.044*	0.276	0.212	0.196	0.823
L_LOF	L_RMF	L-Frontal	L-Frontal	-0.174	0.211	0.411	0.609	0.547	0.206	0.009	0.031*	0.515	0.207	0.014	0.066	0.452	0.208	0.032	0.070	0.234	0.211	0.270	0.850
L_LOF	L_INS	L-Frontal	L-Frontal	-0.360	0.206	0.084	0.284	0.487	0.207	0.021	0.046*	0.314	0.210	0.139	0.260	0.461	0.206	0.028	0.066	-0.180	0.211	0.394	0.930
L_LING	L_PHPC	L-Occipital	L-Occipital	-0.207	0.212	0.331	0.568	0.345	0.209	0.102	0.142	0.263	0.210	0.213	0.341	0.362	0.213	0.093	0.133	-0.045	0.209	0.830	0.986
L_LING	L_PCAL	L-Occipital	L-Parietal	0.006	0.213	0.978	0.982	0.092	0.212	0.666	0.712	0.119	0.212	0.576	0.682	0.061	0.212	0.774	0.801	0.181	0.212	0.395	0.930
L_LING	L_PCUN	L-Occipital	L-Occipital	0.050	0.210	0.810	0.869	0.134	0.208	0.521	0.582	0.169	0.210	0.422	0.556	0.087	0.207	0.674	0.715	0.137	0.213	0.523	0.966
L_LING	L_SP	L-Occipital	L-Parietal	0.159	0.215	0.460	0.637	0.305	0.213	0.156	0.202	0.360	0.210	0.090	0.189	0.143	0.216	0.510	0.562	0.652	0.217	0.004	0.163
L_MOF	L_RAC	L-Frontal	L-Frontal	-0.190	0.213	0.374	0.584	0.421	0.209	0.047	0.076	0.331	0.211	0.119	0.232	0.378	0.210	0.075	0.116	0.111	0.212	0.602	0.974
L_MOF	L_RMF	L-Frontal	L-Frontal	-0.319	0.211	0.134	0.372	0.592	0.205	0.005	0.020*	0.445	0.208	0.035	0.099	0.573	0.205	0.006	0.032*	-0.101	0.211	0.633	0.974
L_MOF	L_SF	L-Frontal	L-Insula	-0.265	0.211	0.212	0.458	0.567	0.205	0.007	0.026*	0.443	0.212	0.039	0.106	0.451	0.210	0.035	0.071	-0.148	0.210	0.482	0.966
L_MOF	L_INS	L-Frontal	L-Frontal	-0.168	0.206	0.416	0.614	0.522	0.206	0.013	0.035*	0.433	0.203	0.035	0.099	0.429	0.207	0.041	0.078	-0.154	0.208	0.463	0.952
L_MT	L_ST	L-Temporal	L-Temporal	-0.341	0.208	0.103	0.316	0.827	0.196	0.000	0.006*	0.768	0.197	0.000	0.019*	0.726	0.200	0.000	0.016	-0.071	0.207	0.732	0.979
L_MT	L_TP	L-Temporal	L-Temporal	0.013	0.213	0.951	0.970	0.752	0.201	0.000	0.008*	0.797	0.198	0.000	0.019*	0.522	0.208	0.014	0.049	0.078	0.214	0.715	0.979
L_PARC	L_PSTC	L-Central sulcus	L-Parietal	-0.287	0.212	0.178	0.426	0.266	0.212	0.212	0.264	0.135	0.213	0.529	0.646	0.526	0.216	0.017	0.054	0.510	0.203	0.014	0.258
L_PARC	L_PC	L-Central sulcus	L-Frontal	-0.385	0.207	0.067	0.243	0.642	0.203	0.002	0.013*	0.418	0.209	0.049	0.122	0.613	0.204	0.003	0.027*	0.177	0.209	0.399	0.930
L_PARC	L_PREC	L-Central sulcus	L-Frontal	-0.281	0.211	0.185	0.428	0.433	0.209	0.041	0.070	0.309	0.211	0.146	0.271	0.546	0.209	0.010	0.042*	0.389	0.207	0.063	0.485
L_PARC	L_PCUN	L-Central sulcus	L-Parietal	-0.188	0.212	0.377	0.586	0.493	0.207	0.019	0.044*	0.289	0.210	0.171	0.299	0.503	0.208	0.017	0.054	0.447	0.209	0.035	0.354

Table 6.3.H: FDR corrected results from comparisons of fractional anisotropy, mean diffusivity, axial diffusivity, radial diffusivity, and fractional Number of Tracks in CPHIV compared to CHU. Asterisks indicate associations that survive threshold for significance corrected for multiple comparisons (FDR $q < 0.05$).

ROI X	ROI Y	Area X	Area Y	Fractional anisotropy				Mean diffusivity				Axial diffusivity				Radial diffusivity				fractional Number of tracks			
				stdB	se	p	FDR q	stdB	se	p	FDR q	stdB	se	p	FDR q	stdB	se	p	FDR q	stdB	se	p	FDR q
L_PARC	L_SF	L-Central sulcus	L-Occipital	-0.031	0.210	0.883	0.918	0.437	0.207	0.038	0.067	0.453	0.208	0.032	0.096	0.377	0.215	0.084	0.125	-0.029	0.208	0.889	0.986
L_PARC	L_SP	L-Central sulcus	L-Limbic	-0.189	0.212	0.376	0.586	0.478	0.209	0.025	0.051	0.218	0.212	0.307	0.455	0.386	0.209	0.068	0.108	0.229	0.203	0.263	0.849
L_POPE	L_PTRI	L-Frontal	L-Parietal	-0.119	0.212	0.577	0.717	0.502	0.207	0.017	0.042*	0.561	0.206	0.008	0.056	0.448	0.209	0.035	0.071	0.670	0.208	0.002	0.131
L_POPE	L_PSTC	L-Frontal	L-Frontal	0.098	0.209	0.641	0.760	0.426	0.209	0.044	0.074	0.654	0.203	0.002	0.037*	0.217	0.211	0.305	0.359	-0.094	0.210	0.656	0.974
L_POPE	L_PREC	L-Frontal	L-Frontal	-0.278	0.209	0.187	0.431	0.647	0.203	0.002	0.013*	0.659	0.203	0.002	0.037*	0.560	0.205	0.008	0.035*	-0.130	0.209	0.534	0.966
L_POPE	L_RMF	L-Frontal	L-Frontal	-0.294	0.211	0.166	0.404	0.550	0.206	0.009	0.031*	0.421	0.209	0.047	0.121	0.524	0.206	0.013	0.047*	0.127	0.213	0.552	0.974
L_POPE	L_INS	L-Frontal	L-Insula	-0.128	0.208	0.539	0.685	0.794	0.198	0.000	0.006*	0.739	0.195	0.000	0.022*	0.624	0.203	0.003	0.026*	0.010	0.211	0.961	0.986
L_PORB	L_PTRI	L-Frontal	L-Frontal	-0.122	0.213	0.570	0.712	0.475	0.204	0.022	0.046*	0.445	0.203	0.031	0.094	0.413	0.207	0.049	0.087	-0.052	0.210	0.806	0.986
L_PORB	L_RMF	L-Frontal	L-Frontal	-0.204	0.214	0.344	0.571	0.516	0.207	0.014	0.038*	0.483	0.207	0.022	0.080	0.469	0.209	0.027	0.066	-0.240	0.213	0.263	0.849
L_PTRI	L_RMF	L-Frontal	L-Frontal	-0.237	0.212	0.265	0.500	0.487	0.207	0.021	0.046*	0.437	0.208	0.039	0.105	0.448	0.209	0.035	0.071	0.102	0.213	0.634	0.974
L_PTRI	L_INS	L-Frontal	L-Insula	-0.160	0.211	0.449	0.631	0.616	0.204	0.003	0.016*	0.340	0.212	0.113	0.224	0.533	0.204	0.011	0.042*	0.207	0.212	0.330	0.879
L_PCAL	L_PCUN	L-Parietal	L-Parietal	0.084	0.213	0.694	0.805	0.037	0.210	0.860	0.875	0.074	0.210	0.723	0.797	0.004	0.211	0.984	0.984	0.177	0.213	0.408	0.930
L_PCAL	L_SP	L-Parietal	L-Occipital	0.173	0.213	0.419	0.614	0.393	0.212	0.067	0.099	0.353	0.210	0.097	0.199	0.038	0.215	0.860	0.870	0.019	0.214	0.931	0.986
L_PSTC	L_PC	L-Parietal	L-Limbic	-0.454	0.209	0.032	0.201	0.470	0.211	0.029	0.056	0.000	0.213	0.999	0.999	0.561	0.209	0.009	0.038*	0.222	0.212	0.299	0.866
L_PSTC	L_PREC	L-Parietal	L-Frontal	-0.308	0.211	0.148	0.387	0.439	0.209	0.038	0.067	0.530	0.210	0.013	0.066	0.424	0.210	0.047	0.085	0.132	0.209	0.528	0.966
L_PSTC	L_PCUN	L-Parietal	L-Occipital	-0.203	0.209	0.333	0.568	0.537	0.209	0.012	0.034*	0.196	0.209	0.352	0.500	0.396	0.210	0.062	0.102	0.350	0.216	0.108	0.671
L_PSTC	L_SP	L-Parietal	L-Parietal	-0.403	0.212	0.060	0.243	0.425	0.209	0.045	0.075	0.342	0.209	0.105	0.214	0.416	0.209	0.049	0.087	0.185	0.213	0.388	0.930
L_PSTC	L_ST	L-Parietal	L-Parietal	-0.458	0.212	0.034	0.201	0.525	0.207	0.013	0.035*	0.467	0.211	0.029	0.092	0.445	0.210	0.037	0.073	0.113	0.215	0.601	0.974
L_PSTC	L_SMAR	L-Parietal	L-Temporal	-0.353	0.207	0.091	0.294	0.468	0.208	0.027	0.053	0.516	0.208	0.015	0.066	0.433	0.209	0.041	0.078	0.027	0.212	0.898	0.986
L_PSTC	L_INS	L-Parietal	L-Insula	-0.162	0.212	0.445	0.631	0.641	0.203	0.002	0.013*	0.640	0.200	0.002	0.039*	0.482	0.208	0.023	0.061	0.267	0.209	0.204	0.823
L_PC	L_PREC	L-Limbic	L-Limbic	-0.133	0.211	0.529	0.684	0.596	0.208	0.005	0.022*	0.284	0.211	0.181	0.310	0.347	0.210	0.101	0.143	-0.015	0.209	0.942	0.986
L_PC	L_PCUN	L-Limbic	R-Limbic	-0.234	0.204	0.255	0.489	0.531	0.205	0.011	0.033*	0.379	0.209	0.072	0.165	0.491	0.204	0.018	0.054	0.686	0.206	0.001	0.130
L_PC	L_SF	L-Limbic	R-Limbic	0.146	0.212	0.493	0.662	0.425	0.209	0.045	0.075	0.512	0.207	0.015	0.067	0.253	0.212	0.235	0.287	0.166	0.213	0.438	0.938
L_PC	L_SP	L-Limbic	L-Frontal	-0.244	0.212	0.252	0.488	0.483	0.208	0.023	0.048*	0.276	0.212	0.195	0.323	0.479	0.208	0.024	0.062	0.263	0.210	0.213	0.823
L_PC	R_CAC	L-Limbic	L-Occipital	-0.046	0.221	0.836	0.887	0.127	0.213	0.552	0.612	0.061	0.217	0.778	0.837	0.131	0.215	0.543	0.590	0.280	0.217	0.201	0.823
L_PC	R_PC	L-Limbic	L-Parietal	-0.185	0.214	0.389	0.593	-0.083	0.214	0.700	0.739	-0.203	0.215	0.347	0.499	0.039	0.214	0.854	0.866	-0.096	0.214	0.653	0.974
L_PREC	L_SF	L-Frontal	L-Frontal	-0.299	0.212	0.161	0.404	0.456	0.209	0.031	0.060	0.323	0.211	0.130	0.249	0.396	0.211	0.064	0.103	0.204	0.209	0.330	0.879
L_PREC	L_SP	L-Frontal	L-Parietal	-0.449	0.207	0.032	0.201	0.556	0.206	0.008	0.030*	0.274	0.210	0.195	0.323	0.581	0.205	0.006	0.031*	0.216	0.213	0.312	0.871
L_PREC	L_ST	L-Frontal	L-Temporal	-0.482	0.211	0.025	0.189	0.544	0.208	0.010	0.032*	0.125	0.214	0.562	0.670	0.605	0.207	0.004	0.030*	0.097	0.216	0.653	0.974
L_PREC	L_SMAR	L-Frontal	L-Parietal	-0.200	0.208	0.339	0.571	0.488	0.208	0.021	0.046*	0.470	0.211	0.029	0.091	0.637	0.207	0.003	0.026*	0.013	0.214	0.951	0.986
L_PREC	L_INS	L-Frontal	L-Insula	-0.133	0.209	0.525	0.684	0.599	0.204	0.004	0.019*	0.636	0.201	0.002	0.039*	0.416	0.208	0.048	0.087	0.230	0.210	0.275	0.854
L_PCUN	L_SP	L-Occipital	L-Parietal	-0.213	0.211	0.316	0.548	0.523	0.207	0.013	0.035*	0.601	0.207	0.005	0.049*	0.471	0.208	0.026	0.064	0.613	0.203	0.003	0.163
L_RAC	L_RMF	L-Frontal	R-Frontal	-0.184	0.215	0.393	0.593	0.600	0.214	0.006	0.024*	0.298	0.216	0.170	0.299	0.423	0.213	0.050	0.088	0.514	0.213	0.018	0.278
L_RAC	L_SF	L-Frontal	L-Frontal	-0.517	0.206	0.014	0.131	0.527	0.207	0.012	0.035*	0.197	0.212	0.355	0.501	0.600	0.204	0.004	0.028*	0.404	0.210	0.057	0.465
L_RAC	R_RAC	L-Frontal	L-Frontal	0.088	0.217	0.685	0.797	-0.095	0.208	0.650	0.702	-0.027	0.209	0.897	0.924	-0.123	0.211	0.560	0.606	0.033	0.216	0.878	0.986
L_RMF	L_SF	L-Frontal	L-Frontal	-0.393	0.210	0.065	0.243	0.435	0.208	0.039	0.069	0.283	0.211	0.183	0.310	0.452	0.207	0.032	0.069	-0.071	0.213	0.738	0.979
L_RMF	L_INS	L-Frontal	L-Insula	-0.124	0.210	0.556	0.702	0.567	0.215	0.010	0.031*	0.324	0.210	0.127	0.244	0.320	0.209	0.129	0.173	-0.072	0.206	0.729	0.979
L_SP	L_ST	L-Parietal	L-Temporal	-0.513	0.209	0.016	0.147	0.535	0.209	0.012	0.035*	0.290	0.214	0.178	0.308	0.537	0.209	0.012	0.044*	0.097	0.216	0.653	0.974
L_SP	L_SMAR	L-Parietal	L-Parietal	-0.351	0.208	0.094	0.297	0.587	0.205	0.005	0.022*	0.446	0.206	0.033	0.098	0.560	0.206	0.008	0.036*	-0.111	0.213	0.602	0.974
L_SP	L_INS	L-Parietal	L-Insula	-0.348	0.205	0.093	0.295	0.606	0.204	0.004	0.017*	0.483	0.204	0.020	0.077	0.554	0.206	0.008	0.037*	0.243	0.213	0.257	0.849
L_ST	L_SMAR	L-Temporal	L-Parietal	-0.235	0.213	0.274	0.503	0.449	0.210	0.035	0.065	0.298	0.212	0.164	0.294	0.430	0.213	0.047	0.086	-0.239	0.213	0.266	0.849
L_ST	L_TP	L-Temporal	L-Temporal	-0.196	0.213	0.359	0.580	0.694	0.203	0.001	0.010*	0.653	0.205	0.002	0.039*	0.586	0.206	0.005	0.030*	0.089	0.211	0.674	0.976
L_ST	L_TT	L-Temporal	L-Temporal	-0.567	0.205	0.007	0.101	0.760	0.199	0.000	0.008*	0.134	0.213	0.529	0.646	0.725	0.200	0.000	0.016*	0.117	0.212	0.584	0.974
L_ST	L_INS	L-Temporal	L-Insula	-0.235	0.212	0.272	0.503	0.688	0.202	0.001	0.010*	0.715	0.199	0.001	0.026	0.564	0.206	0.007	0.035*	-0.219	0.210	0.300	0.866
L_SMAR	L_TT	L-Parietal	L-Temporal	-0.486	0.217	0.028	0.193	0.471	0.209	0.027	0.054	0.285	0.213	0.183	0.310	0.381	0.211	0.075	0.116	0.041	0.209	0.845	0.986
L_SMAR	L_INS	L-Parietal	L-Insula	-0.257	0.208	0.221	0.462	0.501	0.207	0.017	0.043*	0.399	0.205	0.055	0.134	0.443	0.209	0.036	0.073	-0.033	0.209	0.875	0.986
L_TP	L_INS	L-Temporal	L-Insula	-0.105	0.214	0.625	0.756	0.626	0.206	0.003	0.016*	0.567	0.207	0.007	0.056	0.555	0.208	0.009	0.039*	-0.139	0.213	0.515	0.966

Table 6.3.I: FDR corrected results from comparisons of fractional anisotropy, mean diffusivity, axial diffusivity, radial diffusivity, and fractional Number of Tracks in CPHIV compared to CHU. Asterisks indicate associations that survive threshold for significance corrected for multiple comparisons (FDR $q < 0.05$).

ROI X	ROI Y	Area X	Area Y	Fractional anisotropy				Mean diffusivity				Axial diffusivity				Radial diffusivity				fractional Number of tracks			
				stdB	se	p	FDR q	stdB	se	p	FDR q	stdB	se	p	FDR q	stdB	se	p	FDR q	stdB	se	p	FDR q
L_TT	L_INS	L-Temporal	L-Insula	-0.476	0.208	0.024	0.189	0.772	0.199	0.000	0.008	0.559	0.207	0.008	0.056	0.730	0.200	0.000	0.016*	0.134	0.208	0.522	0.966
R_BSTS	R_FUS	R-Temporal	R-Parietal	-0.542	0.208	0.011	0.121	0.671	0.204	0.001	0.011*	0.486	0.212	0.024	0.085	0.689	0.204	0.001	0.021*	0.250	0.211	0.239	0.849
R_BSTS	R_IP	R-Temporal	R-Insula	-0.388	0.209	0.066	0.243	0.577	0.204	0.006	0.023*	0.360	0.205	0.082	0.178	0.576	0.206	0.006	0.032*	0.568	0.205	0.007	0.183
R_BSTS	R_IT	R-Temporal	R-Occipital	-0.426	0.209	0.044	0.217	0.617	0.204	0.003	0.016*	0.425	0.207	0.043	0.115	0.606	0.205	0.004	0.028*	0.346	0.208	0.099	0.632
R_BSTS	R_MT	R-Temporal	R-Parietal	-0.420	0.207	0.046	0.217	0.670	0.202	0.001	0.010*	0.491	0.207	0.020	0.076	0.643	0.203	0.002	0.024*	0.485	0.206	0.020	0.286
R_BSTS	R_ST	R-Temporal	R-Temporal	-0.499	0.207	0.018	0.152	0.747	0.200	0.000	0.008*	0.483	0.206	0.021	0.080	0.749	0.199	0.000	0.016*	0.076	0.209	0.718	0.979
R_BSTS	R_SMAR	R-Temporal	R-Temporal	-0.128	0.213	0.549	0.695	0.340	0.210	0.109	0.149	0.237	0.208	0.258	0.399	0.302	0.211	0.156	0.203	-0.486	0.208	0.021	0.286
R_BSTS	R_TT	R-Temporal	R-Temporal	-0.398	0.212	0.064	0.243	0.556	0.208	0.009	0.031	0.157	0.215	0.468	0.600	0.593	0.207	0.005	0.030*	-0.036	0.216	0.866	0.986
R_BSTS	R_INS	R-Temporal	R-Temporal	-0.426	0.208	0.043	0.217	0.381	0.210	0.073	0.107	0.113	0.213	0.598	0.700	0.399	0.211	0.062	0.102	0.047	0.213	0.825	0.986
R_CAC	R_CMF	R-Limbic	R-Frontal	-0.347	0.211	0.103	0.316	0.490	0.209	0.021	0.046*	0.170	0.216	0.433	0.567	0.452	0.209	0.033	0.071	-0.277	0.212	0.195	0.823
R_CAC	R_ISTH	R-Limbic	R-Frontal	0.230	0.207	0.270	0.503	0.607	0.211	0.005	0.021*	0.512	0.210	0.017	0.069	0.084	0.210	0.690	0.729	-0.111	0.208	0.594	0.974
R_CAC	R_PC	R-Limbic	R-Frontal	-0.107	0.202	0.595	0.727	0.492	0.206	0.019	0.044*	0.584	0.209	0.006	0.053	0.392	0.201	0.054	0.092	0.133	0.211	0.531	0.966
R_CAC	R_RAC	R-Limbic	R-Frontal	-0.006	0.211	0.978	0.982	0.432	0.208	0.040	0.069	0.397	0.209	0.061	0.144	0.241	0.209	0.251	0.304	-0.162	0.211	0.443	0.941
R_CAC	R_RMF	R-Limbic	R-Limbic	-0.194	0.208	0.352	0.577	0.313	0.211	0.141	0.184	0.162	0.214	0.449	0.583	0.324	0.208	0.122	0.166	-0.564	0.204	0.007	0.183
R_CAC	R_SF	R-Limbic	R-Limbic	-0.181	0.211	0.392	0.593	0.421	0.209	0.046	0.076	0.337	0.210	0.113	0.224	0.388	0.208	0.065	0.104	-0.370	0.206	0.076	0.565
R_CMF	R_POPE	R-Frontal	R-Frontal	-0.345	0.210	0.104	0.317	0.465	0.210	0.029	0.057	0.188	0.213	0.379	0.523	0.417	0.210	0.050	0.088	-0.056	0.213	0.795	0.986
R_CMF	R_PSTC	R-Frontal	R-Parietal	-0.477	0.212	0.027	0.193	0.370	0.210	0.082	0.117	0.231	0.212	0.280	0.423	0.386	0.210	0.069	0.109	0.296	0.211	0.165	0.797
R_CMF	R_PREC	R-Frontal	R-Frontal	-0.394	0.210	0.064	0.243	0.414	0.209	0.051	0.080	0.255	0.211	0.229	0.363	0.446	0.209	0.035	0.071	-0.048	0.214	0.822	0.986
R_CMF	R_RMF	R-Frontal	R-Frontal	-0.157	0.213	0.463	0.638	0.500	0.208	0.018	0.043*	0.362	0.209	0.086	0.185	0.379	0.210	0.074	0.114	-0.112	0.212	0.598	0.974
R_CMF	R_SF	R-Frontal	R-Insula	-0.337	0.209	0.110	0.324	0.454	0.208	0.031	0.060	0.487	0.208	0.021	0.080	0.454	0.208	0.032	0.070	-0.103	0.212	0.628	0.974
R_CMF	R_INS	R-Frontal	R-Frontal	-0.227	0.209	0.280	0.506	0.438	0.212	0.042	0.071	0.121	0.212	0.569	0.675	0.426	0.207	0.043	0.079	0.039	0.211	0.853	0.986
R_CUN	R_IP	R-Occipital	R-Limbic	0.087	0.213	0.683	0.796	0.505	0.209	0.017	0.042*	0.498	0.210	0.020	0.076	0.118	0.213	0.582	0.627	0.115	0.212	0.588	0.974
R_CUN	R_ISTH	R-Occipital	R-Occipital	0.030	0.215	0.890	0.923	0.225	0.212	0.290	0.349	0.199	0.212	0.349	0.499	0.140	0.216	0.517	0.568	0.015	0.214	0.946	0.986
R_CUN	R_LOCC	R-Occipital	R-Parietal	-0.041	0.213	0.847	0.892	0.546	0.210	0.011	0.033*	0.461	0.208	0.029	0.091	0.275	0.212	0.198	0.250	-0.211	0.211	0.320	0.873
R_CUN	R_LING	R-Occipital	R-Parietal	-0.212	0.214	0.325	0.559	-0.148	0.214	0.491	0.554	-0.191	0.213	0.371	0.516	-0.041	0.215	0.849	0.862	0.095	0.211	0.652	0.974
R_CUN	R_PCAL	R-Occipital	R-Occipital	-0.164	0.213	0.443	0.631	0.063	0.214	0.767	0.793	0.013	0.214	0.950	0.967	0.091	0.213	0.672	0.714	-0.138	0.212	0.517	0.966
R_CUN	R_PCUN	R-Occipital	R-Occipital	0.147	0.211	0.486	0.659	0.560	0.208	0.008	0.030*	0.517	0.207	0.014	0.066	0.427	0.212	0.047	0.086	-0.009	0.212	0.967	0.987
R_CUN	R_SP	R-Occipital	R-Parietal	-0.079	0.212	0.709	0.818	0.735	0.202	0.000	0.009*	0.724	0.202	0.001	0.026*	0.604	0.209	0.005	0.030	-0.139	0.213	0.515	0.966
R_ENT	R_FUS	R-Temporal	R-Occipital	0.007	0.213	0.973	0.982	0.393	0.212	0.067	0.099*	0.578	0.208	0.007	0.055	0.253	0.211	0.235	0.287	-0.144	0.213	0.500	0.966
R_ENT	R_IT	R-Temporal	R-Temporal	0.065	0.213	0.761	0.849	0.563	0.212	0.009	0.031*	0.425	0.210	0.046	0.120	0.205	0.212	0.338	0.394	-0.104	0.211	0.624	0.974
R_ENT	R_MT	R-Temporal	R-Temporal	-0.041	0.219	0.852	0.896	0.444	0.216	0.042	0.072	0.508	0.211	0.018	0.074	0.295	0.218	0.179	0.229	-0.234	0.220	0.290	0.865
R_ENT	R_PARH	R-Temporal	R-Temporal	-0.074	0.216	0.732	0.832	0.525	0.206	0.013	0.035*	0.468	0.209	0.028	0.089	0.471	0.208	0.026	0.064	-0.076	0.210	0.717	0.979
R_ENT	R_ST	R-Temporal	R-Occipital	-0.406	0.209	0.055	0.230	0.736	0.199	0.000	0.008*	0.644	0.202	0.002	0.039*	0.681	0.201	0.001	0.021*	0.449	0.218	0.043	0.387
R_ENT	R_TP	R-Temporal	R-Insula	-0.289	0.213	0.179	0.426	0.366	0.207	0.081	0.116	0.580	0.212	0.007	0.056	0.437	0.206	0.037	0.073	-0.017	0.217	0.939	0.986
R_ENT	R_INS	R-Temporal	R-Temporal	-0.211	0.209	0.314	0.546	0.511	0.207	0.015	0.039*	0.516	0.207	0.015	0.066	0.447	0.207	0.033	0.071	-0.163	0.213	0.446	0.943
R_FUS	R_IP	R-Occipital	R-Occipital	-0.385	0.210	0.070	0.246	0.620	0.203	0.003	0.016*	0.517	0.209	0.015	0.067	0.620	0.204	0.003	0.027*	0.215	0.210	0.307	0.871
R_FUS	R_IT	R-Occipital	R-Occipital	-0.148	0.212	0.488	0.659	0.557	0.204	0.008	0.028*	0.537	0.205	0.010	0.062	0.497	0.206	0.018	0.054	-0.067	0.213	0.752	0.979
R_FUS	R_LOCC	R-Occipital	R-Temporal	-0.303	0.211	0.153	0.393	0.586	0.202	0.005	0.020*	0.453	0.212	0.035	0.099	0.598	0.203	0.004	0.028*	0.085	0.210	0.685	0.977
R_FUS	R_LING	R-Occipital	R-Temporal	-0.253	0.212	0.234	0.469	0.107	0.213	0.615	0.671	0.012	0.214	0.955	0.970	0.165	0.212	0.439	0.493	-0.200	0.210	0.344	0.887
R_FUS	R_MT	R-Occipital	R-Insula	-0.267	0.212	0.211	0.458	0.646	0.202	0.002	0.013*	0.608	0.203	0.003	0.049	0.590	0.205	0.005	0.030*	-0.082	0.210	0.696	0.979
R_FUS	R_PARH	R-Occipital	R-Parietal	-0.157	0.213	0.462	0.637	0.439	0.209	0.038	0.067	0.429	0.216	0.050	0.124	0.525	0.209	0.014	0.049	0.062	0.214	0.771	0.982
R_FUS	R_ST	R-Occipital	R-Occipital	-0.340	0.210	0.109	0.324	0.661	0.201	0.001	0.011*	0.596	0.204	0.004	0.049*	0.583	0.204	0.005	0.030*	-0.063	0.210	0.764	0.982
R_FUS	R_TP	R-Occipital	R-Temporal	-0.139	0.214	0.519	0.683	0.335	0.206	0.106	0.146	0.417	0.217	0.058	0.139	0.365	0.206	0.080	0.121	-0.307	0.214	0.155	0.774
R_FUS	R_INS	R-Occipital	R-Temporal	-0.160	0.214	0.455	0.636	0.514	0.208	0.015	0.039*	0.459	0.209	0.031	0.094	0.393	0.211	0.065	0.104	-0.553	0.207	0.009	0.210
R_IP	R_IT	R-Parietal	R-Limbic	-0.319	0.207	0.127	0.362	0.673	0.202	0.001	0.010*	0.507	0.203	0.014	0.066	0.675	0.202	0.001	0.021*	0.322	0.211	0.130	0.734
R_IP	R_ISTH	R-Parietal	R-Occipital	-0.290	0.215	0.182	0.426	0.199	0.215	0.357	0.419	0.029	0.216	0.894	0.923	0.544	0.216	0.014	0.049*	-0.039	0.212	0.853	0.986

Table 6.3.J: FDR corrected results from comparisons of fractional anisotropy, mean diffusivity, axial diffusivity, radial diffusivity, and fractional Number of Tracks in CPHIV compared to CHU. Asterisks indicate associations that survive threshold for significance corrected for multiple comparisons (FDR $q < 0.05$).

ROI X	ROI Y	Area X	Area Y	Fractional anisotropy				Mean diffusivity				Axial diffusivity				Radial diffusivity				fractional Number of tracks			
				stdB	se	p	FDR q	stdB	se	p	FDR q	stdB	se	p	FDR q	stdB	se	p	FDR q	stdB	se	p	FDR q
R_IP	R_LOCC	R-Parietal	R-Occipital	-0.092	0.213	0.667	0.782	0.473	0.207	0.024	0.051	0.469	0.210	0.028	0.091	0.424	0.209	0.045	0.083	0.118	0.213	0.580	0.974
R_IP	R_LING	R-Parietal	R-Occipital	-0.257	0.212	0.228	0.469	0.433	0.212	0.044	0.074	0.418	0.212	0.052	0.128	0.411	0.213	0.056	0.095	-0.023	0.201	0.910	0.986
R_IP	R_MT	R-Parietal	R-Parietal	-0.568	0.201	0.006	0.100	0.761	0.199	0.000	0.008*	0.414	0.206	0.047	0.121	0.830	0.195	0.000	0.006*	0.505	0.206	0.016	0.267
R_IP	R_PARH	R-Parietal	R-Frontal	-0.477	0.214	0.029	0.193	0.492	0.218	0.026	0.053	0.178	0.219	0.418	0.553	0.444	0.215	0.042	0.078	0.252	0.218	0.251	0.849
R_IP	R_PCAL	R-Parietal	R-Parietal	-0.134	0.213	0.531	0.684	0.082	0.213	0.701	0.739	0.086	0.212	0.685	0.770	0.065	0.214	0.763	0.791	-0.175	0.210	0.408	0.930
R_IP	R_PSTC	R-Parietal	R-Parietal	-0.206	0.212	0.334	0.568	0.498	0.210	0.020	0.045*	0.192	0.210	0.363	0.507	0.314	0.211	0.140	0.188	-0.313	0.210	0.139	0.756
R_IP	R_PREC	R-Parietal	R-Temporal	-0.098	0.211	0.644	0.760	0.256	0.212	0.231	0.284	0.224	0.208	0.286	0.430	0.217	0.212	0.309	0.363	-0.326	0.210	0.125	0.715
R_IP	R_PCUN	R-Parietal	R-Temporal	-0.178	0.213	0.404	0.602	0.637	0.205	0.003	0.015*	0.515	0.210	0.016	0.068	0.598	0.208	0.005	0.030*	0.250	0.212	0.241	0.849
R_IP	R_SP	R-Parietal	R-Occipital	-0.160	0.211	0.451	0.631	0.511	0.207	0.015	0.039*	0.475	0.205	0.023	0.081	0.554	0.210	0.010	0.041*	-0.019	0.213	0.930	0.986
R_IP	R_ST	R-Parietal	R-Parietal	-0.561	0.204	0.007	0.101	0.818	0.196	0.000	0.006*	0.570	0.199	0.005	0.051	0.802	0.197	0.000	0.008*	0.093	0.210	0.658	0.974
R_IP	R_SMAR	R-Parietal	R-Temporal	-0.216	0.209	0.303	0.533	0.501	0.212	0.020	0.045*	0.329	0.206	0.114	0.226	0.369	0.210	0.082	0.124	-0.122	0.213	0.569	0.974
R_IP	R_INS	R-Parietal	R-Insula	-0.402	0.206	0.054	0.230	0.613	0.204	0.003	0.017*	0.374	0.205	0.070	0.162	0.606	0.204	0.004	0.028*	0.188	0.211	0.376	0.930
R_IT	R_LOCC	R-Temporal	R-Temporal	-0.104	0.213	0.625	0.756	0.616	0.204	0.003	0.016*	0.562	0.207	0.008	0.056	0.517	0.209	0.015	0.051	-0.030	0.216	0.889	0.986
R_IT	R_MT	R-Temporal	R-Occipital	-0.211	0.212	0.322	0.557	0.638	0.203	0.002	0.014*	0.555	0.204	0.008	0.056	0.578	0.205	0.006	0.031*	-0.018	0.211	0.934	0.986
R_IT	R_ST	R-Temporal	R-Insula	-0.255	0.212	0.231	0.469	0.680	0.201	0.001	0.010*	0.593	0.204	0.005	0.049*	0.588	0.204	0.005	0.030*	-0.146	0.211	0.491	0.966
R_IT	R_TP	R-Temporal	R-Temporal	-0.186	0.214	0.388	0.593	0.383	0.205	0.065	0.098	0.522	0.214	0.017	0.069	0.411	0.206	0.048	0.087	-0.072	0.217	0.739	0.979
R_IT	R_INS	R-Temporal	R-Temporal	-0.197	0.214	0.358	0.580	0.585	0.207	0.006	0.023*	0.344	0.214	0.112	0.224	0.456	0.210	0.032	0.070	-0.112	0.214	0.603	0.974
R_ISTH	R_LING	R-Limbic	R-Occipital	-0.137	0.212	0.520	0.683	0.171	0.209	0.415	0.481	0.102	0.208	0.627	0.728	0.193	0.211	0.364	0.422	0.175	0.210	0.405	0.930
R_ISTH	R_PARH	R-Limbic	R-Occipital	-0.071	0.213	0.741	0.836	0.568	0.206	0.007	0.026*	0.220	0.210	0.296	0.442	0.477	0.210	0.025	0.063	0.154	0.213	0.470	0.954
R_ISTH	R_PARC	R-Limbic	R-Central sulcus	-0.202	0.212	0.341	0.571	0.500	0.211	0.020	0.045*	0.123	0.212	0.564	0.671	0.467	0.212	0.030	0.068	-0.239	0.212	0.263	0.849
R_ISTH	R_PC	R-Limbic	R-Limbic	-0.159	0.210	0.450	0.631	0.579	0.208	0.006	0.025*	0.204	0.211	0.336	0.487	0.488	0.208	0.021	0.059	-0.038	0.208	0.854	0.986
R_ISTH	R_PCUN	R-Limbic	R-Occipital	-0.201	0.211	0.343	0.571	0.606	0.208	0.004	0.020*	0.233	0.209	0.268	0.410	0.440	0.209	0.038	0.074	0.244	0.209	0.247	0.849
R_ISTH	R_SP	R-Limbic	R-Parietal	-0.400	0.212	0.062	0.243	0.681	0.207	0.001	0.011*	0.078	0.210	0.711	0.790	0.453	0.208	0.032	0.069	0.175	0.213	0.413	0.930
R_LOCC	R_LING	R-Occipital	R-Occipital	-0.418	0.205	0.044	0.217	0.449	0.211	0.036	0.065	0.185	0.209	0.379	0.523	0.461	0.210	0.031	0.069	0.311	0.206	0.135	0.746
R_LOCC	R_PCAL	R-Occipital	R-Parietal	-0.242	0.210	0.251	0.488	0.481	0.211	0.025	0.051	0.245	0.209	0.243	0.381	0.456	0.211	0.033	0.071	-0.043	0.213	0.842	0.986
R_LOCC	R_PCUN	R-Occipital	R-Occipital	-0.052	0.213	0.808	0.869	0.457	0.212	0.034	0.063	0.513	0.209	0.016	0.068	0.198	0.212	0.352	0.411	-0.108	0.209	0.608	0.974
R_LOCC	R_SP	R-Occipital	R-Parietal	-0.075	0.213	0.724	0.828	0.483	0.207	0.022	0.046*	0.506	0.208	0.017	0.069	0.507	0.211	0.018	0.055	-0.136	0.212	0.524	0.966
R_LOF	R_MOF	R-Frontal	R-Frontal	-0.072	0.213	0.738	0.835	0.697	0.200	0.001	0.010*	0.712	0.199	0.001	0.026	0.543	0.206	0.010	0.041*	0.409	0.214	0.059	0.476
R_LOF	R_POPE	R-Frontal	R-Insula	-0.462	0.207	0.028	0.193	0.352	0.211	0.099	0.138	0.061	0.213	0.774	0.837	0.468	0.210	0.028	0.067	0.066	0.213	0.756	0.979
R_LOF	R_PORB	R-Frontal	R-Frontal	-0.350	0.208	0.096	0.299	0.716	0.200	0.001	0.010*	0.558	0.205	0.008	0.056	0.669	0.201	0.001	0.021*	0.154	0.213	0.471	0.954
R_LOF	R_PTRI	R-Frontal	R-Frontal	-0.412	0.215	0.058	0.237	0.685	0.201	0.001	0.010*	0.508	0.205	0.015	0.066	0.661	0.201	0.001	0.021*	0.518	0.207	0.014	0.258
R_LOF	R_RMF	R-Frontal	R-Frontal	-0.313	0.210	0.140	0.376	0.615	0.204	0.003	0.016*	0.551	0.211	0.011	0.062	0.585	0.204	0.005	0.030*	0.314	0.211	0.140	0.756
R_LOF	R_INS	R-Frontal	R-Frontal	-0.116	0.213	0.588	0.725	0.344	0.210	0.105	0.145	0.298	0.210	0.159	0.288	0.282	0.212	0.185	0.236	0.202	0.213	0.344	0.887
R_LING	R_PARH	R-Occipital	R-Occipital	-0.026	0.213	0.903	0.932	0.204	0.214	0.343	0.408	0.144	0.214	0.503	0.630	0.439	0.212	0.041	0.078	-0.015	0.213	0.942	0.986
R_LING	R_PCAL	R-Occipital	R-Parietal	-0.374	0.210	0.078	0.271	-0.087	0.213	0.686	0.727	-0.174	0.212	0.416	0.551	-0.011	0.213	0.960	0.963	0.086	0.208	0.682	0.976
R_LING	R_PCUN	R-Occipital	R-Occipital	-0.202	0.212	0.344	0.571	0.026	0.213	0.904	0.910	-0.034	0.212	0.872	0.904	0.059	0.214	0.783	0.806	-0.147	0.213	0.492	0.966
R_LING	R_SP	R-Occipital	R-Parietal	-0.171	0.210	0.418	0.614	0.452	0.210	0.034	0.063	0.000	0.206	0.999	0.999	0.138	0.214	0.520	0.570	-0.045	0.213	0.832	0.986
R_MOF	R_RAC	R-Frontal	R-Frontal	-0.062	0.211	0.771	0.853	0.441	0.209	0.037	0.066	0.486	0.208	0.022	0.080	0.310	0.210	0.143	0.190	-0.088	0.212	0.679	0.976
R_MOF	R_RMF	R-Frontal	R-Frontal	-0.441	0.207	0.036	0.204	0.634	0.203	0.002	0.014*	0.414	0.211	0.053	0.129	0.674	0.201	0.001	0.021*	-0.071	0.207	0.734	0.979
R_MOF	R_SF	R-Frontal	R-Frontal	-0.644	0.204	0.002	0.069	0.589	0.205	0.005	0.021*	0.293	0.211	0.169	0.298	0.623	0.203	0.003	0.026*	-0.112	0.212	0.598	0.974
R_MOF	R_FP	R-Frontal	R-Frontal	-0.130	0.208	0.534	0.685	0.697	0.204	0.001	0.010*	0.597	0.205	0.005	0.049*	0.575	0.205	0.006	0.032*	-0.564	0.211	0.009	0.210
R_MT	R_ST	R-Temporal	R-Temporal	-0.216	0.211	0.310	0.540	0.745	0.200	0.000	0.008	0.676	0.202	0.001	0.036*	0.637	0.203	0.002	0.026*	-0.222	0.213	0.299	0.866
R_MT	R_TP	R-Temporal	R-Insula	-0.311	0.212	0.145	0.382	0.523	0.207	0.013	0.035*	0.404	0.213	0.060	0.143	0.495	0.206	0.018	0.055	-0.223	0.215	0.303	0.867
R_MT	R_INS	R-Temporal	R-Temporal	-0.231	0.213	0.282	0.506	0.575	0.208	0.007	0.026*	0.472	0.211	0.028	0.089	0.499	0.209	0.019	0.056	-0.493	0.216	0.025	0.302
R_PARC	R_PSTC	R-Central sulcus	R-Parietal	-0.529	0.207	0.012	0.122	0.389	0.211	0.068	0.100	-0.024	0.212	0.911	0.931	0.382	0.209	0.071	0.111	-0.282	0.211	0.185	0.823
R_PARC	R_PC	R-Central sulcus	R-Frontal	-0.418	0.211	0.051	0.224	0.509	0.207	0.016	0.039*	0.283	0.212	0.184	0.310	0.512	0.207	0.015	0.051	-0.225	0.212	0.291	0.865
R_PARC	R_PREC	R-Central sulcus	R-Occipital	-0.433	0.209	0.041	0.217	0.329	0.211	0.122	0.163	0.115	0.213	0.590	0.696	0.417	0.211	0.051	0.089	-0.117	0.210	0.577	0.974

Table 6.3.K.: FDR corrected results from comparisons of fractional anisotropy, mean diffusivity, axial diffusivity, radial diffusivity, and fractional Number of Tracks in CPHIV compared to CHU. Asterisks indicate associations that survive threshold for significance corrected for multiple comparisons (FDR $q < 0.05$).

ROI X	ROI Y	Area X	Area Y	Fractional anisotropy				Mean diffusivity				Axial diffusivity				Radial diffusivity				fractional Number of tracks			
				stdB	se	p	FDR q	stdB	se	p	FDR q	stdB	se	p	FDR q	stdB	se	p	FDR q	stdB	se	p	FDR q
R_PARC	R_PCUN	R-Central sulcus	R-Frontal	-0.098	0.211	0.645	0.760	0.419	0.209	0.048	0.078	0.473	0.208	0.025	0.086	0.514	0.210	0.016	0.051	-0.353	0.211	0.097	0.632
R_PARC	R_SF	R-Central sulcus	R-Limbic	-0.318	0.211	0.134	0.372	0.336	0.209	0.111	0.151	0.129	0.210	0.540	0.657	0.391	0.209	0.064	0.104	-0.318	0.209	0.132	0.734
R_PARC	R_SP	R-Central sulcus	R-Parietal	-0.339	0.212	0.113	0.331	0.519	0.208	0.014	0.038*	0.150	0.213	0.485	0.614	0.436	0.208	0.039	0.075	-0.118	0.213	0.580	0.974
R_POPE	R_PTRI	R-Frontal	R-Frontal	-0.376	0.206	0.071	0.250	0.394	0.211	0.065	0.098	0.290	0.209	0.169	0.298	0.480	0.208	0.023	0.062	0.043	0.210	0.838	0.986
R_POPE	R_PSTC	R-Frontal	R-Parietal	-0.207	0.213	0.334	0.568	0.370	0.210	0.081	0.117	0.290	0.211	0.173	0.301	0.362	0.210	0.088	0.128	0.202	0.212	0.343	0.887
R_POPE	R_PREC	R-Frontal	R-Frontal	-0.361	0.209	0.087	0.288	0.542	0.206	0.010	0.031*	0.319	0.211	0.134	0.252	0.594	0.204	0.004	0.030*	-0.122	0.213	0.569	0.974
R_POPE	R_RMF	R-Frontal	R-Insula	-0.295	0.210	0.164	0.404	0.495	0.206	0.018	0.044*	0.392	0.209	0.063	0.148	0.488	0.207	0.020	0.058	0.032	0.212	0.878	0.986
R_POPE	R_INS	R-Frontal	R-Frontal	-0.077	0.213	0.718	0.823	0.570	0.206	0.007	0.026*	0.498	0.207	0.018	0.074	0.488	0.208	0.021	0.059	-0.239	0.211	0.261	0.849
R_PORB	R_PTRI	R-Frontal	R-Frontal	-0.014	0.212	0.949	0.970	0.402	0.212	0.061	0.093	0.518	0.205	0.013	0.066	0.357	0.211	0.094	0.134	-0.043	0.214	0.839	0.986
R_PORB	R_RMF	R-Frontal	R-Frontal	-0.307	0.209	0.145	0.382	0.412	0.211	0.054	0.084	0.353	0.209	0.095	0.197	0.515	0.206	0.014	0.050	-0.055	0.214	0.797	0.986
R_PTRI	R_RMF	R-Frontal	R-Frontal	-0.281	0.209	0.181	0.426	0.541	0.205	0.010	0.031*	0.487	0.207	0.021	0.078	0.508	0.206	0.015	0.051	0.234	0.208	0.263	0.849
R_PTRI	R_INS	R-Frontal	R-Insula	-0.161	0.212	0.449	0.631	0.279	0.211	0.190	0.238	0.126	0.212	0.555	0.665	0.304	0.211	0.153	0.200	0.038	0.211	0.859	0.986
R_PCAL	R_PCUN	R-Parietal	R-Occipital	0.054	0.213	0.802	0.869	-0.034	0.213	0.874	0.884	0.454	0.214	0.036	0.101	-0.108	0.213	0.615	0.659	-0.273	0.211	0.199	0.823
R_PCAL	R_SP	R-Parietal	R-Parietal	-0.111	0.209	0.595	0.727	0.608	0.205	0.004	0.018*	0.232	0.208	0.267	0.410	0.447	0.212	0.038	0.074	-0.111	0.212	0.602	0.974
R_PSTC	R_PREC	R-Parietal	R-Frontal	-0.416	0.209	0.049	0.221	0.365	0.210	0.086	0.122	0.476	0.217	0.031	0.094	0.401	0.210	0.059	0.099	-0.290	0.211	0.172	0.800
R_PSTC	R_PCUN	R-Parietal	R-Parietal	-0.266	0.211	0.210	0.458	0.701	0.204	0.001	0.010*	0.181	0.213	0.396	0.530	0.394	0.209	0.062	0.102	-0.411	0.209	0.052	0.436
R_PSTC	R_SP	R-Parietal	R-Occipital	-0.315	0.211	0.138	0.374	0.527	0.210	0.014	0.037*	0.212	0.212	0.321	0.471	0.506	0.209	0.017	0.054	0.105	0.213	0.621	0.974
R_PSTC	R_SMAR	R-Parietal	R-Parietal	-0.131	0.213	0.539	0.685	0.257	0.212	0.229	0.282	0.220	0.211	0.300	0.446	0.236	0.212	0.269	0.323	0.010	0.213	0.962	0.986
R_PSTC	R_INS	R-Parietal	R-Insula	-0.193	0.212	0.366	0.580	0.642	0.208	0.003	0.015*	0.298	0.210	0.160	0.288	0.523	0.211	0.015	0.051	0.133	0.213	0.532	0.966
R_PC	R_PREC	R-Limbic	R-Frontal	-0.197	0.212	0.354	0.577	0.444	0.211	0.038	0.067	0.181	0.212	0.395	0.530	0.296	0.212	0.166	0.215	-0.031	0.208	0.883	0.986
R_PC	R_PCUN	R-Limbic	R-Occipital	-0.063	0.211	0.764	0.849	0.414	0.209	0.050	0.080	0.589	0.206	0.005	0.051	0.587	0.210	0.006	0.032*	0.180	0.211	0.396	0.930
R_PC	R_SF	R-Limbic	R-Frontal	-0.228	0.209	0.277	0.504	0.429	0.206	0.040	0.069	0.421	0.209	0.047	0.121	0.500	0.202	0.015	0.051	-0.114	0.211	0.591	0.974
R_PC	R_SP	R-Limbic	R-Parietal	-0.053	0.217	0.808	0.869	0.560	0.212	0.010	0.031*	0.656	0.210	0.002	0.039*	0.530	0.215	0.015	0.051	-0.077	0.216	0.722	0.979
R_PREC	R_SF	R-Frontal	R-Frontal	-0.390	0.210	0.066	0.243	0.421	0.212	0.051	0.080	0.257	0.212	0.227	0.361	0.456	0.208	0.031	0.069	-0.033	0.211	0.875	0.986
R_PREC	R_SP	R-Frontal	R-Parietal	-0.196	0.209	0.349	0.575	0.555	0.210	0.010	0.031*	0.183	0.211	0.390	0.529	0.460	0.214	0.034	0.071	-0.157	0.213	0.462	0.952
R_PREC	R_SMAR	R-Frontal	R-Parietal	-0.182	0.210	0.387	0.593	0.242	0.212	0.257	0.312	0.147	0.211	0.488	0.617	0.510	0.214	0.019	0.056	-0.169	0.213	0.428	0.934
R_PREC	R_INS	R-Frontal	R-Insula	-0.267	0.211	0.210	0.458	0.640	0.208	0.003	0.015*	0.267	0.212	0.209	0.340	0.418	0.209	0.049	0.087	-0.079	0.213	0.712	0.979
R_PCUN	R_SP	R-Occipital	R-Parietal	-0.295	0.212	0.167	0.404	0.494	0.206	0.019	0.044*	0.598	0.205	0.004	0.049*	0.484	0.207	0.022	0.059	-0.017	0.213	0.936	0.986
R_RAC	R_RMF	R-Frontal	R-Frontal	-0.335	0.207	0.109	0.324	0.392	0.209	0.064	0.097	0.142	0.215	0.509	0.633	0.452	0.206	0.031	0.069	-0.096	0.213	0.655	0.974
R_RAC	R_SF	R-Frontal	R-Frontal	-0.338	0.211	0.113	0.331	0.537	0.207	0.011	0.033*	0.182	0.214	0.396	0.530	0.406	0.213	0.060	0.100	-0.063	0.214	0.770	0.982
R_RMF	R_SF	R-Frontal	R-Frontal	-0.261	0.212	0.222	0.462	0.409	0.213	0.058	0.089	0.457	0.211	0.033	0.098	0.373	0.213	0.083	0.125	-0.071	0.211	0.736	0.979
R_RMF	R_FP	R-Frontal	R-Frontal	-0.433	0.205	0.037	0.205	0.691	0.204	0.001	0.010*	0.493	0.208	0.020	0.077	0.675	0.203	0.001	0.021*	-0.066	0.211	0.755	0.979
R_RMF	R_INS	R-Frontal	R-Insula	-0.236	0.211	0.266	0.500	0.567	0.204	0.007	0.026*	0.467	0.208	0.027	0.088	0.527	0.205	0.012	0.044*	0.183	0.212	0.391	0.930
R_SP	R_SMAR	R-Parietal	R-Insula	-0.176	0.206	0.395	0.594	0.390	0.210	0.066	0.099	0.511	0.204	0.014	0.066	0.358	0.209	0.090	0.130	0.056	0.212	0.793	0.986
R_SP	R_INS	R-Parietal	R-Parietal	-0.281	0.208	0.181	0.426	0.467	0.208	0.027	0.054	0.332	0.209	0.116	0.226	0.446	0.208	0.034	0.071	0.144	0.213	0.498	0.966
R_ST	R_SMAR	R-Temporal	R-Parietal	-0.440	0.210	0.039	0.211	0.489	0.208	0.021	0.046	0.171	0.211	0.420	0.554	0.497	0.207	0.018	0.055	-0.585	0.209	0.006	0.183
R_ST	R_TP	R-Temporal	R-Insula	-0.511	0.211	0.017	0.152	0.694	0.204	0.001	0.010*	0.475	0.210	0.026	0.088	0.718	0.204	0.001	0.019*	-0.001	0.218	0.997	0.997
R_ST	R_TT	R-Temporal	R-Temporal	-0.452	0.212	0.036	0.204	0.687	0.202	0.001	0.010*	0.481	0.207	0.022	0.080	0.584	0.206	0.006	0.031*	-0.358	0.215	0.100	0.632
R_ST	R_INS	R-Temporal	R-Temporal	-0.295	0.211	0.165	0.404	0.527	0.206	0.012	0.035*	0.438	0.207	0.037	0.102	0.483	0.208	0.022	0.060	-0.328	0.211	0.123	0.715
R_SMAR	R_TT	R-Parietal	R-Insula	-0.645	0.209	0.003	0.080	0.612	0.211	0.005	0.020*	-0.081	0.213	0.704	0.784	0.503	0.208	0.017	0.054	-0.088	0.209	0.675	0.976
R_SMAR	R_INS	R-Parietal	R-Temporal	-0.268	0.209	0.203	0.453	0.387	0.210	0.068	0.100	0.292	0.209	0.166	0.295	0.360	0.209	0.088	0.128	0.413	0.205	0.047	0.407
R_TP	R_INS	R-Temporal	R-Insula	-0.460	0.210	0.031	0.201	0.629	0.207	0.003	0.016*	0.489	0.211	0.023	0.081	0.578	0.208	0.007	0.032*	-0.390	0.211	0.068	0.516
R_TT	R_INS	R-Temporal	R-Insula	-0.246	0.208	0.240	0.474	0.627	0.210	0.004	0.017*	0.257	0.206	0.217	0.346	0.380	0.209	0.072	0.113	-0.104	0.209	0.619	0.974

Table 6.4.A: FDR corrected results from comparisons of nodal degree, strength, nodal efficiency, local efficiency and transitivity in CPHIV compared to CHU.

ROI	Degree				Strength				Nodal efficiency				Local efficiency				Transitivity			
	std B	se	p	FDR q	c	se	p	FDR q	std B	se	p	FDR q	std B	se	p	FDR q	std B	se	p	FDR q
L CER	-0.044	0.213	0.836	0.957	0.016	0.210	0.940	0.965	-0.103	0.212	0.628	0.738	-0.122	0.211	0.565	0.731	-0.205	0.211	0.332	0.944
L THAL	-0.220	0.212	0.301	0.667	-0.314	0.209	0.137	0.681	-0.150	0.211	0.481	0.727	-0.162	0.211	0.446	0.727	-0.382	0.206	0.066	0.733
L CAU	-0.229	0.212	0.281	0.667	0.155	0.211	0.464	0.823	-0.509	0.216	0.021	0.368	-0.169	0.211	0.425	0.727	-0.176	0.212	0.408	0.944
L PUT	-0.184	0.209	0.382	0.730	-0.066	0.213	0.759	0.897	-0.119	0.212	0.576	0.727	-0.400	0.215	0.065	0.362	-0.320	0.210	0.132	0.799
L PAL	-0.444	0.217	0.044	0.379	-0.230	0.211	0.279	0.797	-0.148	0.211	0.487	0.727	-0.396	0.214	0.067	0.362	-0.017	0.211	0.937	0.970
BST	-0.181	0.212	0.396	0.730	-0.224	0.211	0.291	0.797	-0.490	0.215	0.025	0.368	-0.151	0.212	0.476	0.727	-0.494	0.206	0.018	0.565
L HPC	-0.145	0.211	0.494	0.744	-0.203	0.213	0.342	0.797	-0.284	0.209	0.178	0.727	-0.383	0.213	0.075	0.362	-0.555	0.202	0.007	0.565
L AMG	-0.167	0.210	0.427	0.730	-0.049	0.209	0.814	0.932	-0.134	0.211	0.526	0.727	-0.169	0.211	0.426	0.727	-0.365	0.208	0.083	0.750
L ACC	-0.218	0.211	0.304	0.667	-0.226	0.211	0.286	0.797	-0.190	0.210	0.369	0.727	-0.169	0.211	0.425	0.727	0.116	0.212	0.586	0.944
L VDC	-0.239	0.208	0.253	0.667	-0.549	0.218	0.013	0.270	-0.222	0.211	0.297	0.727	-0.396	0.218	0.073	0.362	-0.167	0.209	0.426	0.944
R CER	-0.035	0.211	0.867	0.961	0.015	0.213	0.943	0.965	-0.103	0.212	0.628	0.738	-0.072	0.212	0.736	0.790	-0.306	0.209	0.146	0.799
R THAL	-0.209	0.212	0.327	0.667	-0.453	0.209	0.032	0.311	-0.193	0.212	0.366	0.727	-0.129	0.212	0.544	0.729	-0.298	0.204	0.147	0.799
R CAU	-0.155	0.210	0.462	0.744	0.084	0.212	0.695	0.890	-0.248	0.210	0.240	0.727	-0.117	0.212	0.580	0.731	-0.163	0.213	0.447	0.944
R PUT	-0.545	0.215	0.013	0.237	-0.020	0.211	0.924	0.965	-0.172	0.211	0.416	0.727	-0.138	0.212	0.515	0.727	-0.119	0.213	0.577	0.944
R PAL	-0.240	0.209	0.255	0.667	-0.191	0.211	0.368	0.797	-0.094	0.212	0.657	0.739	-0.156	0.211	0.462	0.727	-0.259	0.210	0.221	0.874
R HPC	-0.332	0.210	0.118	0.667	-0.290	0.210	0.170	0.681	-0.142	0.211	0.503	0.727	-0.134	0.212	0.526	0.727	-0.185	0.209	0.378	0.944
R AMG	-0.271	0.210	0.200	0.667	-0.210	0.207	0.313	0.797	-0.131	0.212	0.539	0.727	-0.136	0.211	0.521	0.727	-0.268	0.211	0.207	0.871
R ACC	-0.231	0.209	0.272	0.667	-0.247	0.211	0.246	0.764	-0.609	0.211	0.005	0.368	-0.092	0.212	0.665	0.751	0.253	0.211	0.234	0.885
R VDC	-0.460	0.215	0.035	0.379	-0.445	0.217	0.043	0.340	-0.126	0.211	0.552	0.727	-0.115	0.212	0.588	0.731	-0.094	0.212	0.659	0.944
L BSTS	-0.139	0.211	0.513	0.744	0.467	0.215	0.032	0.311	-0.485	0.206	0.021	0.368	-0.314	0.210	0.139	0.623	-0.130	0.213	0.543	0.944
L CAC	-0.213	0.211	0.317	0.667	0.093	0.212	0.663	0.890	-0.100	0.211	0.637	0.739	-0.181	0.211	0.392	0.727	-0.007	0.213	0.975	0.975
L CMF	0.095	0.211	0.654	0.849	-0.112	0.209	0.593	0.888	-0.202	0.211	0.339	0.727	-0.479	0.208	0.024	0.284	-0.090	0.210	0.670	0.944
L CUN	0.017	0.205	0.935	0.980	0.341	0.212	0.111	0.643	-0.146	0.209	0.485	0.727	-0.065	0.209	0.758	0.804	-0.029	0.211	0.890	0.970

Table 6.4.B: FDR corrected results from comparisons of nodal degree, strength, nodal efficiency, local efficiency and transitivity in CPHIV compared to CHU.

ROI	Degree				Strength				Nodal efficiency				Local efficiency				Transitivity			
	std B	se	p	FDR q	std B	se	p	FDR q	std B	se	p	FDR q	std B	se	p	FDR q	std B	se	p	FDR q
L ENT	-0.343	0.210	0.106	0.667	0.271	0.212	0.204	0.681	-0.157	0.212	0.460	0.727	-0.187	0.210	0.376	0.727	0.079	0.212	0.708	0.944
L FUS	-0.138	0.211	0.515	0.744	0.375	0.210	0.077	0.487	-0.051	0.211	0.809	0.828	-0.076	0.211	0.718	0.781	-0.072	0.213	0.736	0.944
L IP	0.099	0.213	0.642	0.846	0.113	0.211	0.592	0.888	-0.042	0.212	0.845	0.855	-0.100	0.211	0.636	0.748	-0.244	0.208	0.245	0.890
L IT*	-0.781	0.211	<0.001	0.032*	0.035	0.214	0.871	0.959	-0.144	0.211	0.497	0.727	-0.151	0.210	0.474	0.727	0.387	0.209	0.067	0.733
L ISTH	-0.235	0.207	0.260	0.667	0.171	0.206	0.407	0.797	-0.180	0.211	0.396	0.727	-0.144	0.211	0.498	0.727	-0.345	0.210	0.104	0.750
L OCC	-0.084	0.211	0.691	0.871	0.320	0.209	0.130	0.681	-0.086	0.211	0.685	0.745	-0.133	0.211	0.530	0.727	-0.048	0.213	0.822	0.967
L LOF	-0.150	0.211	0.479	0.744	0.308	0.211	0.148	0.681	-0.177	0.211	0.404	0.727	-0.154	0.211	0.468	0.727	0.164	0.212	0.441	0.944
L LING	-0.165	0.207	0.428	0.730	0.474	0.203	0.022	0.270	-0.191	0.209	0.362	0.727	-0.224	0.209	0.285	0.727	-0.026	0.212	0.904	0.970
L MOF	-0.394	0.207	0.061	0.440	-0.072	0.205	0.727	0.897	-0.449	0.214	0.038	0.441	-0.179	0.211	0.397	0.727	0.075	0.212	0.724	0.944
L MT	-0.137	0.212	0.518	0.744	0.195	0.204	0.341	0.797	-0.180	0.211	0.394	0.727	-0.162	0.211	0.446	0.727	0.009	0.211	0.966	0.975
L PARH	-0.307	0.211	0.149	0.667	0.082	0.206	0.691	0.890	-0.193	0.211	0.361	0.727	-0.302	0.209	0.152	0.631	-0.020	0.213	0.924	0.970
L PARC	-0.164	0.209	0.436	0.730	0.392	0.208	0.063	0.456	-0.417	0.217	0.058	0.507	-0.150	0.211	0.479	0.727	0.060	0.204	0.771	0.944
L POPE	-0.281	0.211	0.185	0.667	0.043	0.208	0.837	0.940	-0.200	0.210	0.343	0.727	-0.547	0.214	0.012	0.284	-0.149	0.210	0.481	0.944
L PORB	0.005	0.208	0.980	0.984	-0.081	0.210	0.701	0.890	-0.164	0.210	0.438	0.727	-0.059	0.210	0.780	0.810	0.064	0.210	0.760	0.944
L PTRI	-0.019	0.210	0.927	0.980	0.181	0.212	0.395	0.797	-0.216	0.210	0.306	0.727	-0.103	0.211	0.627	0.748	-0.357	0.210	0.091	0.750
L PCAL	0.021	0.211	0.922	0.980	0.298	0.211	0.162	0.681	-0.093	0.210	0.660	0.739	-0.058	0.210	0.782	0.810	-0.059	0.213	0.784	0.945
L PSTC	-0.211	0.207	0.312	0.667	0.292	0.210	0.167	0.681	-0.181	0.210	0.390	0.727	-0.192	0.210	0.363	0.727	0.098	0.212	0.645	0.944
L PC	-0.100	0.209	0.634	0.846	0.290	0.212	0.173	0.681	-0.068	0.211	0.748	0.794	-0.214	0.211	0.313	0.727	-0.179	0.212	0.401	0.944
L PREC	-0.124	0.209	0.554	0.753	0.172	0.207	0.409	0.797	-0.133	0.212	0.530	0.727	-0.169	0.211	0.425	0.727	-0.025	0.213	0.906	0.970
L PCUN	-0.046	0.210	0.828	0.957	0.636	0.200	0.002	0.176	-0.163	0.212	0.442	0.727	-0.136	0.210	0.520	0.727	0.078	0.211	0.714	0.944
L RAC	-0.248	0.210	0.240	0.667	0.525	0.220	0.019	0.270	-0.133	0.211	0.532	0.727	-0.193	0.211	0.360	0.727	-0.062	0.212	0.769	0.944
L RMF	-0.034	0.210	0.873	0.961	0.138	0.213	0.518	0.833	-0.157	0.211	0.458	0.727	-0.558	0.216	0.011	0.284	-0.011	0.208	0.958	0.975
L SF	-0.221	0.208	0.290	0.667	0.081	0.208	0.697	0.890	-0.092	0.210	0.663	0.739	-0.191	0.210	0.366	0.727	0.160	0.212	0.451	0.944
L SP	-0.091	0.212	0.669	0.856	0.252	0.211	0.235	0.758	-0.135	0.211	0.525	0.727	-0.133	0.210	0.530	0.727	0.184	0.207	0.376	0.944

Table 6.4C: FDR corrected results from comparisons of nodal degree, strength, nodal efficiency, local efficiency and transitivity in CPHIV compared to CHU.

ROI	Degree				Strength				Nodal efficiency				Local efficiency				Transitivity			
	std B	se	p	FDR q	std B	se	std B	se	p	FDR q	std B		std B	se	p	FDR q	std B		std B	se
L ST	-0.130	0.210	0.539	0.744	-0.164	0.212	0.440	0.797	-0.190	0.211	0.372	0.727	-0.250	0.210	0.237	0.727	-0.136	0.212	0.522	0.944
L SMAR	-0.204	0.208	0.329	0.667	-0.275	0.211	0.195	0.681	-0.115	0.211	0.586	0.727	-0.433	0.213	0.045	0.362	0.463	0.209	0.029	0.565
L FP	-0.280	0.212	0.189	0.667	-0.016	0.213	0.939	0.965	-0.248	0.210	0.241	0.727	-0.309	0.209	0.143	0.623	0.125	0.222	0.576	0.944
L TP	-0.290	0.211	0.172	0.667	0.107	0.210	0.613	0.888	-0.437	0.214	0.044	0.441	-0.393	0.216	0.072	0.362	0.273	0.210	0.197	0.871
L TT	0.045	0.213	0.834	0.957	0.162	0.207	0.437	0.797	-0.443	0.218	0.046	0.441	-0.098	0.213	0.647	0.751	-0.478	0.207	0.023	0.565
L INS	-0.603	0.216	0.006	0.237	0.091	0.213	0.670	0.890	-0.154	0.211	0.468	0.727	-0.472	0.213	0.029	0.284	-0.187	0.212	0.380	0.944
R BSTS	0.007	0.213	0.973	0.984	0.366	0.206	0.078	0.487	-0.144	0.210	0.494	0.727	-0.024	0.213	0.909	0.928	-0.144	0.210	0.492	0.944
R CAC	-0.166	0.211	0.431	0.730	-0.597	0.208	0.005	0.187	-0.207	0.210	0.326	0.727	-0.577	0.215	0.009	0.284	-0.167	0.213	0.434	0.944
R CMF	-0.280	0.211	0.187	0.667	-0.030	0.213	0.888	0.965	-0.171	0.211	0.420	0.727	-0.392	0.214	0.071	0.362	-0.093	0.212	0.661	0.944
R CUN	-0.253	0.211	0.233	0.667	-0.136	0.213	0.527	0.833	-0.361	0.213	0.094	0.681	-0.409	0.216	0.061	0.362	0.145	0.211	0.494	0.944
R ENT	-0.181	0.212	0.397	0.730	-0.187	0.213	0.380	0.797	-0.215	0.211	0.310	0.727	-0.094	0.211	0.659	0.751	-0.189	0.212	0.377	0.944
R FUS	-0.437	0.208	0.038	0.379	-0.166	0.208	0.425	0.797	-0.180	0.211	0.395	0.727	-0.216	0.210	0.307	0.727	0.026	0.214	0.902	0.970
R IP	-0.191	0.211	0.367	0.726	0.276	0.209	0.191	0.681	-0.167	0.211	0.431	0.727	-0.146	0.210	0.488	0.727	-0.280	0.210	0.184	0.871
R IT	-0.244	0.210	0.247	0.667	-0.012	0.213	0.956	0.967	-0.130	0.210	0.538	0.727	-0.146	0.210	0.489	0.727	-0.030	0.213	0.888	0.970
R ISTH	-0.501	0.215	0.022	0.321	0.138	0.205	0.504	0.827	-0.164	0.211	0.439	0.727	-0.143	0.212	0.501	0.727	-0.073	0.210	0.730	0.944
R OCC	-0.278	0.211	0.191	0.667	-0.008	0.214	0.970	0.970	-0.208	0.210	0.326	0.727	-0.212	0.211	0.316	0.727	-0.032	0.212	0.882	0.970
R LOF	-0.075	0.209	0.721	0.883	0.441	0.207	0.036	0.311	-0.175	0.211	0.410	0.727	-0.089	0.212	0.676	0.754	-0.276	0.211	0.194	0.871
R LING	-0.536	0.213	0.014	0.237	0.057	0.203	0.781	0.906	-0.346	0.214	0.109	0.727	-0.195	0.211	0.357	0.727	-0.266	0.211	0.210	0.871
R MOF	0.133	0.213	0.533	0.744	0.125	0.211	0.554	0.861	-0.146	0.212	0.492	0.727	-0.120	0.212	0.572	0.731	-0.310	0.210	0.144	0.799
R MT	-0.237	0.211	0.263	0.667	0.090	0.210	0.671	0.890	-0.570	0.213	0.009	0.368	-0.111	0.211	0.598	0.733	0.135	0.213	0.526	0.944
R PARH	-0.077	0.212	0.718	0.883	0.111	0.213	0.605	0.888	-0.064	0.212	0.762	0.799	-0.079	0.213	0.712	0.781	-0.142	0.211	0.503	0.944
R PARC	-0.136	0.212	0.521	0.744	-0.276	0.212	0.196	0.681	-0.199	0.211	0.348	0.727	-0.148	0.211	0.485	0.727	-0.336	0.204	0.103	0.750
R POPE	-0.273	0.210	0.197	0.667	-0.145	0.212	0.496	0.827	-0.141	0.211	0.508	0.727	-0.487	0.216	0.027	0.284	-0.453	0.209	0.032	0.565
R PORB	-0.413	0.206	0.048	0.379	-0.143	0.213	0.503	0.827	-0.125	0.211	0.554	0.727	-0.200	0.212	0.346	0.727	0.185	0.209	0.377	0.944

Table 6.4.D: FDR corrected results from comparisons of nodal degree, strength, nodal efficiency, local efficiency and transitivity in CPHIV compared to CHU.

ROI	Degree				Strength				Nodal efficiency				Local efficiency				Transitivity			
	std B	se	p	FDR q	std B		std B	se	p	FDR q	std B		std B	se	p	FDR q	std B		std B	se
R PTRI	-0.270	0.211	0.205	0.667	0.202	0.211	0.340	0.797	-0.121	0.211	0.567	0.727	-0.229	0.211	0.281	0.727	-0.168	0.211	0.427	0.944
R PCAL	-0.255	0.211	0.229	0.667	-0.168	0.210	0.426	0.797	-0.113	0.212	0.593	0.727	-0.475	0.213	0.029	0.284	-0.095	0.212	0.654	0.944
R PSTC	-0.229	0.211	0.280	0.667	-0.169	0.212	0.427	0.797	-0.168	0.211	0.428	0.727	-0.176	0.211	0.405	0.727	0.056	0.212	0.793	0.945
R PC	-0.055	0.211	0.795	0.957	-0.149	0.212	0.484	0.827	-0.082	0.212	0.698	0.750	-0.132	0.212	0.535	0.727	-0.224	0.212	0.293	0.944
R PREC	-0.437	0.216	0.046	0.379	-0.211	0.210	0.319	0.797	-0.116	0.211	0.582	0.727	-0.180	0.211	0.397	0.727	0.019	0.214	0.931	0.970
L PCUN	-0.146	0.212	0.493	0.744	0.022	0.211	0.919	0.965	-0.405	0.217	0.065	0.515	-0.126	0.212	0.555	0.731	-0.099	0.208	0.635	0.944
R RAC	-0.029	0.212	0.893	0.971	0.064	0.212	0.763	0.897	-0.131	0.211	0.538	0.727	-0.194	0.210	0.357	0.727	-0.218	0.207	0.295	0.944
R RMF	-0.545	0.213	0.012	0.237	-0.080	0.210	0.706	0.890	-0.178	0.211	0.400	0.727	-0.102	0.212	0.631	0.748	0.102	0.212	0.632	0.944
R SF	-0.235	0.211	0.268	0.667	-0.086	0.210	0.682	0.890	-0.494	0.211	0.022	0.368	-0.167	0.211	0.431	0.727	0.071	0.214	0.739	0.944
R SP	-0.133	0.211	0.530	0.744	0.065	0.214	0.761	0.897	-0.028	0.212	0.896	0.896	-0.417	0.218	0.059	0.362	-0.399	0.210	0.060	0.733
R ST	-0.172	0.210	0.414	0.730	-0.220	0.208	0.294	0.797	-0.177	0.211	0.405	0.727	-0.135	0.211	0.523	0.727	-0.067	0.213	0.755	0.944
R SMAR	-0.004	0.212	0.984	0.984	0.069	0.212	0.747	0.897	-0.108	0.211	0.610	0.737	0.022	0.210	0.917	0.928	0.034	0.214	0.873	0.970
R FP	0.009	0.210	0.968	0.984	-0.582	0.208	0.006	0.187	-0.148	0.211	0.486	0.727	-0.564	0.227	0.015	0.284	-0.076	0.216	0.727	0.944
R TP	-0.037	0.213	0.862	0.961	-0.517	0.214	0.018	0.270	-0.057	0.212	0.788	0.817	0.009	0.210	0.967	0.967	-0.089	0.212	0.677	0.944
R TT	-0.048	0.214	0.824	0.957	-0.189	0.211	0.374	0.797	-0.088	0.212	0.680	0.745	-0.501	0.222	0.026	0.284	0.113	0.212	0.595	0.944
R INS	-0.247	0.212	0.246	0.667	-0.042	0.212	0.843	0.940	-0.177	0.212	0.404	0.727	-0.152	0.211	0.472	0.727	-0.079	0.213	0.713	0.944

Table 6.5.A: DTI Tractography generated white matter tracts and corresponding tract identification.

ROI 1	ROI 2	Value	Max	Total	%	JHU WM Atlas WM label	Value	Max	Total	%	JHU WM Atlas probabilistic tract
L_THAL	L_SP	9	5	10	50	Forceps major	28	25	53	47	Posterior corona radiata L
L_THAL	L_ST	11	8	15	53.3	Inferior fronto-occipital fasciculus L	40	20	40	50	Fornix (cres) / Stria terminalis (can not be resolved with current resolution) L
L_THAL	L_INS	1	199	352	56.5	Anterior thalamic radiation L	20	190	544	35	Posterior limb of internal capsule L
L_THAL	R_ISTH	9	37	56	66.1	Forceps major	5	150	237	63	Splenium of corpus callosum
L_CAU	L_PUT	1	256	461	55.5	Anterior thalamic radiation L	20	275	995	28	Posterior limb of internal capsule L
L_CAU	L_PAL	1	167	249	67.1	Anterior thalamic radiation L	20	239	425	56	Posterior limb of internal capsule L
L_CAU	L_HPC	1	39	76	51.3	Anterior thalamic radiation L	4	51	189	27	Body of corpus callosum
L_CAU	L_AMG	1	106	125	84.8	Anterior thalamic radiation L	20	65	130	50	Posterior limb of internal capsule L
L_CAU	L_ACC	1	3	3	100	Anterior thalamic radiation L	18	7	8	88	Anterior limb of internal capsule L
L_CAU	L_VDC	1	109	145	75.2	Anterior thalamic radiation L	20	74	144	51	Posterior limb of internal capsule L
L_CAU	R_CAU	10	190	233	81.5	Forceps minor	3	229	434	53	Genu of corpus callosum
L_CAU	L_CAC	10	82	137	59.9	Forceps minor	4	160	453	35	Body of corpus callosum
L_CAU	L_CMF	1	16	16	100	Anterior thalamic radiation L	26	113	234	48	Superior corona radiate L
L_CAU	L_ISTH	5	56	72	77.8	Cingulum (cingulate gyrus) L	4	148	412	36	Body of corpus callosum
L_CAU	L_LOF	10	72	162	44.4	Forceps minor	24	76	161	47	Anterior corona radiata L
L_CAU	L_MOF	10	120	239	50.2	Forceps minor	24	94	228	41	Anterior corona radiata L
L_CAU	L_PARC	3	18	18	100	Corticospinal tract L	28	53	98	54	Posterior corona radiata L
L_CAU	L_PSTC	3	27	27	100	Corticospinal tract L	28	63	78	81	Posterior corona radiata L
L_CAU	L_PC	5	53	77	68.8	Cingulum (cingulate gyrus) L	4	188	454	41	Body of corpus callosum
L_CAU	L_PREC	3	66	76	86.8	Corticospinal tract L	26	141	196	72	Superior corona radiate L
L_CAU	L_PCUN	5	41	49	83.7	Cingulum (cingulate gyrus) L	4	115	280	41	Body of corpus callosum
L_CAU	L_RAC	10	127	247	51.4	Forceps minor	3	119	303	39	Genu of corpus callosum
L_CAU	L_RMF	10	220	406	54.2	Forceps minor	24	291	392	74	Anterior corona radiata L
L_CAU	L_SF	10	159	275	57.8	Forceps minor	24	168	379	44	Anterior corona radiata L
L_CAU	L_SP	3	2	2	100	Corticospinal tract L	28	70	71	99	Posterior corona radiata L
L_CAU	L_INS	1	127	188	67.6	Anterior thalamic radiation L	26	92	400	23	Superior corona radiate L

Table 6.5.B: DTI Tractography generated white matter tracts and corresponding tract identification.

ROI 1	ROI 2	Value	Max	Total	%	JHU WM Atlas WM label	Value	Max	Total	%	JHU WM Atlas probabilistic tract
L_CER	L_THAL	1	33	50	66	Anterior thalamic radiation L	16	39	147	27	Cerebral peduncle L
L_CER	BST	3	27	53	50.9	Corticospinal tract L	1	244	575	42	Middle cerebellar peduncle
L_CER	L_VDC	3	24	43	55.8	Corticospinal tract L	16	64	185	35	Cerebral peduncle L
L_CER	R_CER	4	2	3	66.7	Corticospinal tract R	1	113	217	52	Middle cerebellar peduncle
L_CER	R_VDC	4	21	32	65.6	Corticospinal tract R	15	43	113	38	Cerebral peduncle R
L_CER	L_ENT	0	-	-	-	Unclassified	1	91	107	85	Middle cerebellar peduncle
L_CER	L_FUS	0	-	-	-	Unclassified	1	142	197	72	Middle cerebellar peduncle
L_CER	L_LING	7	11	14	78.6	Cingulum (hippocampus) L	12	47	99	47	Inferior cerebellar peduncle L
L_CER	L_PHPC	7	11	11	100	Cingulum (hippocampus) L	38	22	24	92	Cingulum (hippocampus) L
L_THAL	L_CAU	1	152	224	67.9	Anterior thalamic radiation L	20	156	345	45	Posterior limb of internal capsule L
L_THAL	L_PUT	1	215	388	55.4	Anterior thalamic radiation L	20	291	714	41	Posterior limb of internal capsule L
L_THAL	L_PAL	1	226	329	68.7	Anterior thalamic radiation L	20	262	376	70	Posterior limb of internal capsule L
L_THAL	BST	3	58	136	42.6	Corticospinal tract L	16	92	319	29	Cerebral peduncle L
L_THAL	L_HPC	1	165	237	69.6	Anterior thalamic radiation L	16	85	282	30	Cerebral peduncle L
L_THAL	L_AMG	1	199	251	79.3	Anterior thalamic radiation L	20	114	200	57	Posterior limb of internal capsule L
L_THAL	L_ACC	1	9	9	100	Anterior thalamic radiation L	20	6	9	67	Posterior limb of internal capsule L
L_THAL	L_VDC	1	236	336	70.2	Anterior thalamic radiation L	20	137	321	43	Posterior limb of internal capsule L
L_THAL	R_THAL	1	63	225	28	Anterior thalamic radiation L	5	271	602	45	Splenium of corpus callosum
L_THAL	R_HPC	9	40	79	50.6	Forceps major	5	90	145	62	Splenium of corpus callosum
L_THAL	R_VDC	1	33	85	38.8	Anterior thalamic radiation L	15	26	131	20	Cerebral peduncle R
L_THAL	L_ISTH	9	39	73	53.4	Forceps major	5	140	337	42	Splenium of corpus callosum
L_THAL	L_MOF	1	109	110	99.1	Anterior thalamic radiation L	20	32	68	47	Posterior limb of internal capsule L
L_THAL	L_PHPC	1	27	68	39.7	Anterior thalamic radiation L	16	48	112	43	Cerebral peduncle L
L_THAL	L_PARC	3	6	6	100	Corticospinal tract L	26	10	11	91	Superior corona radiate L
L_THAL	L_PSTC	15	1	1	100	Superior longitudinal fasciculus L	28	17	38	45	Posterior corona radiata L
L_THAL	L_PC	5	17	38	44.7	Cingulum (cingulate gyrus) L	26	90	217	41	Superior corona radiate L

Table 6.5.C: DTI Tractography generated white matter tracts and corresponding tract identification.

ROI 1	ROI 2	Value	Max	Total	%	JHU WM Atlas WM label	Value	Max	Total	%	JHU WM Atlas probabilistic tract
L_THAL	L_PREC	3	57	70	81.4	Corticospinal tract L	26	113	149	76	Superior corona radiata L
L_THAL	L_SP	9	5	10	50	Forceps major	28	25	53	47	Posterior corona radiata L
L_THAL	L_ST	11	8	15	53.3	Inferior fronto-occipital fasciculus L	40	20	40	50	Fornix (cres) / Stria terminalis (can not be resolved with current resolution) L
L_THAL	L_INS	1	199	352	56.5	Anterior thalamic radiation L	20	190	544	35	Posterior limb of internal capsule L
L_THAL	R_ISTH	9	37	56	66.1	Forceps major	5	150	237	63	Splenium of corpus callosum
L_CAU	L_PUT	1	256	461	55.5	Anterior thalamic radiation L	20	275	995	28	Posterior limb of internal capsule L
L_CAU	L_PAL	1	167	249	67.1	Anterior thalamic radiation L	20	239	425	56	Posterior limb of internal capsule L
L_CAU	L_HPC	1	39	76	51.3	Anterior thalamic radiation L	4	51	189	27	Body of corpus callosum
L_CAU	L_AMG	1	106	125	84.8	Anterior thalamic radiation L	20	65	130	50	Posterior limb of internal capsule L
L_CAU	L_ACC	1	3	3	100	Anterior thalamic radiation L	18	7	8	88	Anterior limb of internal capsule L
L_CAU	L_VDC	1	109	145	75.2	Anterior thalamic radiation L	20	74	144	51	Posterior limb of internal capsule L
L_CAU	R_CAU	10	190	233	81.5	Forceps minor	3	229	434	53	Genu of corpus callosum
L_CAU	L_CAC	10	82	137	59.9	Forceps minor	4	160	453	35	Body of corpus callosum
L_CAU	L_CMF	1	16	16	100	Anterior thalamic radiation L	26	113	234	48	Superior corona radiata L
L_CAU	L_ISTH	5	56	72	77.8	Cingulum (cingulate gyrus) L	4	148	412	36	Body of corpus callosum
L_CAU	L_LOF	10	72	162	44.4	Forceps minor	24	76	161	47	Anterior corona radiata L
L_CAU	L_MOF	10	120	239	50.2	Forceps minor	24	94	228	41	Anterior corona radiata L
L_CAU	L_PARC	3	18	18	100	Corticospinal tract L	28	53	98	54	Posterior corona radiata L
L_CAU	L_PSTC	3	27	27	100	Corticospinal tract L	28	63	78	81	Posterior corona radiata L
L_CAU	L_PC	5	53	77	68.8	Cingulum (cingulate gyrus) L	4	188	454	41	Body of corpus callosum
L_CAU	L_PREC	3	66	76	86.8	Corticospinal tract L	26	141	196	72	Superior corona radiata L
L_CAU	L_PCUN	5	41	49	83.7	Cingulum (cingulate gyrus) L	4	115	280	41	Body of corpus callosum
L_CAU	L_RAC	10	127	247	51.4	Forceps minor	3	119	303	39	Genu of corpus callosum
L_CAU	L_RMF	10	220	406	54.2	Forceps minor	24	291	392	74	Anterior corona radiata L
L_CAU	L_SF	10	159	275	57.8	Forceps minor	24	168	379	44	Anterior corona radiata L
L_CAU	L_SP	3	2	2	100	Corticospinal tract L	28	70	71	99	Posterior corona radiata L

Table 6.5.D: DTI Tractography generated white matter tracts and corresponding tract identification.

ROI 1	ROI 2	Value	Max	Total	%	JHU WM Atlas WM label	Value	Max	Total	%	JHU WM Atlas probabilistic tract
L_CAU	L_INS	1	127	188	67.6	Anterior thalamic radiation L	26	92	400	23	Superior corona radiate L
L_CAU	R_CAC	10	63	64	98.4	Forceps minor	3	72	144	50	Genu of corpus callosum
L_PUT	L_PAL	1	75	185	40.5	Anterior thalamic radiation L	20	172	357	48	Posterior limb of internal capsule L
L_PUT	L_HPC	11	32	53	60.4	Inferior fronto-occipital fasciculus L	22	72	226	32	Retrolenticular part of internal capsule L
L_PUT	L_AMG	11	43	89	48.3	Inferior fronto-occipital fasciculus L	34	54	175	31	External capsule L
L_PUT	L_ACC	1	10	12	83.3	Anterior thalamic radiation L	18	10	29	34	Anterior limb of internal capsule L
L_PUT	L_VDC	1	74	155	47.7	Anterior thalamic radiation L	34	82	278	29	External capsule L
L_PUT	L_CMF	3	36	58	62.1	Corticospinal tract L	26	194	497	39	Superior corona radiate L
L_PUT	L_IP	15	36	39	92.3	Superior longitudinal fasciculus L	34	52	186	28	External capsule L
L_PUT	L_ISTH	3	34	80	42.5	Corticospinal tract L	26	87	435	20	Superior corona radiate L
L_PUT	L_LOF	11	75	182	41.2	Inferior fronto-occipital fasciculus L	24	148	256	58	Anterior corona radiata L
L_PUT	L_MOF	1	64	180	35.6	Anterior thalamic radiation L	24	90	182	49	Anterior corona radiata L
L_PUT	L_PARC	3	49	49	100	Corticospinal tract L	28	69	187	37	Posterior corona radiata L
L_PUT	L_POPE	11	40	93	43	Inferior fronto-occipital fasciculus L	34	111	365	30	External capsule L
L_PUT	L_PTRI	11	67	137	48.9	Inferior fronto-occipital fasciculus L	24	129	186	69	Anterior corona radiata L
L_PUT	L_PSTC	3	90	120	75	Corticospinal tract L	26	134	434	31	Superior corona radiate L
L_PUT	L_PC	3	60	72	83.3	Corticospinal tract L	26	154	393	39	Superior corona radiate L
L_PUT	L_PREC	3	151	172	87.8	Corticospinal tract L	26	261	532	49	Superior corona radiate L
L_PUT	L_RAC	1	78	181	43.1	Anterior thalamic radiation L	24	136	235	58	Anterior corona radiata L
L_PUT	L_RMF	10	164	448	36.6	Forceps minor	24	347	674	51	Anterior corona radiata L
L_PUT	L_SF	10	89	245	36.3	Forceps minor	26	166	533	31	Superior corona radiate L
L_PUT	L_SP	3	47	89	52.8	Corticospinal tract L	26	108	418	26	Superior corona radiate L
L_PUT	L_ST	11	45	46	97.8	Inferior fronto-occipital fasciculus L	40	42	138	30	Fornix (cres) / Stria terminalis (can not be resolved with current resolution) L
L_PUT	L_SMAR	15	21	34	61.8	Superior longitudinal fasciculus L	34	56	132	42	External capsule L
L_PUT	L_TT	11	15	15	100	Inferior fronto-occipital fasciculus L	34	38	54	70	External capsule L
L_PUT	L_INS	11	108	224	48.2	Inferior fronto-occipital fasciculus L	34	287	785	37	External capsule L

Table 6.5.E: DTI Tractography generated white matter tracts and corresponding tract identification.

ROI 1	ROI 2	Value	Max	Total	%	JHU WM Atlas WM label	Value	Max	Total	%	JHU WM Atlas probabilistic tract
L_PAL	L_HPC	3	18	34	52.9	Corticospinal tract L	16	29	81	36	Cerebral peduncle L
L_PAL	L_AMG	1	49	88	55.7	Anterior thalamic radiation L	20	71	126	56	Posterior limb of internal capsule L
L_PAL	L_ACC	1	7	7	100	Anterior thalamic radiation L	18	6	10	60	Anterior limb of internal capsule L
L_PAL	L_VDC	1	79	134	59	Anterior thalamic radiation L	20	95	155	61	Posterior limb of internal capsule L
L_PAL	L_MOF	1	51	58	87.9	Anterior thalamic radiation L	20	35	59	59	Posterior limb of internal capsule L
L_PAL	L_INS	1	56	160	35	Anterior thalamic radiation L	20	112	281	40	Posterior limb of internal capsule L
BST	L_HPC	3	47	70	67.1	Corticospinal tract L	16	67	119	56	Cerebral peduncle L
BST	L_VDC	3	132	207	63.8	Corticospinal tract L	1	148	636	23	Middle cerebellar peduncle
BST	R_CER	4	18	27	66.7	Corticospinal tract R	1	239	504	47	Middle cerebellar peduncle
BST	R_THAL	2	98	184	53.3	Anterior thalamic radiation R	15	80	361	22	Cerebral peduncle R
BST	R_HPC	4	53	69	76.8	Corticospinal tract R	15	68	142	48	Cerebral peduncle R
BST	R_VDC	4	112	215	52.1	Corticospinal tract R	15	129	561	23	Cerebral peduncle R
BST	L_ENT	3	21	35	60	Corticospinal tract L	1	67	148	45	Middle cerebellar peduncle
BST	L_PHPC	3	23	45	51.1	Corticospinal tract L	2	39	135	29	Pontine crossing tract (a part of MCP)
BST	R_ENT	4	55	62	88.7	Corticospinal tract R	1	171	340	50	Middle cerebellar peduncle
BST	R_PARH	4	32	41	78	Corticospinal tract R	1	58	164	35	Middle cerebellar peduncle
L_HPC	L_AMG	13	26	62	41.9	Inferior longitudinal fasciculus L	32	58	148	39	Sagittal stratum (include front-occipital fasciculus) L
L_HPC	L_VDC	3	63	123	51.2	Corticospinal tract L	16	98	212	46	Cerebral peduncle L
L_HPC	L_BSTS	13	75	138	54.3	Inferior longitudinal fasciculus L	32	84	127	66	Sagittal stratum (include front-occipital fasciculus) L
L_HPC	L_ENT	7	17	28	60.7	Cingulum (hippocampus) L	38	53	117	45	Cingulum (hippocampus) L
L_HPC	L_FUS	13	63	105	60	Inferior longitudinal fasciculus L	32	92	156	59	Sagittal stratum (include front-occipital fasciculus) L
L_HPC	L_IP	11	28	61	45.9	Inferior fronto-occipital fasciculus L	32	35	77	45	Sagittal stratum (include front-occipital fasciculus) L
L_HPC	L_IT	13	44	77	57.1	Inferior longitudinal fasciculus L	32	68	113	60	Sagittal stratum (include front-occipital fasciculus) L
L_HPC	L_ISTH	9	29	57	50.9	Forceps major	5	56	136	41	Splenium of corpus callosum
L_HPC	L_LING	7	14	22	63.6	Cingulum (hippocampus) L	38	43	57	75	Cingulum (hippocampus) L
L_HPC	L_MOF	1	28	40	70	Anterior thalamic radiation L	16	29	46	63	Cerebral peduncle L

Table 6.5.F: DTI Tractography generated white matter tracts and corresponding tract identification.

ROI 1	ROI 2	Value	Max	Total	%	JHU WM Atlas WM label	Value	Max	Total	%	JHU WM Atlas probabilistic tract
L_HPC	L_MT	13	82	114	71.9	Inferior longitudinal fasciculus L	32	85	87	98	Sagittal stratum (include front-occipital fasciculus) L
L_HPC	L_PHPC	7	17	17	100	Cingulum (hippocampus) L	38	56	56	100	Cingulum (hippocampus) L
L_HPC	L_ST	13	69	137	50.4	Inferior longitudinal fasciculus L	32	100	197	51	Sagittal stratum (include front-occipital fasciculus) L
L_HPC	L_TP	11	8	14	57.1	Inferior fronto-occipital fasciculus L	40	33	61	54	Fornix (cres) / Stria terminalis (can not be resolved with current resolution) L
L_HPC	L_INS	11	53	83	63.9	Inferior fronto-occipital fasciculus L	40	65	230	28	Fornix (cres) / Stria terminalis (can not be resolved with current resolution) L
L_AMG	L_ACC	1	9	9	100	Anterior thalamic radiation L	20	6	9	67	Posterior limb of internal capsule L
L_AMG	L_VDC	1	65	102	63.7	Anterior thalamic radiation L	20	46	150	31	Posterior limb of internal capsule L
L_AMG	L_ENT	17	2	3	66.7	Uncinate fasciculus L	40	7	15	47	Fornix (cres) / Stria terminalis (can not be resolved with current resolution) L
L_AMG	L_FUS	13	48	53	90.6	Inferior longitudinal fasciculus L	32	41	54	76	Sagittal stratum (include front-occipital fasciculus) L
L_AMG	L_IT	13	15	18	83.3	Inferior longitudinal fasciculus L	32	12	23	52	Sagittal stratum (include front-occipital fasciculus) L
L_AMG	L_MOF	1	29	39	74.4	Anterior thalamic radiation L	20	20	46	43	Posterior limb of internal capsule L
L_AMG	L_ST	13	38	78	48.7	Inferior longitudinal fasciculus L	40	52	102	51	Fornix (cres) / Stria terminalis (can not be resolved with current resolution) L
L_AMG	L_TP	17	2	2	100	Uncinate fasciculus L	46	46	6	767	Uncinate fasciculus L
L_AMG	L_INS	11	57	101	56.4	Inferior fronto-occipital fasciculus L	34	65	199	33	External capsule L
L_ACC	L_VDC	1	9	9	100	Anterior thalamic radiation L	20	6	8	75	Posterior limb of internal capsule L
L_ACC	L_MOF	1	8	13	61.5	Anterior thalamic radiation L	20	5	13	38	Posterior limb of internal capsule L
L_VDC	R_THAL	3	19	53	35.8	Corticospinal tract L	16	29	147	20	Cerebral peduncle L
L_VDC	R_VDC	3	35	63	55.6	Corticospinal tract L	16	58	185	31	Cerebral peduncle L
L_VDC	L_ENT	3	32	53	60.4	Corticospinal tract L	16	47	137	34	Cerebral peduncle L
L_VDC	L_MOF	1	38	53	71.7	Anterior thalamic radiation L	16	28	57	49	Cerebral peduncle L
L_VDC	L_PHPC	3	27	37	73	Corticospinal tract L	16	50	54	93	Cerebral peduncle L
L_VDC	L_ST	11	29	30	96.7	Inferior fronto-occipital fasciculus L	40	38	78	49	Fornix (cres) / Stria terminalis (can not be resolved with current resolution) L
L_VDC	L_INS	11	62	150	41.3	Inferior fronto-occipital fasciculus L	34	91	273	33	External capsule L
R_CER	R_THAL	2	8	12	66.7	Anterior thalamic radiation R	15	19	35	54	Cerebral peduncle R
R_CER	R_VDC	4	11	18	61.1	Corticospinal tract R	15	37	68	54	Cerebral peduncle R
R_CER	R_ENT	0	-	-	-	Unclassified	1	119	143	83	Middle cerebellar peduncle

Table 6.5.G: DTI Tractography generated white matter tracts and corresponding tract identification.

ROI 1	ROI 2	Value	Max	Total	%	JHU WM Atlas WM label	Value	Max	Total	%	JHU WM Atlas probabilistic tract
R_CER	R_FUS	0	-	-	-	Unclassified	1	108	159	68	Middle cerebellar peduncle
R_CER	R_PARH	0	-	-	-	Unclassified	1	35	45	78	Middle cerebellar peduncle
R_THAL	R_CAU	2	138	239	57.7	Anterior thalamic radiation R	19	236	453	52	Posterior limb of internal capsule R
R_THAL	R_PUT	2	113	305	37	Anterior thalamic radiation R	19	287	599	48	Posterior limb of internal capsule R
R_THAL	R_PAL	2	118	200	59	Anterior thalamic radiation R	19	259	333	78	Posterior limb of internal capsule R
R_THAL	R_HPC	2	129	215	60	Anterior thalamic radiation R	19	114	310	37	Posterior limb of internal capsule R
R_THAL	R_AMG	2	124	175	70.9	Anterior thalamic radiation R	19	156	250	62	Posterior limb of internal capsule R
R_THAL	R_ACC	2	58	75	77.3	Anterior thalamic radiation R	19	57	80	71	Posterior limb of internal capsule R
R_THAL	R_VDC	2	175	264	66.3	Anterior thalamic radiation R	19	165	323	51	Posterior limb of internal capsule R
R_THAL	L_ISTH	9	35	37	94.6	Forceps major	5	141	217	65	Splenium of corpus callosum
R_THAL	R_ISTH	9	38	58	65.5	Forceps major	5	120	263	46	Splenium of corpus callosum
R_THAL	R_LOF	2	58	136	42.6	Anterior thalamic radiation R	19	82	193	42	Posterior limb of internal capsule R
R_THAL	R_PARH	2	25	47	53.2	Anterior thalamic radiation R	15	46	56	82	Cerebral peduncle R
R_THAL	R_PARC	4	57	57	100	Corticospinal tract R	25	65	126	52	Superior corona radiata R
R_THAL	R_PSTC	4	25	31	80.6	Corticospinal tract R	27	23	44	52	Posterior corona radiata R
R_THAL	R_PC	4	46	48	95.8	Corticospinal tract R	4	78	148	53	Body of corpus callosum
R_THAL	R_PREC	4	132	141	93.6	Corticospinal tract R	25	154	259	59	Superior corona radiata R
R_THAL	R_SP	16	10	10	100	Superior longitudinal fasciculus R	27	14	33	42	Posterior corona radiata R
R_THAL	R_INS	12	78	214	36.4	Inferior fronto-occipital fasciculus R	19	174	435	40	Posterior limb of internal capsule R
R_CAU	R_PUT	2	190	386	49.2	Anterior thalamic radiation R	19	276	812	34	Posterior limb of internal capsule R
R_CAU	R_PAL	2	130	213	61	Anterior thalamic radiation R	19	242	420	58	Posterior limb of internal capsule R
R_CAU	R_HPC	2	62	119	52.1	Anterior thalamic radiation R	4	66	254	26	Body of corpus callosum
R_CAU	R_AMG	2	88	123	71.5	Anterior thalamic radiation R	19	116	171	68	Posterior limb of internal capsule R
R_CAU	R_ACC	2	2	2	100	Anterior thalamic radiation R	17	6	9	67	Anterior limb of internal capsule R
R_CAU	R_VDC	2	103	156	66	Anterior thalamic radiation R	19	135	236	57	Posterior limb of internal capsule R
R_CAU	L_CAC	10	92	93	98.9	Forceps minor	4	127	227	56	Body of corpus callosum

Table 6.5.H: DTI Tractography generated white matter tracts and corresponding tract identification.

ROI 1	ROI 2	Value	Max	Total	%	JHU WM Atlas WM label	Value	Max	Total	%	JHU WM Atlas probabilistic tract
R_CAU	L_RAC	10	36	36	100	Forceps minor	3	37	37	100	Genu of corpus callosum
R_CAU	R_CAC	10	106	161	65.8	Forceps minor	4	128	452	28	Body of corpus callosum
R_CAU	R_CMF	2	4	7	57.1	Anterior thalamic radiation R	25	69	168	41	Superior corona radiata R
R_CAU	R_ISTH	6	21	37	56.8	Cingulum (cingulate gyrus) R	4	141	295	48	Body of corpus callosum
R_CAU	R_LOF	2	81	153	52.9	Anterior thalamic radiation R	23	85	199	43	Anterior corona radiata R
R_CAU	R_MOF	10	127	220	57.7	Forceps minor	23	97	156	62	Anterior corona radiata R
R_CAU	R_PARC	4	21	21	100	Corticospinal tract R	25	52	101	51	Superior corona radiata R
R_CAU	R_PSTC	4	20	32	62.5	Corticospinal tract R	27	46	67	69	Posterior corona radiata R
R_CAU	R_PC	6	13	27	48.1	Cingulum (cingulate gyrus) R	4	181	276	66	Body of corpus callosum
R_CAU	R_PREC	4	80	92	87	Corticospinal tract R	25	136	223	61	Superior corona radiata R
R_CAU	R_PCUN	6	12	12	100	Cingulum (cingulate gyrus) R	4	84	149	56	Body of corpus callosum
R_CAU	R_RAC	10	99	160	61.9	Forceps minor	3	86	216	40	Genu of corpus callosum
R_CAU	R_RMF	10	201	373	53.9	Forceps minor	23	226	350	65	Anterior corona radiata R
R_CAU	R_SF	10	159	267	59.6	Forceps minor	23	173	365	47	Anterior corona radiata R
R_CAU	R_SP	16	11	13	84.6	Superior longitudinal fasciculus R	27	23	38	61	Posterior corona radiata R
R_CAU	R_INS	2	72	179	40.2	Anterior thalamic radiation R	19	115	255	45	Posterior limb of internal capsule R
R_PUT	R_PAL	12	46	92	50	Inferior fronto-occipital fasciculus R	33	78	169	46	External capsule R
R_PUT	R_HPC	12	87	137	63.5	Inferior fronto-occipital fasciculus R	33	90	316	28	External capsule R
R_PUT	R_AMG	12	73	85	85.9	Inferior fronto-occipital fasciculus R	33	90	150	60	External capsule R
R_PUT	R_ACC	2	47	75	62.7	Anterior thalamic radiation R	19	57	95	60	Posterior limb of internal capsule R
R_PUT	R_VDC	12	79	151	52.3	Inferior fronto-occipital fasciculus R	33	104	249	42	External capsule R
R_PUT	R_CMF	4	47	133	35.3	Corticospinal tract R	25	187	521	36	Superior corona radiata R
R_PUT	R_IP	16	60	81	74.1	Superior longitudinal fasciculus R	33	67	310	22	External capsule R
R_PUT	R_LOF	12	98	187	52.4	Inferior fronto-occipital fasciculus R	23	170	329	52	Anterior corona radiata R
R_PUT	R_MOF	10	91	255	35.7	Forceps minor	23	163	284	57	Anterior corona radiata R
R_PUT	R_PARC	4	74	77	96.1	Corticospinal tract R	25	86	176	49	Superior corona radiata R

Table 6.5.I: DTI Tractography generated white matter tracts and corresponding tract identification.

ROI 1	ROI 2	Value	Max	Total	%	JHU WM Atlas WM label	Value	Max	Total	%	JHU WM Atlas probabilistic tract
R_PUT	R_POPE	12	106	153	69.3	Inferior fronto-occipital fasciculus R	33	159	280	57	External capsule R
R_PUT	R_PTRI	12	105	151	69.5	Inferior fronto-occipital fasciculus R	33	120	251	48	External capsule R
R_PUT	R_PSTC	16	81	128	63.3	Superior longitudinal fasciculus R	33	72	338	21	External capsule R
R_PUT	R_PREC	4	152	259	58.7	Corticospinal tract R	25	299	683	44	Superior corona radiata R
R_PUT	R_RAC	2	77	179	43	Anterior thalamic radiation R	23	92	303	30	Anterior corona radiata R
R_PUT	R_RMF	10	256	547	46.8	Forceps minor	23	405	691	59	Anterior corona radiata R
R_PUT	R_SF	10	193	418	46.2	Forceps minor	23	261	619	42	Anterior corona radiata R
R_PUT	R_SP	16	51	65	78.5	Superior longitudinal fasciculus R	33	60	253	24	External capsule R
R_PUT	R_ST	12	49	77	63.6	Inferior fronto-occipital fasciculus R	41	39	157	25	Superior longitudinal fasciculus R
R_PUT	R_SMAR	16	26	29	89.7	Superior longitudinal fasciculus R	33	33	105	31	External capsule R
R_PUT	R_INS	12	134	223	60.1	Inferior fronto-occipital fasciculus R	33	329	632	52	External capsule R
R_PAL	R_HPC	4	26	40	65	Corticospinal tract R	19	42	81	52	Posterior limb of internal capsule R
R_PAL	R_AMG	4	16	27	59.3	Corticospinal tract R	19	16	42	38	Posterior limb of internal capsule R
R_PAL	R_ACC	2	39	60	65	Anterior thalamic radiation R	19	63	73	86	Posterior limb of internal capsule R
R_PAL	R_VDC	2	56	85	65.9	Anterior thalamic radiation R	19	53	102	52	Posterior limb of internal capsule R
R_PAL	R_LOF	12	26	44	59.1	Inferior fronto-occipital fasciculus R	33	53	72	74	External capsule R
R_PAL	R_PREC	4	28	28	100	Corticospinal tract R	25	30	54	56	Superior corona radiata R
R_PAL	R_INS	12	48	69	69.6	Inferior fronto-occipital fasciculus R	33	83	106	78	External capsule R
R_HPC	R_AMG	12	30	72	41.7	Inferior fronto-occipital fasciculus R	39	54	168	32	Fornix (cres) / Stria terminalis (can not be resolved with current resolution) R
R_HPC	R_VDC	4	82	163	50.3	Corticospinal tract R	15	114	289	39	Cerebral peduncle R
R_HPC	R_BSTS	12	40	77	51.9	Inferior fronto-occipital fasciculus R	31	60	128	47	Sagittal stratum (include front-occipital fasciculus) R
R_HPC	R_ENT	8	37	61	60.7	Cingulum (hippocampus) R	37	74	149	50	Cingulum (hippocampus) R
R_HPC	R_FUS	14	64	111	57.7	Inferior longitudinal fasciculus R	31	82	125	66	Sagittal stratum (include front-occipital fasciculus) R
R_HPC	R_IP	12	51	106	48.1	Inferior fronto-occipital fasciculus R	29	94	279	34	Posterior thalamic radiation (include optic radiation) R
R_HPC	R_IT	14	66	80	82.5	Inferior longitudinal fasciculus R	31	64	66	97	Sagittal stratum (include front-occipital fasciculus) R
R_HPC	R_ISTH	8	37	77	48.1	Cingulum (hippocampus) R	37	68	169	40	Cingulum (hippocampus) R

Table 6.5.J: DTI Tractography generated white matter tracts and corresponding tract identification.

ROI 1	ROI 2	Value	Max	Total	%	JHU WM Atlas WM label	Value	Max	Total	%	JHU WM Atlas probabilistic tract
R_HPC	R_LING	8	34	45	75.6	Cingulum (hippocampus) R	37	56	86	65	Cingulum (hippocampus) R
R_HPC	R_MT	14	64	79	81	Inferior longitudinal fasciculus R	31	64	64	100	Sagittal stratum (include front-occipital fasciculus) R
R_HPC	R_PARH	8	41	48	85.4	Cingulum (hippocampus) R	37	81	97	84	Cingulum (hippocampus) R
R_HPC	R_PCUN	9	8	9	88.9	Forceps major	5	16	21	76	Splenium of corpus callosum
R_HPC	R_ST	12	73	147	49.7	Inferior fronto-occipital fasciculus R	31	80	160	50	Sagittal stratum (include front-occipital fasciculus) R
R_HPC	R_INS	12	115	151	76.2	Inferior fronto-occipital fasciculus R	33	87	305	29	External capsule R
R_AMG	R_ACC	2	49	75	65.3	Anterior thalamic radiation R	19	60	87	69	Posterior limb of internal capsule R
R_AMG	R_VDC	2	57	99	57.6	Anterior thalamic radiation R	19	40	133	30	Posterior limb of internal capsule R
R_AMG	R_ENT	8	3	3	100	Cingulum (hippocampus) R	37	4	8	50	Cingulum (hippocampus) R
R_AMG	R_FUS	8	8	8	100	Cingulum (hippocampus) R	37	15	18	83	Cingulum (hippocampus) R
R_AMG	R_IT	0	-	-	-	Unclassified	45	2	2	100	Uncinate fasciculus R
R_AMG	R_LOF	12	16	27	59.3	Inferior fronto-occipital fasciculus R	33	39	48	81	External capsule R
R_AMG	R_ST	12	17	17	100	Inferior fronto-occipital fasciculus R	39	33	49	67	Fornix (cres) / Stria terminalis (can not be resolved with current resolution) R
R_AMG	R_TP	0	-	-	-	Unclassified	45	2	3	67	Uncinate fasciculus R
R_AMG	R_INS	12	83	101	82.2	Inferior fronto-occipital fasciculus R	33	100	186	54	External capsule R
R_ACC	R_VDC	2	55	101	54.5	Anterior thalamic radiation R	19	66	129	51	Posterior limb of internal capsule R
R_ACC	R_LOF	2	15	19	78.9	Anterior thalamic radiation R	33	12	24	50	External capsule R
R_ACC	R_MOF	0	-	-	-	Unclassified	17	3	3	100	Anterior limb of internal capsule R
R_ACC	R_INS	2	12	16	75	Anterior thalamic radiation R	33	12	22	55	External capsule R
R_VDC	R_ENT	4	54	75	72	Corticospinal tract R	15	65	224	29	Cerebral peduncle R
R_VDC	R_LOF	12	23	41	56.1	Inferior fronto-occipital fasciculus R	33	51	64	80	External capsule R
R_VDC	R_PARH	4	35	49	71.4	Corticospinal tract R	15	68	99	69	Cerebral peduncle R
R_VDC	R_INS	12	88	103	85.4	Inferior fronto-occipital fasciculus R	33	109	202	54	External capsule R
R_CAU	R_ACC	2	2	2	100	Anterior thalamic radiation R	17	6	9	67	Anterior limb of internal capsule R
R_CAU	R_VDC	2	103	156	66	Anterior thalamic radiation R	19	135	236	57	Posterior limb of internal capsule R
R_CAU	L_CAC	10	92	93	98.9	Forceps minor	4	127	227	56	Body of corpus callosum

Table 6.5.K: DTI Tractography generated white matter tracts and corresponding tract identification.

ROI 1	ROI 2	Value	Max	Total	%	JHU WM Atlas WM label	Value	Max	Total	%	JHU WM Atlas probabilistic tract
R_CAU	L_RAC	10	36	36	100	Forceps minor	3	37	37	100	Genu of corpus callosum
R_CAU	R_CAC	10	106	161	65.8	Forceps minor	4	128	452	28	Body of corpus callosum
R_CAU	R_CMF	2	4	7	57.1	Anterior thalamic radiation R	25	69	168	41	Superior corona radiata R
R_CAU	R_ISTH	6	21	37	56.8	Cingulum (cingulate gyrus) R	4	141	295	48	Body of corpus callosum
R_CAU	R_LOF	2	81	153	52.9	Anterior thalamic radiation R	23	85	199	43	Anterior corona radiata R
R_CAU	R_MOF	10	127	220	57.7	Forceps minor	23	97	156	62	Anterior corona radiata R
R_CAU	R_PARC	4	21	21	100	Corticospinal tract R	25	52	101	51	Superior corona radiata R
R_CAU	R_PSTC	4	20	32	62.5	Corticospinal tract R	27	46	67	69	Posterior corona radiata R
R_CAU	R_PC	6	13	27	48.1	Cingulum (cingulate gyrus) R	4	181	276	66	Body of corpus callosum
R_CAU	R_PREC	4	80	92	87	Corticospinal tract R	25	136	223	61	Superior corona radiata R
R_CAU	R_PCUN	6	12	12	100	Cingulum (cingulate gyrus) R	4	84	149	56	Body of corpus callosum
R_CAU	R_RAC	10	99	160	61.9	Forceps minor	3	86	216	40	Genu of corpus callosum
R_CAU	R_RMF	10	201	373	53.9	Forceps minor	23	226	350	65	Anterior corona radiata R
R_CAU	R_SF	10	159	267	59.6	Forceps minor	23	173	365	47	Anterior corona radiata R
R_CAU	R_SP	16	11	13	84.6	Superior longitudinal fasciculus R	27	23	38	61	Posterior corona radiata R
R_CAU	R_INS	2	72	179	40.2	Anterior thalamic radiation R	19	115	255	45	Posterior limb of internal capsule R
R_PUT	R_PAL	12	46	92	50	Inferior fronto-occipital fasciculus R	33	78	169	46	External capsule R
R_PUT	R_HPC	12	87	137	63.5	Inferior fronto-occipital fasciculus R	33	90	316	28	External capsule R
R_PUT	R_AMG	12	73	85	85.9	Inferior fronto-occipital fasciculus R	33	90	150	60	External capsule R
R_PUT	R_ACC	2	47	75	62.7	Anterior thalamic radiation R	19	57	95	60	Posterior limb of internal capsule R
R_PUT	R_VDC	12	79	151	52.3	Inferior fronto-occipital fasciculus R	33	104	249	42	External capsule R
R_PUT	R_CMF	4	47	133	35.3	Corticospinal tract R	25	187	521	36	Superior corona radiata R
R_PUT	R_IP	16	60	81	74.1	Superior longitudinal fasciculus R	33	67	310	22	External capsule R
R_PUT	R_LOF	12	98	187	52.4	Inferior fronto-occipital fasciculus R	23	170	329	52	Anterior corona radiata R
R_PUT	R_MOF	10	91	255	35.7	Forceps minor	23	163	284	57	Anterior corona radiata R
R_PUT	R_PARC	4	74	77	96.1	Corticospinal tract R	25	86	176	49	Superior corona radiata R

Table 6.5.L: DTI Tractography generated white matter tracts and corresponding tract identification.

ROI 1	ROI 2	Value	Max	Total	%	JHU WM Atlas WM label	Value	Max	Total	%	JHU WM Atlas probabilistic tract
R_PUT	R_POPE	12	106	153	69.3	Inferior fronto-occipital fasciculus R	33	159	280	57	External capsule R
R_PUT	R_PTRI	12	105	151	69.5	Inferior fronto-occipital fasciculus R	33	120	251	48	External capsule R
R_PUT	R_PSTC	16	81	128	63.3	Superior longitudinal fasciculus R	33	72	338	21	External capsule R
R_PUT	R_PREC	4	152	259	58.7	Corticospinal tract R	25	299	683	44	Superior corona radiata R
R_PUT	R_RAC	2	77	179	43	Anterior thalamic radiation R	23	92	303	30	Anterior corona radiata R
R_PUT	R_RMF	10	256	547	46.8	Forceps minor	23	405	691	59	Anterior corona radiata R
R_PUT	R_SF	10	193	418	46.2	Forceps minor	23	261	619	42	Anterior corona radiata R
R_PUT	R_SP	16	51	65	78.5	Superior longitudinal fasciculus R	33	60	253	24	External capsule R
R_PUT	R_ST	12	49	77	63.6	Inferior fronto-occipital fasciculus R	41	39	157	25	Superior longitudinal fasciculus R
R_PUT	R_SMAR	16	26	29	89.7	Superior longitudinal fasciculus R	33	33	105	31	External capsule R
R_PUT	R_INS	12	134	223	60.1	Inferior fronto-occipital fasciculus R	33	329	632	52	External capsule R
R_PAL	R_HPC	4	26	40	65	Corticospinal tract R	19	42	81	52	Posterior limb of internal capsule R
R_PAL	R_AMG	4	16	27	59.3	Corticospinal tract R	19	16	42	38	Posterior limb of internal capsule R
R_PAL	R_ACC	2	39	60	65	Anterior thalamic radiation R	19	63	73	86	Posterior limb of internal capsule R
R_PAL	R_VDC	2	56	85	65.9	Anterior thalamic radiation R	19	53	102	52	Posterior limb of internal capsule R
R_PAL	R_LOF	12	26	44	59.1	Inferior fronto-occipital fasciculus R	33	53	72	74	External capsule R
R_PAL	R_PREC	4	28	28	100	Corticospinal tract R	25	30	54	56	Superior corona radiata R
R_PAL	R_INS	12	48	69	69.6	Inferior fronto-occipital fasciculus R	33	83	106	78	External capsule R
R_HPC	R_AMG	12	30	72	41.7	Inferior fronto-occipital fasciculus R	39	54	168	32	Fornix (cres) / Stria terminalis (can not be resolved with current resolution) R
R_HPC	R_VDC	4	82	163	50.3	Corticospinal tract R	15	114	289	39	Cerebral peduncle R
R_HPC	R_BSTS	12	40	77	51.9	Inferior fronto-occipital fasciculus R	31	60	128	47	Sagittal stratum (include front-occipital fasciculus) R
R_HPC	R_ENT	8	37	61	60.7	Cingulum (hippocampus) R	37	74	149	50	Cingulum (hippocampus) R
R_HPC	R_FUS	14	64	111	57.7	Inferior longitudinal fasciculus R	31	82	125	66	Sagittal stratum (include front-occipital fasciculus) R
R_HPC	R_IP	12	51	106	48.1	Inferior fronto-occipital fasciculus R	29	94	279	34	Posterior thalamic radiation (include optic radiation) R
R_HPC	R_IT	14	66	80	82.5	Inferior longitudinal fasciculus R	31	64	66	97	Sagittal stratum (include front-occipital fasciculus) R
R_HPC	R_ISTH	8	37	77	48.1	Cingulum (hippocampus) R	37	68	169	40	Cingulum (hippocampus) R

Table 6.5.M: DTI Tractography generated white matter tracts and corresponding tract identification.

ROI 1	ROI 2	Value	Max	Total	%	JHU WM Atlas WM label	Value	Max	Total	%	JHU WM Atlas probabilistic tract
R_HPC	R_LING	8	34	45	75.6	Cingulum (hippocampus) R	37	56	86	65	Cingulum (hippocampus) R
R_HPC	R_MT	14	64	79	81	Inferior longitudinal fasciculus R	31	64	64	100	Sagittal stratum (include front-occipital fasciculus) R
R_HPC	R_PARH	8	41	48	85.4	Cingulum (hippocampus) R	37	81	97	84	Cingulum (hippocampus) R
R_HPC	R_PCUN	9	8	9	88.9	Forceps major	5	16	21	76	Splenium of corpus callosum
R_HPC	R_ST	12	73	147	49.7	Inferior fronto-occipital fasciculus R	31	80	160	50	Sagittal stratum (include front-occipital fasciculus) R
R_HPC	R_INS	12	115	151	76.2	Inferior fronto-occipital fasciculus R	33	87	305	29	External capsule R
R_AMG	R_ACC	2	49	75	65.3	Anterior thalamic radiation R	19	60	87	69	Posterior limb of internal capsule R
R_AMG	R_VDC	2	57	99	57.6	Anterior thalamic radiation R	19	40	133	30	Posterior limb of internal capsule R
R_AMG	R_ENT	8	3	3	100	Cingulum (hippocampus) R	37	4	8	50	Cingulum (hippocampus) R
R_AMG	R_FUS	8	8	8	100	Cingulum (hippocampus) R	37	15	18	83	Cingulum (hippocampus) R
R_AMG	R_IT	0	-	-	-	Unclassified	45	2	2	100	Uncinate fasciculus R
R_AMG	R_LOF	12	16	27	59.3	Inferior fronto-occipital fasciculus R	33	39	48	81	External capsule R
R_AMG	R_ST	12	17	17	100	Inferior fronto-occipital fasciculus R	39	33	49	67	Fornix (cres) / Stria terminalis (can not be resolved with current resolution) R
R_AMG	R_TP	0	-	-	-	Unclassified	45	2	3	67	Uncinate fasciculus R
R_AMG	R_INS	12	83	101	82.2	Inferior fronto-occipital fasciculus R	33	100	186	54	External capsule R
R_ACC	R_VDC	2	55	101	54.5	Anterior thalamic radiation R	19	66	129	51	Posterior limb of internal capsule R
R_ACC	R_LOF	2	15	19	78.9	Anterior thalamic radiation R	33	12	24	50	External capsule R
R_ACC	R_MOF	0	-	-	-	Unclassified	17	3	3	100	Anterior limb of internal capsule R
R_ACC	R_INS	2	12	16	75	Anterior thalamic radiation R	33	12	22	55	External capsule R
R_VDC	R_ENT	4	54	75	72	Corticospinal tract R	15	65	224	29	Cerebral peduncle R
R_VDC	R_LOF	12	23	41	56.1	Inferior fronto-occipital fasciculus R	33	51	64	80	External capsule R
R_VDC	R_PARH	4	35	49	71.4	Corticospinal tract R	15	68	99	69	Cerebral peduncle R
R_VDC	R_INS	12	88	103	85.4	Inferior fronto-occipital fasciculus R	33	109	202	54	External capsule R
L_BSTS	L_FUS	13	177	246	72	Inferior longitudinal fasciculus L	32	98	150	65	Sagittal stratum (include front-occipital fasciculus) L
L_BSTS	L_IP	15	13	21	61.9	Superior longitudinal fasciculus L	42	19	23	83	Superior longitudinal fasciculus L
L_BSTS	L_IT	13	103	125	82.4	Inferior longitudinal fasciculus L	32	36	43	84	Sagittal stratum (include front-occipital fasciculus) L

Table 6.5.N: DTI Tractography generated white matter tracts and corresponding tract identification.

ROI 1	ROI 2	Value	Max	Total	%	JHU WM Atlas WM label	Value	Max	Total	%	JHU WM Atlas probabilistic tract
L_BSTS	L_MT	13	159	198	80.3	Inferior longitudinal fasciculus L	32	63	79	80	Sagittal stratum (include front-occipital fasciculus) L
L_BSTS	L_ST	13	167	260	64.2	Inferior longitudinal fasciculus L	32	94	183	51	Sagittal stratum (include front-occipital fasciculus) L
L_BSTS	L_SMAR	15	37	54	68.5	Superior longitudinal fasciculus L	42	31	33	94	Superior longitudinal fasciculus L
L_CAC	L_CMF	5	2	2	100	Cingulum (cingulate gyrus) L	26	91	144	63	Superior corona radiata L
L_CAC	L_ISTH	5	63	68	92.6	Cingulum (cingulate gyrus) L	36	93	211	44	Cingulum (cingulate gyrus) L
L_CAC	L_PC	5	62	68	91.2	Cingulum (cingulate gyrus) L	36	98	248	40	Cingulum (cingulate gyrus) L
L_CAC	L_RAC	5	46	66	69.7	Cingulum (cingulate gyrus) L	36	56	87	64	Cingulum (cingulate gyrus) L
L_CAC	L_RMF	10	18	31	58.1	Forceps minor	24	35	68	51	Anterior corona radiata L
L_CAC	L_SF	0	-	-	-	Unclassified	26	78	113	69	Superior corona radiata L
L_CAC	R_CAC	10	44	45	97.8	Forceps minor	3	4	37	11	Genu of corpus callosum
L_CMF	L_POPE	15	8	11	72.7	Superior longitudinal fasciculus L	26	108	220	49	Superior corona radiata L
L_CMF	L_PSTC	15	52	52	100	Superior longitudinal fasciculus L	42	41	76	54	Superior longitudinal fasciculus L
L_CMF	L_PREC	15	65	65	100	Superior longitudinal fasciculus L	26	107	170	63	Superior corona radiata L
L_CMF	L_RMF	1	1	1	100	Anterior thalamic radiation L	24	52	103	50	Anterior corona radiata L
L_CMF	L_SF	0	-	-	-	Unclassified	26	131	188	70	Superior corona radiata L
L_CMF	L_INS	15	28	40	70	Superior longitudinal fasciculus L	26	153	365	42	Superior corona radiata L
L_CUN	L_IP	9	16	16	100	Forceps major	28	7	17	41	Posterior corona radiata L
L_CUN	L_ISTH	9	17	17	100	Forceps major	5	20	27	74	Splenium of corpus callosum
L_CUN	L_LOCC	9	35	35	100	Forceps major	5	1	1	100	Splenium of corpus callosum
L_CUN	L_LING	9	35	35	100	Forceps major	5	21	22	95	Splenium of corpus callosum
L_CUN	L_PCAL	9	28	28	100	Forceps major	5	1	1	100	Splenium of corpus callosum
L_CUN	L_PCUN	9	34	34	100	Forceps major	5	27	40	68	Splenium of corpus callosum
L_CUN	L_SP	9	2	2	100	Forceps major	28	4	6	67	Posterior corona radiata L
L_ENT	L_FUS	0	-	-	-	Unclassified	1	55	66	83	Middle cerebellar peduncle
L_ENT	L_IT	0	-	-	-	Unclassified	0	-	-	-	Unclassified
L_ENT	L_MOF	0	-	-	-	Unclassified	46	9	9	100	Uncinate fasciculus L

Table 6.5.O: DTI Tractography generated white matter tracts and corresponding tract identification.

ROI 1	ROI 2	Value	Max	Total	%	JHU WM Atlas WM label	Value	Max	Total	%	JHU WM Atlas probabilistic tract
L_ENT	L_MT	17	2	2	100	Uncinate fasciculus L	0	-	-	-	Unclassified
L_ENT	L_PHPC	7	17	17	100	Cingulum (hippocampus) L	38	49	49	100	Cingulum (hippocampus) L
L_ENT	L_ST	11	28	61	45.9	Inferior fronto-occipital fasciculus L	40	37	65	57	Fornix (cres) / Stria terminalis (can not be resolved with current resolution) L
L_ENT	L_TP	17	4	4	100	Uncinate fasciculus L	0	-	-	-	Unclassified
L_ENT	L_INS	11	43	75	57.3	Inferior fronto-occipital fasciculus L	40	40	133	30	Fornix (cres) / Stria terminalis (can not be resolved with current resolution) L
L_FUS	L_IP	13	112	189	59.3	Inferior longitudinal fasciculus L	30	67	139	48	Posterior thalamic radiation (include optic radiation) L
L_FUS	L_IT	13	209	246	85	Inferior longitudinal fasciculus L	32	66	104	63	Sagittal stratum (include front-occipital fasciculus) L
L_FUS	L_LOCC	13	92	121	76	Inferior longitudinal fasciculus L	30	28	47	60	Posterior thalamic radiation (include optic radiation) L
L_FUS	L_LING	13	81	200	40.5	Inferior longitudinal fasciculus L	30	65	108	60	Posterior thalamic radiation (include optic radiation) L
L_FUS	L_MT	13	221	253	87.4	Inferior longitudinal fasciculus L	32	84	98	86	Sagittal stratum (include front-occipital fasciculus) L
L_FUS	L_PHPC	7	5	5	100	Cingulum (hippocampus) L	38	6	8	75	Cingulum (hippocampus) L
L_FUS	L_PCAL	13	43	98	43.9	Inferior longitudinal fasciculus L	30	18	24	75	Posterior thalamic radiation (include optic radiation) L
L_FUS	L_ST	13	178	259	68.7	Inferior longitudinal fasciculus L	32	103	163	63	Sagittal stratum (include front-occipital fasciculus) L
L_FUS	L_TP	13	6	6	100	Inferior longitudinal fasciculus L	32	2	2	100	Sagittal stratum (include front-occipital fasciculus) L
L_IP	L_IT	13	2	2	100	Inferior longitudinal fasciculus L	0	-	-	-	Unclassified
L_IP	L_ISTH	9	31	40	77.5	Forceps major	5	54	104	52	Splenium of corpus callosum
L_IP	L_LOCC	9	43	53	81.1	Forceps major	30	34	62	55	Posterior thalamic radiation (include optic radiation) L
L_IP	L_MT	13	52	139	37.4	Inferior longitudinal fasciculus L	32	126	156	81	Sagittal stratum (include front-occipital fasciculus) L
L_IP	L_PCAL	9	13	22	59.1	Forceps major	30	9	12	75	Posterior thalamic radiation (include optic radiation) L
L_IP	L_PSTC	15	46	47	97.9	Superior longitudinal fasciculus L	42	44	58	76	Superior longitudinal fasciculus L
L_IP	L_PREC	15	208	208	100	Superior longitudinal fasciculus L	42	160	189	85	Superior longitudinal fasciculus L
L_IP	L_PCUN	9	229	229	100	Forceps major	5	170	209	81	Splenium of corpus callosum
L_IP	L_SP	15	63	66	95.5	Superior longitudinal fasciculus L	42	68	193	35	Superior longitudinal fasciculus L
L_IP	L_ST	13	72	83	86.7	Inferior longitudinal fasciculus L	30	60	143	42	Posterior thalamic radiation (include optic radiation) L
L_IP	L_SMAR	15	13	61	21.3	Superior longitudinal fasciculus L	42	86	178	48	Superior longitudinal fasciculus L
L_IP	L_INS	15	169	170	99.4	Superior longitudinal fasciculus L	42	117	139	84	Superior longitudinal fasciculus L

Table 6.5.P: DTI Tractography generated white matter tracts and corresponding tract identification.

ROI 1	ROI 2	Value	Max	Total	%	JHU WM Atlas WM label	Value	Max	Total	%	JHU WM Atlas probabilistic tract
L_IT	L_LOCC	13	103	112	92	Inferior longitudinal fasciculus L	0	97	279	35	Unclassified
L_IT	L_LING	13	37	75	49.3	Inferior longitudinal fasciculus L	30	72	75	96	Posterior thalamic radiation (include optic radiation) L
L_IT	L_MT	13	139	148	93.9	Inferior longitudinal fasciculus L	32	22	22	100	Sagittal stratum (include front-occipital fasciculus) L
L_IT	L_ST	13	144	211	68.2	Inferior longitudinal fasciculus L	30	42	122	34	Posterior thalamic radiation (include optic radiation) L
L_IT	L_TP	0	-	-	-	Unclassified	0	-	-	-	Unclassified
L_ISTH	L_LING	9	14	27	51.9	Forceps major	5	23	45	51	Splenium of corpus callosum
L_ISTH	L_PHPC	7	9	15	60	Cingulum (hippocampus) L	38	54	75	72	Cingulum (hippocampus) L
L_ISTH	L_PARC	5	24	33	72.7	Cingulum (cingulate gyrus) L	36	39	115	34	Cingulum (cingulate gyrus) L
L_ISTH	L_PC	5	33	48	68.8	Cingulum (cingulate gyrus) L	36	64	209	31	Cingulum (cingulate gyrus) L
L_ISTH	L_PCUN	9	30	47	63.8	Forceps major	5	54	95	57	Splenium of corpus callosum
L_ISTH	L_SP	9	15	15	100	Forceps major	28	73	158	46	Posterior corona radiata L
L_ISTH	R_ISTH	9	32	32	100	Forceps major	5	87	113	77	Splenium of corpus callosum
L_LOCC	L_LING	9	83	168	49.4	Forceps major	30	80	107	75	Posterior thalamic radiation (include optic radiation) L
L_LOCC	L_PCAL	9	69	72	95.8	Forceps major	30	32	36	89	Posterior thalamic radiation (include optic radiation) L
L_LOCC	L_PCUN	9	75	75	100	Forceps major	30	46	103	45	Posterior thalamic radiation (include optic radiation) L
L_LOCC	L_SP	9	10	11	90.9	Forceps major	28	10	24	42	Posterior corona radiata L
L_LOF	L_MOF	10	79	103	76.7	Forceps minor	24	47	64	73	Anterior corona radiata L
L_LOF	L_PORB	0	-	-	-	Unclassified	24	-	-	-	Anterior corona radiata L
L_LOF	L_PTRI	11	19	34	55.9	Inferior fronto-occipital fasciculus L	24	28	28	100	Anterior corona radiata L
L_LOF	L_RAC	10	29	60	48.3	Forceps minor	24	45	45	100	Anterior corona radiata L
L_LOF	L_RMF	10	85	154	55.2	Forceps minor	24	95	95	100	Anterior corona radiata L
L_LOF	L_INS	0	-	-	-	Unclassified	24	10	12	83	Anterior corona radiata L
L_LING	L_PHPC	7	15	23	65.2	Cingulum (hippocampus) L	38	50	64	78	Cingulum (hippocampus) L
L_LING	L_PCAL	9	69	97	71.1	Forceps major	30	34	59	58	Posterior thalamic radiation (include optic radiation) L
L_LING	L_PCUN	9	52	60	86.7	Forceps major	5	37	60	62	Splenium of corpus callosum
L_LING	L_SP	9	25	38	65.8	Forceps major	5	21	34	62	Splenium of corpus callosum

Table 6.5.Q: DTI Tractography generated white matter tracts and corresponding tract identification.

ROI 1	ROI 2	Value	Max	Total	%	JHU WM Atlas WM label	Value	Max	Total	%	JHU WM Atlas probabilistic tract
L_MOF	L_RAC	10	79	79	100	Forceps minor	3	1	1	100	Genu of corpus callosum
L_MOF	L_RMF	10	105	105	100	Forceps minor	24	3	3	100	Anterior corona radiata L
L_MOF	L_SF	10	127	127	100	Forceps minor	24	2	2	100	Anterior corona radiata L
L_MOF	L_INS	10	26	60	43.3	Forceps minor	24	32	65	49	Anterior corona radiata L
L_MT	L_ST	13	190	222	85.6	Inferior longitudinal fasciculus L	32	48	55	87	Sagittal stratum (include front-occipital fasciculus) L
L_MT	L_TP	17	2	2	100	Uncinate fasciculus L	0	-	-	-	Unclassified
L_PARC	L_PSTC	3	19	19	100	Corticospinal tract L	28	5	8	63	Posterior corona radiata L
L_PARC	L_PC	5	5	9	55.6	Cingulum (cingulate gyrus) L	36	20	53	38	Cingulum (cingulate gyrus) L
L_PARC	L_PREC	3	45	47	95.7	Corticospinal tract L	26	64	68	94	Superior corona radiata L
L_PARC	L_PCUN	5	20	24	83.3	Cingulum (cingulate gyrus) L	36	31	65	48	Cingulum (cingulate gyrus) L
L_PARC	L_SF	3	6	6	100	Corticospinal tract L	26	20	24	83	Superior corona radiata L
L_PARC	L_SP	0	-	-	-	Unclassified	28	4	4	100	Posterior corona radiata L
L_POPE	L_PTRI	11	19	26	73.1	Inferior fronto-occipital fasciculus L	24	15	15	100	Anterior corona radiata L
L_POPE	L_PSTC	15	49	49	100	Superior longitudinal fasciculus L	42	5	5	100	Superior longitudinal fasciculus L
L_POPE	L_PREC	15	51	51	100	Superior longitudinal fasciculus L	26	22	45	49	Superior corona radiata L
L_POPE	L_RMF	11	23	40	57.5	Inferior fronto-occipital fasciculus L	24	29	75	39	Anterior corona radiata L
L_POPE	L_INS	15	13	27	48.1	Superior longitudinal fasciculus L	26	66	208	32	Superior corona radiata L
L_PORB	L_PTRI	0	-	-	-	Unclassified	0	-	-	-	Unclassified
L_PORB	L_RMF	0	-	-	-	Unclassified	0	-	-	-	Unclassified
L_PTRI	L_RMF	11	51	135	37.8	Inferior fronto-occipital fasciculus L	24	82	82	100	Anterior corona radiata L
L_PTRI	L_INS	11	17	32	53.1	Inferior fronto-occipital fasciculus L	24	38	38	100	Anterior corona radiata L
L_PCAL	L_PCUN	9	66	66	100	Forceps major	30	39	69	57	Posterior thalamic radiation (include optic radiation) L
L_PCAL	L_SP	9	6	6	100	Forceps major	0	-	-	-	Unclassified
L_PSTC	L_PC	3	13	13	100	Corticospinal tract L	28	6	10	60	Posterior corona radiata L
L_PSTC	L_PREC	15	256	268	95.5	Superior longitudinal fasciculus L	42	155	200	78	Superior longitudinal fasciculus L
L_PSTC	L_PCUN	3	5	8	62.5	Corticospinal tract L	28	28	11	255	Posterior corona radiata L

Table 6.5.R: DTI Tractography generated white matter tracts and corresponding tract identification.

ROI 1	ROI 2	Value	Max	Total	%	JHU WM Atlas WM label	Value	Max	Total	%	JHU WM Atlas probabilistic tract
L_PSTC	L_SP	15	215	220	97.7	Superior longitudinal fasciculus L	42	162	198	82	Superior longitudinal fasciculus L
L_PSTC	L_ST	15	47	50	94	Superior longitudinal fasciculus L	42	31	39	79	Superior longitudinal fasciculus L
L_PSTC	L_SMAR	15	262	262	100	Superior longitudinal fasciculus L	42	174	196	89	Superior longitudinal fasciculus L
L_PSTC	L_INS	15	157	186	84.4	Superior longitudinal fasciculus L	42	121	297	41	Superior longitudinal fasciculus L
L_PC	L_PREC	3	46	46	100	Corticospinal tract L	26	95	123	77	Superior corona radiate L
L_PC	L_PCUN	5	27	32	84.4	Cingulum (cingulate gyrus) L	36	45	110	41	Cingulum (cingulate gyrus) L
L_PC	L_SF	5	10	17	58.8	Cingulum (cingulate gyrus) L	26	91	149	61	Superior corona radiate L
L_PC	L_SP	0	-	-	-	Unclassified	28	4	4	100	Posterior corona radiata L
L_PC	R_PC	0	-	-	-	Unclassified	4	40	40	100	Body of corpus callosum
L_PREC	L_SF	15	23	23	100	Superior longitudinal fasciculus L	26	48	72	67	Superior corona radiate L
L_PREC	L_SP	15	218	222	98.2	Superior longitudinal fasciculus L	42	165	205	80	Superior longitudinal fasciculus L
L_PREC	L_ST	15	49	53	92.5	Superior longitudinal fasciculus L	42	34	42	81	Superior longitudinal fasciculus L
L_PREC	L_SMAR	15	307	307	100	Superior longitudinal fasciculus L	42	195	234	83	Superior longitudinal fasciculus L
L_PREC	L_INS	15	145	152	95.4	Superior longitudinal fasciculus L	26	124	294	42	Superior corona radiate L
L_PCUN	L_SP	9	23	23	100	Forceps major	5	73	151	48	Splenium of corpus callosum
L_RAC	L_RMF	10	115	115	100	Forceps minor	24	1	1	100	Anterior corona radiata L
L_RAC	L_SF	10	97	97	100	Forceps minor	24	1	1	100	Anterior corona radiata L
L_RAC	R_RAC	0	-	-	-	Unclassified	3	1	1	100	Genu of corpus callosum
L_RMF	L_SF	10	167	167	100	Forceps minor	24	35	76	46	Anterior corona radiata L
L_RMF	L_INS	1	96	199	48.2	Anterior thalamic radiation L	24	196	338	58	Anterior corona radiata L
L_SP	L_ST	13	28	50	56	Inferior longitudinal fasciculus L	32	20	34	59	Sagittal stratum (include front-occipital fasciculus) L
L_SP	L_SMAR	15	182	182	100	Superior longitudinal fasciculus L	42	132	150	88	Superior longitudinal fasciculus L
L_SP	L_INS	15	102	127	80.3	Superior longitudinal fasciculus L	42	115	310	37	Superior longitudinal fasciculus L
L_ST	L_SMAR	15	67	134	50	Superior longitudinal fasciculus L	42	51	121	42	Superior longitudinal fasciculus L
L_ST	L_TP	13	45	72	62.5	Inferior longitudinal fasciculus L	40	15	25	60	Fornix (cres) / Stria terminalis (can not be resolved with current resolution) L
L_ST	L_TT	0	-	-	-	Unclassified	22	12	12	100	Retrolenticular part of internal capsule L

Table 6.5.T: DTI Tractography generated white matter tracts and corresponding tract identification.

ROI 1	ROI 2	Value	Max	Total	%	JHU WM Atlas WM label	Value	Max	Total	%	JHU WM Atlas probabilistic tract
L_ST	L_INS	15	36	96	37.5	Superior longitudinal fasciculus L	22	43	159	27	Retrolenticular part of internal capsule L
L_SMAR	L_TT	15	1	1	100	Superior longitudinal fasciculus L	22	9	9	100	Retrolenticular part of internal capsule L
L_SMAR	L_INS	15	228	242	94.2	Superior longitudinal fasciculus L	42	172	311	55	Superior longitudinal fasciculus L
L_TP	L_INS	17	32	60	53.3	Uncinate fasciculus L	46	32	85	38	Uncinate fasciculus L
L_TT	L_INS	11	12	12	100	Inferior fronto-occipital fasciculus L	34	31	39	79	External capsule L
R_BSTS	R_FUS	14	81	122	66.4	Inferior longitudinal fasciculus R	31	77	110	70	Sagittal stratum (include front-occipital fasciculus) R
R_BSTS	R_IP	16	160	280	57.1	Superior longitudinal fasciculus R	41	129	216	60	Superior longitudinal fasciculus R
R_BSTS	R_IT	14	37	39	94.9	Inferior longitudinal fasciculus R	31	59	60	98	Sagittal stratum (include front-occipital fasciculus) R
R_BSTS	R_MT	14	82	103	79.6	Inferior longitudinal fasciculus R	31	85	119	71	Sagittal stratum (include front-occipital fasciculus) R
R_BSTS	R_ST	16	123	275	44.7	Superior longitudinal fasciculus R	41	88	260	34	Superior longitudinal fasciculus R
R_BSTS	R_SMAR	16	181	225	80.4	Superior longitudinal fasciculus R	41	168	176	95	Superior longitudinal fasciculus R
R_BSTS	R_TT	0	-	-	-	Unclassified	0	-	-	-	Unclassified
R_BSTS	R_INS	16	106	227	46.7	Superior longitudinal fasciculus R	41	70	116	60	Superior longitudinal fasciculus R
R_CAC	R_CMF	6	6	6	100	Cingulum (cingulate gyrus) R	25	76	145	52	Superior corona radiate R
R_CAC	R_ISTH	6	32	38	84.2	Cingulum (cingulate gyrus) R	35	142	190	75	Cingulum (cingulate gyrus) R
R_CAC	R_PC	6	30	34	88.2	Cingulum (cingulate gyrus) R	35	104	146	71	Cingulum (cingulate gyrus) R
R_CAC	R_RAC	10	18	28	64.3	Forceps minor	35	52	60	87	Cingulum (cingulate gyrus) R
R_CAC	R_RMF	10	37	37	100	Forceps minor	23	16	17	94	Anterior corona radiata R
R_CAC	R_SF	10	25	35	71.4	Forceps minor	25	66	140	47	Superior corona radiate R
R_CMF	R_POPE	12	14	22	63.6	Inferior fronto-occipital fasciculus R	25	35	90	39	Superior corona radiate R
R_CMF	R_PSTC	16	45	45	100	Superior longitudinal fasciculus R	41	24	25	96	Superior longitudinal fasciculus R
R_CMF	R_PREC	16	43	43	100	Superior longitudinal fasciculus R	25	70	130	54	Superior corona radiate R
R_CMF	R_RMF	12	13	19	68.4	Inferior fronto-occipital fasciculus R	23	11	11	100	Anterior corona radiata R
R_CMF	R_SF	0	-	-	-	Unclassified	25	120	196	61	Superior corona radiate R
R_CMF	R_INS	16	45	115	39.1	Superior longitudinal fasciculus R	25	71	245	29	Superior corona radiate R
R_CUN	R_IP	9	23	23	100	Forceps major	0	-	-	-	Unclassified

Table 6.5.U: DTI Tractography generated white matter tracts and corresponding tract identification.

ROI 1	ROI 2	Value	Max	Total	%	JHU WM Atlas WM label	Value	Max	Total	%	JHU WM Atlas probabilistic tract
R_CUN	R_ISTH	0	-	-	-	Unclassified	35	11	11	100	Cingulum (cingulate gyrus) R
R_CUN	R_LOCC	9	28	33	84.8	Forceps major	0	-	-	-	Unclassified
R_CUN	R_LING	9	19	27	70.4	Forceps major	0	-	-	-	Unclassified
R_CUN	R_PCAL	9	24	24	100	Forceps major	0	-	-	-	Unclassified
R_CUN	R_PCUN	9	3	3	100	Forceps major	35	2	2	100	Cingulum (cingulate gyrus) R
R_CUN	R_SP	9	11	11	100	Forceps major	0	-	-	-	Unclassified
R_ENT	R_FUS	8	8	8	100	Cingulum (hippocampus) R	1	63	96	66	Middle cerebellar peduncle
R_ENT	R_IT	0	-	-	-	Unclassified	0	-	-	-	Unclassified
R_ENT	R_PARH	8	29	29	100	Cingulum (hippocampus) R	37	60	64	94	Cingulum (hippocampus) R
R_ENT	R_ST	12	9	10	90	Inferior fronto-occipital fasciculus R	39	16	25	64	Fornix (cres) / Stria terminalis (can not be resolved with current resolution) R
R_ENT	R_TP	18	1	1	100	Uncinate fasciculus R	0	-	-	-	Unclassified
R_ENT	R_INS	12	43	61	70.5	Inferior fronto-occipital fasciculus R	33	51	110	46	External capsule R
R_FUS	R_IP	14	120	206	58.3	Inferior longitudinal fasciculus R	31	87	232	38	Sagittal stratum (include front-occipital fasciculus) R
R_FUS	R_IT	14	103	104	99	Inferior longitudinal fasciculus R	31	59	60	98	Sagittal stratum (include front-occipital fasciculus) R
R_FUS	R_LOCC	14	41	63	65.1	Inferior longitudinal fasciculus R	29	17	24	71	Posterior thalamic radiation (include optic radiation) R
R_FUS	R_LING	12	49	94	52.1	Inferior fronto-occipital fasciculus R	29	34	44	77	Posterior thalamic radiation (include optic radiation) R
R_FUS	R_MT	14	120	128	93.8	Inferior longitudinal fasciculus R	31	68	68	100	Sagittal stratum (include front-occipital fasciculus) R
R_FUS	R_PARH	14	55	61	90.2	Inferior longitudinal fasciculus R	31	36	46	78	Sagittal stratum (include front-occipital fasciculus) R
R_FUS	R_ST	14	107	123	87	Inferior longitudinal fasciculus R	31	47	55	85	Sagittal stratum (include front-occipital fasciculus) R
R_FUS	R_TP	14	52	55	94.5	Inferior longitudinal fasciculus R	31	22	22	100	Sagittal stratum (include front-occipital fasciculus) R
R_FUS	R_INS	12	24	43	55.8	Inferior fronto-occipital fasciculus R	33	35	76	46	External capsule R
R_IP	R_IT	14	86	87	98.9	Inferior longitudinal fasciculus R	31	47	50	94	Sagittal stratum (include front-occipital fasciculus) R
R_IP	R_ISTH	16	8	8	100	Superior longitudinal fasciculus R	5	43	90	48	Splenium of corpus callosum
R_IP	R_LOCC	9	42	57	73.7	Forceps major	29	54	96	56	Posterior thalamic radiation (include optic radiation) R
R_IP	R_LING	12	85	181	47	Inferior fronto-occipital fasciculus R	29	187	278	67	Posterior thalamic radiation (include optic radiation) R
R_IP	R_MT	14	97	132	73.5	Inferior longitudinal fasciculus R	31	90	110	82	Sagittal stratum (include front-occipital fasciculus) R

Table 6.5.V: DTI Tractography generated white matter tracts and corresponding tract identification.

ROI 1	ROI 2	Value	Max	Total	%	JHU WM Atlas WM label	Value	Max	Total	%	JHU WM Atlas probabilistic tract
R_IP	R_PARH	14	32	49	65.3	Inferior longitudinal fasciculus R	31	37	67	55	Sagittal stratum (include front-occipital fasciculus) R
R_IP	R_PCAL	9	62	70	88.6	Forceps major	29	53	77	69	Posterior thalamic radiation (include optic radiation) R
R_IP	R_PSTC	16	324	331	97.9	Superior longitudinal fasciculus R	41	287	345	83	Superior longitudinal fasciculus R
R_IP	R_PREC	16	277	283	97.9	Superior longitudinal fasciculus R	41	227	256	89	Superior longitudinal fasciculus R
R_IP	R_PCUN	9	63	75	84	Forceps major	29	79	250	32	Posterior thalamic radiation (include optic radiation) R
R_IP	R_SP	16	97	137	70.8	Superior longitudinal fasciculus R	41	77	209	37	Superior longitudinal fasciculus R
R_IP	R_ST	16	106	308	34.4	Superior longitudinal fasciculus R	41	124	394	31	Superior longitudinal fasciculus R
R_IP	R_SMAR	16	221	227	97.4	Superior longitudinal fasciculus R	41	208	256	81	Superior longitudinal fasciculus R
R_IP	R_INS	16	83	155	53.5	Superior longitudinal fasciculus R	41	112	423	26	Superior longitudinal fasciculus R
R_IT	R_LOCC	14	3	3	100	Inferior longitudinal fasciculus R	29	1	1	100	Posterior thalamic radiation (include optic radiation) R
R_IT	R_MT	14	93	94	98.9	Inferior longitudinal fasciculus R	31	31	31	100	Sagittal stratum (include front-occipital fasciculus) R
R_IT	R_ST	14	90	102	88.2	Inferior longitudinal fasciculus R	31	28	29	97	Sagittal stratum (include front-occipital fasciculus) R
R_IT	R_TP	14	33	35	94.3	Inferior longitudinal fasciculus R	31	13	13	100	Sagittal stratum (include front-occipital fasciculus) R
R_IT	R_INS	18	9	14	64.3	Uncinate fasciculus R	45	20	24	83	Uncinate fasciculus R
R_ISTH	R_LING	8	12	12	100	Cingulum (hippocampus) R	37	13	13	100	Cingulum (hippocampus) R
R_ISTH	R_PARH	8	39	44	88.6	Cingulum (hippocampus) R	37	63	69	91	Cingulum (hippocampus) R
R_ISTH	R_PARC	4	7	14	50	Corticospinal tract R	27	47	146	32	Posterior corona radiata R
R_ISTH	R_PC	6	22	33	66.7	Cingulum (cingulate gyrus) R	35	95	196	48	Cingulum (cingulate gyrus) R
R_ISTH	R_PCUN	9	12	18	66.7	Forceps major	5	64	140	46	Splenium of corpus callosum
R_ISTH	R_SP	16	10	15	66.7	Superior longitudinal fasciculus R	27	108	253	43	Posterior corona radiata R
R_LOCC	R_LING	12	74	162	45.7	Inferior fronto-occipital fasciculus R	29	87	102	85	Posterior thalamic radiation (include optic radiation) R
R_LOCC	R_PCAL	9	58	80	72.5	Forceps major	29	7	7	100	Posterior thalamic radiation (include optic radiation) R
R_LOCC	R_PCUN	9	50	53	94.3	Forceps major	29	38	58	66	Posterior thalamic radiation (include optic radiation) R
R_LOCC	R_SP	9	39	39	100	Forceps major	29	26	48	54	Posterior thalamic radiation (include optic radiation) R
R_LOF	R_MOF	10	58	92	63	Forceps minor	23	62	62	100	Anterior corona radiata R
R_LOF	R_POPE	2	35	68	51.5	Anterior thalamic radiation R	23	58	62	94	Anterior corona radiata R

Table 6.5.W: DTI Tractography generated white matter tracts and corresponding tract identification.

ROI 1	ROI 2	Value	Max	Total	%	JHU WM Atlas WM label	Value	Max	Total	%	JHU WM Atlas probabilistic tract
R_LOF	R_PORB	12	1	1	100	Inferior fronto-occipital fasciculus R	23	6	6	100	Anterior corona radiata R
R_LOF	R_PTRI	12	54	83	65.1	Inferior fronto-occipital fasciculus R	23	57	74	77	Anterior corona radiata R
R_LOF	R_RMF	12	93	224	41.5	Inferior fronto-occipital fasciculus R	23	152	166	92	Anterior corona radiata R
R_LOF	R_INS	12	36	75	48	Inferior fronto-occipital fasciculus R	23	69	127	54	Anterior corona radiata R
R_LING	R_PARH	8	32	32	100	Cingulum (hippocampus) R	37	55	55	100	Cingulum (hippocampus) R
R_LING	R_PCAL	9	64	112	57.1	Forceps major	29	48	68	71	Posterior thalamic radiation (include optic radiation) R
R_LING	R_PCUN	9	55	88	62.5	Forceps major	29	77	113	68	Posterior thalamic radiation (include optic radiation) R
R_LING	R_SP	9	40	58	69	Forceps major	29	24	46	52	Posterior thalamic radiation (include optic radiation) R
R_MOF	R_RAC	10	5	5	100	Forceps minor	0	-	-	-	Unclassified
R_MOF	R_RMF	10	146	146	100	Forceps minor	23	7	7	100	Anterior corona radiata R
R_MOF	R_SF	10	144	144	100	Forceps minor	23	2	2	100	Anterior corona radiata R
R_MOF	R_FP	10	71	71	100	Forceps minor	23	3	3	100	Anterior corona radiata R
R_MT	R_ST	14	88	108	81.5	Inferior longitudinal fasciculus R	31	35	36	97	Sagittal stratum (include front-occipital fasciculus) R
R_MT	R_TP	14	55	59	93.2	Inferior longitudinal fasciculus R	31	10	10	100	Sagittal stratum (include front-occipital fasciculus) R
R_MT	R_INS	0	-	-	-	Unclassified	0	-	-	-	Unclassified
R_PARC	R_PSTC	4	18	24	75	Corticospinal tract R	27	50	76	66	Posterior corona radiata R
R_PARC	R_PC	0	-	-	-	Unclassified	27	36	63	57	Posterior corona radiata R
R_PARC	R_PREC	4	36	41	87.8	Corticospinal tract R	25	66	137	48	Superior corona radiata R
R_PARC	R_PCUN	4	3	5	60	Corticospinal tract R	27	39	89	44	Posterior corona radiata R
R_PARC	R_SF	0	-	-	-	Unclassified	25	17	19	89	Superior corona radiata R
R_PARC	R_SP	0	-	-	-	Unclassified	27	42	60	70	Posterior corona radiata R
R_POPE	R_PTRI	12	36	68	52.9	Inferior fronto-occipital fasciculus R	23	50	50	100	Anterior corona radiata R
R_POPE	R_PSTC	16	16	16	100	Superior longitudinal fasciculus R	41	16	19	84	Superior longitudinal fasciculus R
R_POPE	R_PREC	16	15	15	100	Superior longitudinal fasciculus R	41	35	52	67	Superior longitudinal fasciculus R
R_POPE	R_RMF	2	27	55	49.1	Anterior thalamic radiation R	23	45	45	100	Anterior corona radiata R
R_POPE	R_INS	12	78	149	52.3	Inferior fronto-occipital fasciculus R	33	108	251	43	External capsule R

Table 6.5.X: DTI Tractography generated white matter tracts and corresponding tract identification.

ROI 1	ROI 2	Value	Max	Total	%	JHU WM Atlas WM label	Value	Max	Total	%	JHU WM Atlas probabilistic tract
R_PORB	R_PTRI	0	-	-	-	Unclassified	0	-	-	-	Unclassified
R_PORB	R_RMF	12	1	1	100	Inferior fronto-occipital fasciculus R	0	-	-	-	Unclassified
R_PTRI	R_RMF	12	82	153	53.6	Inferior fronto-occipital fasciculus R	23	85	85	100	Anterior corona radiata R
R_PTRI	R_INS	12	54	97	55.7	Inferior fronto-occipital fasciculus R	33	67	135	50	External capsule R
R_PCAL	R_PCUN	9	52	58	89.7	Forceps major	29	39	50	78	Posterior thalamic radiation (include optic radiation) R
R_PCAL	R_SP	9	56	57	98.2	Forceps major	29	27	44	61	Posterior thalamic radiation (include optic radiation) R
R_PSTC	R_PREC	16	119	135	88.1	Superior longitudinal fasciculus R	41	87	161	54	Superior longitudinal fasciculus R
R_PSTC	R_PCUN	16	143	149	96	Superior longitudinal fasciculus R	41	119	237	50	Superior longitudinal fasciculus R
R_PSTC	R_SP	16	205	213	96.2	Superior longitudinal fasciculus R	41	169	284	60	Superior longitudinal fasciculus R
R_PSTC	R_SMAR	16	221	222	99.5	Superior longitudinal fasciculus R	41	187	202	93	Superior longitudinal fasciculus R
R_PSTC	R_INS	16	148	172	86	Superior longitudinal fasciculus R	41	135	292	46	Superior longitudinal fasciculus R
R_PC	R_PREC	4	16	19	84.2	Corticospinal tract R	25	45	134	34	Superior corona radiata R
R_PC	R_PCUN	6	17	19	89.5	Cingulum (cingulate gyrus) R	35	67	113	59	Cingulum (cingulate gyrus) R
R_PC	R_SF	6	17	18	94.4	Cingulum (cingulate gyrus) R	25	49	116	42	Superior corona radiata R
R_PC	R_SP	0	-	-	-	Unclassified	27	-	-	-	Posterior corona radiata R
R_PREC	R_SF	0	-	-	-	Unclassified	25	73	101	72	Superior corona radiata R
R_PREC	R_SP	16	192	205	93.7	Superior longitudinal fasciculus R	41	153	217	71	Superior longitudinal fasciculus R
R_PREC	R_SMAR	16	175	175	100	Superior longitudinal fasciculus R	41	137	138	99	Superior longitudinal fasciculus R
R_PREC	R_INS	16	143	205	69.8	Superior longitudinal fasciculus R	25	143	442	32	Superior corona radiata R
R_PCUN	R_SP	9	32	53	60.4	Forceps major	27	151	346	44	Posterior corona radiata R
R_RAC	R_RMF	10	38	38	100	Forceps minor	0	-	-	-	Unclassified
R_RAC	R_SF	10	33	33	100	Forceps minor	0	-	-	-	Unclassified
R_RMF	R_SF	10	248	284	87.3	Forceps minor	23	70	70	100	Anterior corona radiata R
R_RMF	R_FP	10	5	5	100	Forceps minor	0	-	-	-	Unclassified
R_RMF	R_INS	10	188	363	51.8	Forceps minor	23	273	320	85	Anterior corona radiata R
R_SP	R_SMAR	16	125	125	100	Superior longitudinal fasciculus R	41	97	122	80	Superior longitudinal fasciculus R

Table 6.5.Y: DTI Tractography generated white matter tracts and corresponding tract identification.

ROI 1	ROI 2	Value	Max	Total	%	JHU WM Atlas WM label	Value	Max	Total	%	JHU WM Atlas probabilistic tract
R_SP	R_INS	16	60	75	80	Superior longitudinal fasciculus R	41	56	216	26	Superior longitudinal fasciculus R
R_ST	R_SMAR	16	105	145	72.4	Superior longitudinal fasciculus R	41	113	182	62	Superior longitudinal fasciculus R
R_ST	R_TP	14	39	50	78	Inferior longitudinal fasciculus R	45	2	2	100	Uncinate fasciculus R
R_ST	R_TT	12	3	3	100	Inferior fronto-occipital fasciculus R	21	6	7	86	Retrolenticular part of internal capsule R
R_ST	R_INS	16	16	46	34.8	Superior longitudinal fasciculus R	41	65	170	38	Superior longitudinal fasciculus R
R_SMAR	R_TT	0	-	-	-	Unclassified	21	8	8	100	Retrolenticular part of internal capsule R
R_SMAR	R_INS	16	45	63	71.4	Superior longitudinal fasciculus R	41	54	147	37	Superior longitudinal fasciculus R
R_TP	R_INS	18	22	40	55	Uncinate fasciculus R	33	30	65	46	External capsule R
R_TT	R_INS	12	3	3	100	Inferior fronto-occipital fasciculus R	33	3	6	50	External capsule R

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