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Medical comorbidities and lower myelin content are associated with poor cognition in young adults with perinatally acquired HIV

Short title: Myelin and cognition in young adults with pHIV

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Abstract

Objective: Approximately 40% of adults living with HIV experience cognitive deficits. Little is known about risk factors for cognitive impairment and its association with myelin content in young adults living with perinatally acquired HIV (YApHIV), which is assessed in our cross-sectional study.

Design: A prospective, observational cohort study

Methods: All participants underwent an eleven-test cognitive battery and completed medical and social history surveys. Cognitive impairment was defined as *Z* scores falling ≥1.5 SD below the mean in ≥ 2 domains. Twelve participants underwent myelin water imaging. Neuroimaging data were compared to age and sex matched HIV-uninfected controls. Regression analyses were used to evaluate for risk factors of lower cognitive domain scores and association between myelin content and cognition in YApHIV.

Results: We enrolled 21 virally suppressed YApHIV across 2 sites in the United States. Ten participants (48%) met criteria for cognitive impairment. Participants with any non-HIV related medical comorbidity scored lower across multiple cognitive domains compared to participants without comorbidities. Myelin content did not differ between YApHIV and controls after adjusting for years of education. Lower cognitive scores were associated with lower myelin content in the cingulum and corticospinal tract in YApHIV participants after correcting for multiple comparisons.

Conclusions: Poor cognition in YApHIV may be exacerbated by non-HIV related comorbidities as noted in older adults with horizontally acquired HIV. The corticospinal tract and cingulum may be vulnerable to the legacy effect of untreated HIV in infancy. Myelin content may be a marker of cognitive reserve in YApHIV.

Key words: young adults, perinatal HIV, cognition, myelin, comorbodities

Introduction

Over 6 million young people under the age of 24 are living with perinatally-acquired HIV (pHIV) worldwide[1] including thousands of young adults in the United States[2]. An increase in the availability and efficacy of combination antiretroviral therapy (cART) has reduced AIDS related mortality. As a result, more youth living with pHIV are transitioning from adolescence to adulthood[3]. The neurologic consequences of chronic HIV infection are well-described among individuals who acquired HIV in adulthood, after peak maturation of brain development[4,5]. Much less is known about brain integrity among young adults with perinatally acquired HIV.

Working memory, processing speed, and executive function are commonly affected in children and adolescents with pHIV[6-11]. A few studies have documented similar findings in young adults living with pHIV compared to demographically similar HIV-uninfected controls in higher income countries[12-14]. These studies include primarily younger adults with a median age in their early 20s and although most participants were virally suppressed on cART, all published cohort studies have included virally unsuppressed participants as well. These study features complicate the generalizability of their cognitive findings for the growing cohort of adults in their late 20s and early 30s living with virally suppressed pHIV on cART.

Several cohort studies have demonstrated loss of white matter volume and integrity (i.e. decreased fractional anisotropy and increased diffusivity on diffusion tensor imaging (DTI)) in children and adolescents living with virally suppressed pHIV compared to demographically matched HIV-uninfected controls, suggesting widespread white matter injury[15-18].

Single cell RNA sequencing demonstrates activation of similar microglial populations in persons living with HIV and in those living with demyelinating conditions such as anti-myelin oligodendrocyte glycoprotein disorder and relapsing remitting multiple sclerosis, suggesting a common pathologic immune mediated demyelinating process between HIV and autoimmune demyelination conditions[19]. DTI metrics and volumetric analyses of T1, T2 or Fluid Attenuated Inversion Recovery MRI sequences provide limited information regarding the specific microstructural changes of this white matter injury and associated volume loss. An alternate approach, myelin water imaging (MWI), utilizes differential relaxation times of water trapped in the myelin bilayer compared to free water to quantify myelin content[20]. Myelin water fraction (MWF), the metric of myelin content obtained via MWI, has been histopathologically validated in vitro as a strong correlate of myelin content in multiple sclerosis[21]. Furthermore, MWF is sensitive to individual-level changes in myelin content in vivo across many neurologic conditions including multiple sclerosis, Alzheimer's disease, and cerebral small vessel ischemic disease[22].

In this study, we assess risk factors for cognitive impairment in a cohort of young adults with pHIV living with virally suppressed pHIV, compare myelin content in our cohort to historical HIV-uninfected age- and sex-matched controls, and determine associations between cognitive function and global and regional myelin content using myelin water imaging.

Methods

Study Design

In this cross-sectional study, participants were recruited for cognitive testing and neuroimaging at two sites in the United States: Seattle, WA (n=12) and New Haven, CT (n=9) between August 2018 and February 2023. Our sample size was determined by convenience sampling due to recruitment limitations for in-person studies related to the COVID-19 pandemic. The Institutional Review Boards of the University of Washington and Yale University approved the study; written informed consent was obtained from all participants.

Participants

Young adults, ages 18 years and over, with documented pHIV were eligible for the study if they had a minimum of 6 months on cART from local HIV clinics. Plasma HIV RNA > 400 copies/mL, given high rate of transient viral rebound in the young adult population living with perinatally acquired HIV despite adherence to cART[23], and recent history (<3 months) of neurologic infection or neurologic conditions unrelated to HIV, such as epilepsy, were exclusion criteria. For the MRI portion, additional exclusion

criteria included history of opportunistic CNS infection and safety exclusion criteria for MRI scan (e.g. metal implants, claustrophobia). Controls for the MWI portion consisted of 26 HIV-uninfected, healthy individuals included in a previous validation study at the University of British Columbia, who were age and sex matched to the participants with pHIV.

Clinical variables

Medical history was obtained through surveys and electronic health record review, including medical comorbidities and treatment status (i.e. non-cART medication use), and current cART regimen and adherence. Adherence was determined by participant self-report of missed dosing not exceeding more than two missed dose over the past week and confirmed with review of refill records for six month prior to the study visit. Substance use, smoking and alcohol use were assessed using the WHO Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST)[24] and the Alcohol Use Disorders Identification Test (AUDIT)[25]. Current substance use was defined as a minimum of weekly use in the past three months. Depressive and anxiety symptoms were quantified using Patient Health Questionnaire-9 (PHQ-9) and General Anxiety Disorder 7-item scale (GAD-7), respectively. Recommended cutoff scores were utilized to determine if study participants exhibited symptoms likely to be clinically relevant symptoms on each scale (scores of 5 and above for PHQ-9 and GAD-7)[26,27]. Vascular comorbidities included current smoker, hyperlipidemia, hypertension, and diabetes mellitus type 2. Prior history of AIDS was defined as prior report of a peripheral blood CD4+ T cell concentration < 200/ul or history of an opportunistic infection. Plasma HIV RNA concentration was measured using Abbott RealTime HIV-1 RNA assay on the day of the study visit. Detectable HIV RNA for this assay is set at >40 copies/mL.

Cognitive testing

A neuropsychological test battery that consisted of 11 tests was administered by trained study personnel. Tests included the Hopkins Verbal Learning Test – Revised (HVLT-R), Trail making A & B, Grooved Pegboard, Wechsler Adult Intelligence Scale (WAIS-3) Digit Symbol and Symbol Search subtests, F-A-S Verbal Fluency, Category Fluency, Stroop Interference Task, and the Time Gait Test. Tests performance scores were aggregated into domain scores as follows: language (category fluency), gross motor (timed gait), fine motor (grooved pegboard), verbal learning and memory (HVLT-R), processing speed (WAIS-III Digit Symbol and Symbol Search, Trials A), and executive function (Trials B, Letter Fluency, Stroop). *Z* scores were calculated by standardizing each raw score by age, sex, race, and years of education (as available for individual tests). The Wide Range Achievement Test (WRAT-4) Reading subtest was also administered and used to assess premorbid cognitive functioning, but it was not included in the final domain or global *Z*-scores. Cognitive impairment was defined as *Z* scores falling > 1.5 standard deviations below the normative mean in two or more domains[28]. We chose to apply the Gisslén criteria to define cognitive impairment as the Frascrati criteria may lead to misclassification of cognitively normal participants as impaired, particularly in a diverse population[29]. The neuropsychological assessment was administered on the same day as the MRI scan.

Neuroimaging analyses

MRI scans were performed on a single 3 Tesla Philips Ingenia Elition X. A 48-echo Gradient and Spin Echo acquisition sequence was collected for MWI (TR=1073ms, TE=8ms, acquired voxel size=1x1x5mm^3 with 20 slices, reconstructed voxel size=1x1x2.5mm^3 with 40 slices, SENSE factor=2) and a 3D T1 MPRAGE sequence was acquired for registration and segmentation (TR=7.56ms, TE=3.45ms, voxel size=1x1x1mm^3 with 208 slices)[30]. The multi-echo T2 relaxation data was analyzed using regularized non-negative least squares with the extended phase graph algorithm and stimulated echo correction to obtain a T_2 distribution for each voxel[31]. Myelin water fraction (MWF) was defined as the fraction of signal with T_2 relaxation times under 40 ms[32]. T_2 analysis was performed using in-house software code developed at the University of British Columbia (DECAES)[33].

Regions of Interest

For each participant, the 3DT1 image was registered to the first GRASE echo using FLIRT (FSL toolbox)[34,35]. FAST (FSL toolbox) was applied to the registered 3DT1 to segment white matter (WM), grey matter (GM) and CSF[36]. A threshold of 0.99 and a 2D erosion were applied to create a WM mask. Global WM and six WM regions (anterior and posterior corona radiata, corpus callosum, corticospinal tract, cingulum, and superior longitudinal fasciculus) were obtained from the John Hopkins University atlas registered to the 3DT1[37]. Mean MWF was quantified for global WM and each region of interest.

Statistical analyses

See Table 1 for descriptive statistics. We quantified associations between clinical factors, treated as binary, and cognitive domain Z scores treated as continuous, with linear regression models. To compare MWF between the pHIV participants and HIV-uninfected controls, we used linear regression models with HIV as a predictor and WM regions as responses using repeated analyses to adjust for the matching variables (age and sex) and years of education. To determine associations between MWF and cognitive domain scores, we used linear regression models with WM regions as predictors and Z scores as responses, both treated continuously. To aid in the interpretation of regression coefficients and comparison to prior published neuroimaging studies, we divided each WM region covariate by 0.02, so coefficient estimates correspond to a 0.02 unit difference in myelin water fraction. To control for multiple comparisons, we implemented the Storey's q-value method at a 5% false discovery rate[38]. To assess the association between cognitive impairment and MWF values, we used logistic regression. Statistical analyses were performed using R, version 4.2.1[39].

Results

Clinical characteristics

Demographic and clinical variables of the 21 participants are detailed in Table 1. Three participants started antiretroviral therapy in infancy, while the remainder started antiretroviral therapy in childhood

(ages 2 years and up). Three participants had detectable plasma HIV RNA above 40 copies/mL at the time of the study visit.

Cognitive outcomes

The gross motor domain was the most affected (mean z-score: -2.86), followed by the verbal learning and memory domain (mean z-score: -1.58) (Fig 1). Ten of the 21 participants (48%) met criteria for cognitive impairment. Clinical and demographic variables did not differ between the cognitively impaired and the cognitively normal subgroups.

Participants with one or more vascular comorbidity (current smoker, hyperlipidemia, hypertension, or diabetes) had lower language (p=0.03) and global (p=0.04) *Z*-scores than participants without vascular comorbidities. Participants with any non-HIV related medical comorbidity had lower cognitive scores in language (p=0.02), verbal memory (p=0.02) and executive function (p=0.02) domains compared to those who did not have a non-HIV related medical comorbidity. Participants who used substances had lower scores in the language domain (p=0.04). In contrast, those who screened positive for depression and/or anxiety on symptom scales or who had a prior history of AIDS did not have poorer cognitive scores in our cohort (Table 2).

Neuroimaging markers

Twelve participants completed the MRI portion of the study. Years of education differed between participants and controls who completed the MRI (pHIV participants: 12.6 years vs HIV-uninfected controls: 17.5 years, p<0.001). MWF values between participants compared to controls did not retain significance after adjusting for years of education (Table 3).

Myelin content and cognition

Participants with lower verbal memory scores had decreased myelin water fraction (MWF) in the cingulum (mean difference (95% CI): 0.78 (0.40, 1.16), p<0.05) and participants with lower executive function scores had decreased MWF in the corticospinal tract (mean difference (95% CI): 0.45 (0.23, 0.67), p<0.05) after correcting for multiple comparisons. There were no differences in regional or global MWF values between cognitively impaired or cognitively normal participants.

Discussion

Our findings demonstrate that approximately half of our young adult participants living with virally suppressed pHIV meet criteria for cognitive impairment, demonstrating low scores in the gross motor and verbal memory domains. These deficits may be partially explained by non-HIV related medical comorbidities in addition to the legacy effect of chronic HIV. We also show significant association between regional myelin content and cognition in our cohort. Our findings of lower scores in motor and verbal memory domains are similar to prior published studies of cognition in older adolescents and young

adults living with pHIV[13,14]. One longitudinal study suggested that individuals living with pHIV are at increased risk of developing cognitive deficits after four years of follow-up when compared to demographically similar HIV-uninfected controls suggesting an increasing risk of cognitive impairment with aging into adulthood[40]. In contrast, the US-based Pediatric HIV/AIDS Cohort Study found no differences between young adults living with pHIV and age and sex matched peers who were HIV exposed in utero but uninfected (HEU)[12]. Of note, both the pHIV and HEU young adult subgroups scored lower than age, sex and race adjusted normative means in the working memory and processing speed domains alluding to the fact that external factors may influence cognition in youth affected by HIV and outweigh the influence of HIV directly on cognition in young adults living with HIV.

We utilized the Gisslen criteria of cognitive Z-scores falling 1.5 or more standard deviations below the normative mean in 2 or more domains to define cognitive impairment and identified that 48% of our cohort met criteria for cognitive impairment. Another cohort study applied the Frascrati criteria to identify cognitive impairment in young adults living with pHIV and found rates as high as 83%[14], potentially indicating a higher risk for development of cognitive impairment in young adults living with pHIV, despite adequate viral control on cART, as they age into older adulthood[41]. Participants with any concurrent medical comorbidity, including vascular risk factors and active substance use, had lower cognitive scores compared to those without medical comorbidities. These findings mirror results from the CHARTER study focused on older adults aging with HIV, which demonstrated a higher risk of cognitive decline in individuals living with HIV who experienced comorbid conditions and substance use that was independent of age and cART use[42]. Studies in children with pHIV in Thailand and Zambia have found an association between systemic markers of poor health, such as low hematocrit, and history of malnutrition and lower longitudinal cognitive scores compared to youth with pHIV without these conditions suggesting a strong association between overall health and cognition in individual living with pHIV[43,44]. Importantly, many of these factors are modifiable and may guide clinical care to focus on ameliorating the effects of medical comorbidities in young adults living with virally suppressed HIV to preserve cognitive function.

Myelin water fraction values in the corticospinal tract and cingulum directly correlated with verbal memory and executive function scores in our cohort of young adults living with pHIV. The corticospinal tract is responsible for motor function[45], and the posterior region of the cingulum has been linked to verbal memory[46]. These two cognitive domains were the most affected in our cohort suggesting that the corticospinal tract and cingulum may be particularly vulnerable to the legacy effect of untreated HIV in infancy. The Children with HIV Early Antiretroviral (CHER) trial also identified these white matter tracts as key regions affected in children living with virally suppressed pHIV on cART when compared to HIV-uninfected matched controls using diffusion tensor imaging[47]. These data suggest that the corticospinal tract and the cingulum may be the white matter regions most susceptible to injury related to chronic HIV infection during development.

Though our data support the hypothesis that that myelin content a key substrate of cognitive performance in young adults living with pHIV, differences in regional myelin water fraction values between our cohort of young adults with pHIV and HIV-uninfected controls lost significance after adjusting for years of

education demonstrating the strong influence of education on myelin content. Prior published studies in pediatric cohorts have linked better academic performance to higher myelin water fraction values and this correlation is mitigated by environmental influences such as maternal education and socioeconomic status[48,49]. Myelin content as measured by myelin water fraction, therefore, may be an imaging metric of cognitive reserve. Higher cognitive reserve has been linked to cognitive resilience in many neurologic conditions including HIV[50].

While our study is one of the first to utilize myelin water imaging to assess myelin content in persons living with HIV, a few limitations merit discussion. Our sample size is small, particularly for those who completed neuroimaging, which may have led to insufficient power to detect differences after correcting for multiple comparisons and limits the generalizability of our results. Importantly, we do not have data on prenatal and early life events known to influence development in our cohort. Our control group is not matched for years of education limiting our interpretation of myelin content differences related to HIV. Cross-sectional analyses do not allow us to draw causal relationships between HIV exposure, myelin content, and cognition.

With the limitations above noted, the results from the current study identify cognitive difficulties in a large percentage of young adults living with pHIV that may be exacerbated by non-HIV related comorbidities, including vascular disease and substance use, as seen in older adults with horizontally acquired HIV[42]. We also identify a relationship between myelin content and cognition, suggesting that reduced myelin content may be a neuroimaging marker of cognitive impairment in young adults living with pHIV. Improved understanding of the relationship between change in myelin content and cognitive decline in the setting of chronic, virally suppressed HIV infection, independent of comorbidities and compared to sociodemographic matched controls, may provide opportunities for adjunctive therapies to preserve myelin content and improve cognition in persons living with HIV.

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Figure 1. Cognitive z-scores by domain and global (average) z-scores. Bars represent the maximum and minimum scores.

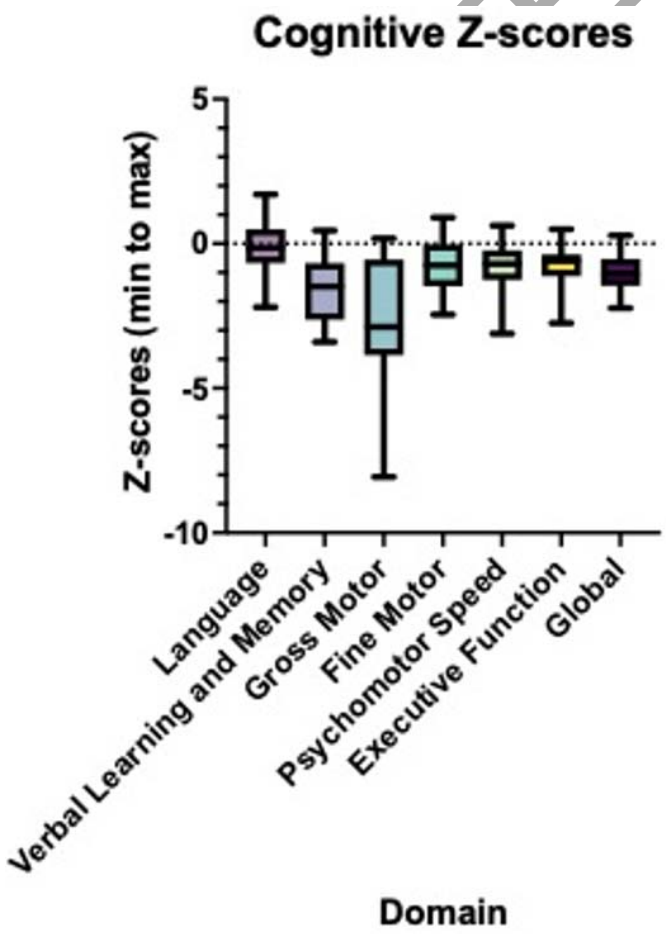

Table 1. Baseline characteristics

		N=21
Age (years)	mean (SD)	27.3 (5.5)
	median (IQR)	26.0 (23.0, 33.0)
	min, max	18.0, 36.0
Female	n (%)	13 (61.9)
Male	n (%)	8 (38.1)
Race		
Black	n (%)	13 (61.9)
White	n (%)	5 (23.8)
Multiracial	n (%)	1 (4.8)
Unknown	n (%)	2 (9.5)
Ethnicity		
Non-Hispanic	n (%)	19 (90.5)
Hispanic	n (%)	2 (9.5)
Education level (years)	mean (SD)	12.7 (1.7)
	median (IQR)	12.0 (12.0, 13.0)
	min, max	11.0, 18.0
Current Smoker	n (%)	6 (30.0)
Current Marijuana user	n (%)	11 (55.0)
Current Illicit substance use (sedatives, hallucinogens, methamphetamine)	n (%)	3 (14.3)
Missing substance use history	n (%)	1 (4.8)
Screened positive for harmful alcohol use On An	n (%)	1 (4.8)
Missing alcohol use history	n (%)	2 (9.5)
Screened positive for depression on PHQ-9	n (%)	6 (30.0)
Screened positive for anxiety on GAD-7	n (%)	5 (25.0)
Any vascular comorbidities	n (%)	9 (42.9)
Current Smoker	n (%)	6 (30)
Hyperlipidemia	n (%)	2 (9.5)
Hypertension	n (%)	2 (9.5)
Any medical comorbidities, other than HIV	n (%)	8 (38.1)
Hyperlipidemia	n(%)	2 (9.5)
Hypertension	n(%)	2 (9.5)
Thyroid disease	n(%)	2 (9.5)
Hepatitis B	n(%)	1 (4.8)
Hepatitis C	n(%)	1 (4.8)
Asthma	n(%)	1 (4.8)
Obesity	n(%)	1 (4.8)

Juvenile Arthritis	n(%)	1 (4.8)
Plasma HIV RNA undetectable (<40 copies/mL)	n (%)	18 (85.7)
Plasma HIV RNA detectable (>40 copies/mL)	n (%)	3 (14.3)
	Range (copies/mL)	47.6 - 222
CD4 count	Average (cells/mm^3) Range (cells/mm^3)	656 60 - 1119
History of CD4 count < 200	n (%)	7 (33.3)
History of opportunistic infections	n (%)	9 (42.8)

Table 2. Cognitive z-scores, mean (SD) of subgroups by clinical risk factors

	History of AIDS		Vascular comorbidities		Comorbidities	
	Yes	No	Any	None	Any	None
Language	-0.42 (1.41)	0.05 (0.69)	-0.71 (1.22)*	0.29 (0.70)*	-0.80 (0.98)*	0.27 (0.93)*
Verbal memory	-1.63 (1.29)	-1.54 (1.06)	-1.86 (1.24)	-1.37 (1.05)	-2.30 (0.81)*	-1.14 (1.10)*
Gross motor	-2.43 (1.33)	-3.06 (2.75)	-3.34 (2.61)	-2.49 (2.09)	-2.42 (1.73)	-3.02 (2.55)
Fine motor	-0.50 (1.02)	-0.92 (0.95)	-1.12 (1.12)	-0.46 (0.79)	-0.99 (1.02)	-0.59 (0.96)
Psychomotor speed	-0.65 (0.83)	-0.81 (0.95)	-1.03 (0.51)	-0.52 (1.05)	-0.98 (0.78)	-0.59 (0.93)
Executive function	-0.79 (1.17)	-0.44 (0.58)	-0.89 (1.11)	-0.36 (0.59)	-1.12 (1.01)*	-0.26 (0.60)*
Global	-1.05 (0.72)	-1.12 (0.67)	-1.44 (0.61)*	-0.83 (0.62)*	-1.41 (0.51)	-0.90 (0.71)

	Substance use		Depression or anxiety	
	Yes	No	Yes	No
Language	-1.30 (1.01)*	0.04 (0.97)*	-0.09 (1.31)	-0.21 (0.94)
Verbal memory	-2.10 (0.66)	-1.49 (1.19)	-0.96 (0.99)	-1.96 (1.08)
Gross motor	-3.87 (0.60)	-2.68 (2.38)	-2.49 (1.57)	-3.02 (2.68)

Fine motor	-1.12 (1.59)	-0.68 (0.89)	-0.52 (0.93)	-0.88 (1.02)
Psychomotor speed	-1.13 (0.40)	-0.68 (0.93)	-0.52 (0.62)	-0.87 (1.01)
Executive function	-0.79 (0.63)	-0.56 (0.92)	-0.26 (0.61)	-0.79 (0.97)

*p<0.05

Table 3. Mean (standard deviation) regional myelin water fraction values for the two samples.

	HIV	Control		
	N=12	N=26	p-value*	Adjusted p-value**
Region of interest				
WM	0.10 (0.02)	0.11 (0.01)	0.52	0.45
ACR	0.08 (0.02)	0.08 (0.01)	0.20	0.54
CC	0.11 (0.02)	0.12 (0.01)	0.08	0.77
CNG	0.06 (0.02)	0.08 (0.02)	0.01	0.98
CST	0.19 (0.02)	0.21 (0.01)	<0.01	0.49
PCR	0.11 (0.02)	0.11 (0.01)	0.77	0.80
SLF	0.13 (0.02)	0.13 (0.01)	0.98	0.22

WM: Global White Matter, ACR: Anterior Corona Radiata, CC: Corpus Callosum, CNG: Cingulum, CST: Corticospinal Tract, PCR: Posterior Corona Radiata, SLF: Superior Longitudinal Fasciculus

*p-value adjusted for age and sex

**adjusted p-value including education level along with age and sex