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BACKGROUND

Neurodevelopmental impairment is common in children with perinatally acquired HIV (pHIV), occurring in approximately half of children and adolescents living with pHIV^{1,2}. Little is known about the cognitive profile of adults with virally suppressed perinatally acquired HIV (pHIV). Additionally, the mechanism behind neurologic injury in pHIV is poorly understood. Conventional and diffusion tensor imaging have demonstrated diffuse structural white matter changes in children with pHIV^{3,4}, but the microstructural pathology occurring in white matter tracts of individuals with pHIV remains unknown. Myelin water imaging (MWI), a novel imaging modality, quantifies myelin content using differences in relaxation times of water contained in the myelin bilayer and total water diffusion⁵. MWI has been pathologically validated in patients with multiple sclerosis (MS) who display decreased myelin water fraction, a metric of myelin content obtained using MWI⁶. Additionally, a decrease in myelin water fraction correlates with poor cognition in patients with MS to a greater extent than quantitative measures of white matter lesions found on conventional brain imaging sequences⁷. To date, this imaging modality has not been assessed in persons living with HIV. Here, we define the cognitive profile of virally suppressed adults with pHIV and demonstrate the association between myelin water fraction (MWF), a metric of myelin content obtained through MWI, and cognition in our cohort of adults living with virally suppressed perinatally acquired HIV (pHIV).

METHODS

Seventeen adults with pHIV (ages 21-36 years, 11 Female and 6 Male), virally suppressed on antiretroviral therapy (ART), underwent an 11-test cognitive battery covering seven domains. Raw scores were adjusted for age, education, sex, and race/ethnicity. Domain specific z-scores were determined using normative data. Cognitive impairment was defined as >1.5 standard deviations below the normative mean in 2 or more domains. Eight participants underwent MWI. A Gradient and Spin Echo acquisition sequence was used for MWI data processing. We calculated voxel-wise T2 distributions with a non-negative least squares fitting and flip angle optimization in MATLAB. Voxel-wise MWF was calculated by summing T2 amplitudes between 15-40 milliseconds and dividing by the sum of all T2 amplitudes (Figure 1). Global and frontal lobe MWF means were assessed, and these data were compared to 16 historical age and sex matched uninfected controls. Correlations were assessed using Spearman rank correlation coefficient.

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Gross motor impairment is common in virally suppressed adults living with perinatally acquired HIV (pHIV) on ART (Figure 2). Myelin water fraction (MWF) is a magnetic resonance imaging metric, which quantifies myelin content using differences in relaxation times between water trapped within the myelin bilayer and free water. Global and regional reduced MWF is seen in adults living with pHIV compared to age and sex matched uninfected controls (Figure 3). Reduced global MWF correlates with lower executive function scores in adults living with pHIV (Figure 4).

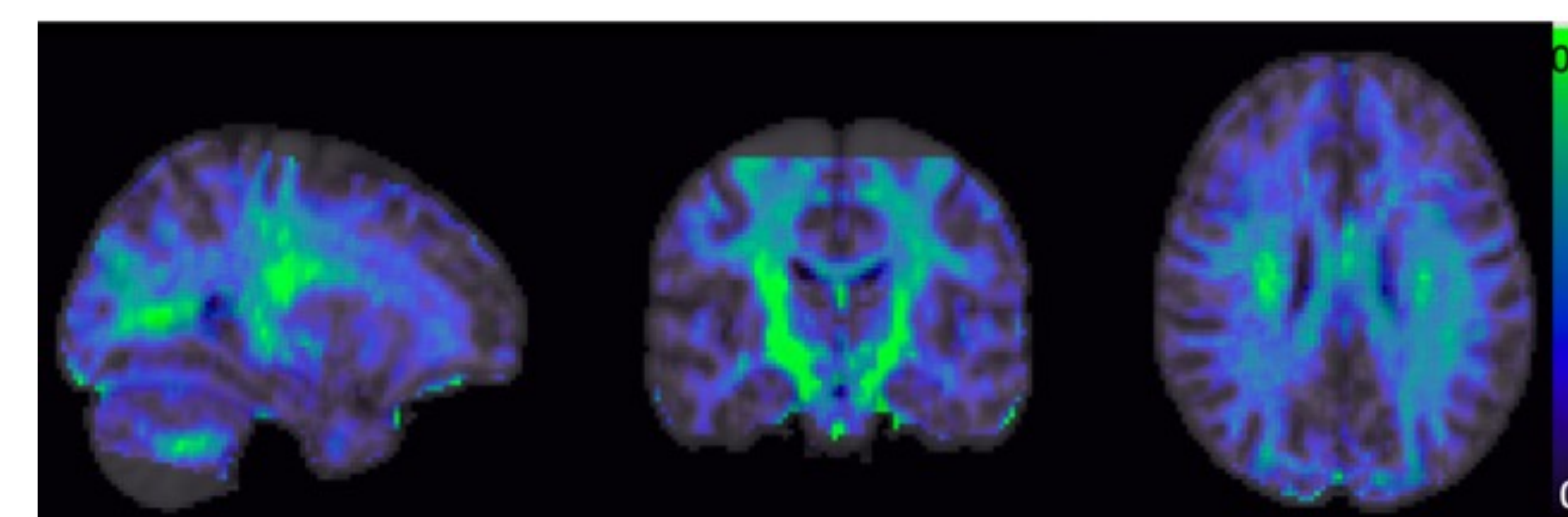


Figure 1. Myelin water fraction (MWF) map of one representative participant overlaid on standard 2mm Montreal Neurological Institute space template. Regions in blue represent areas with relatively low MWF and regions in green represent areas of relatively high MWF.

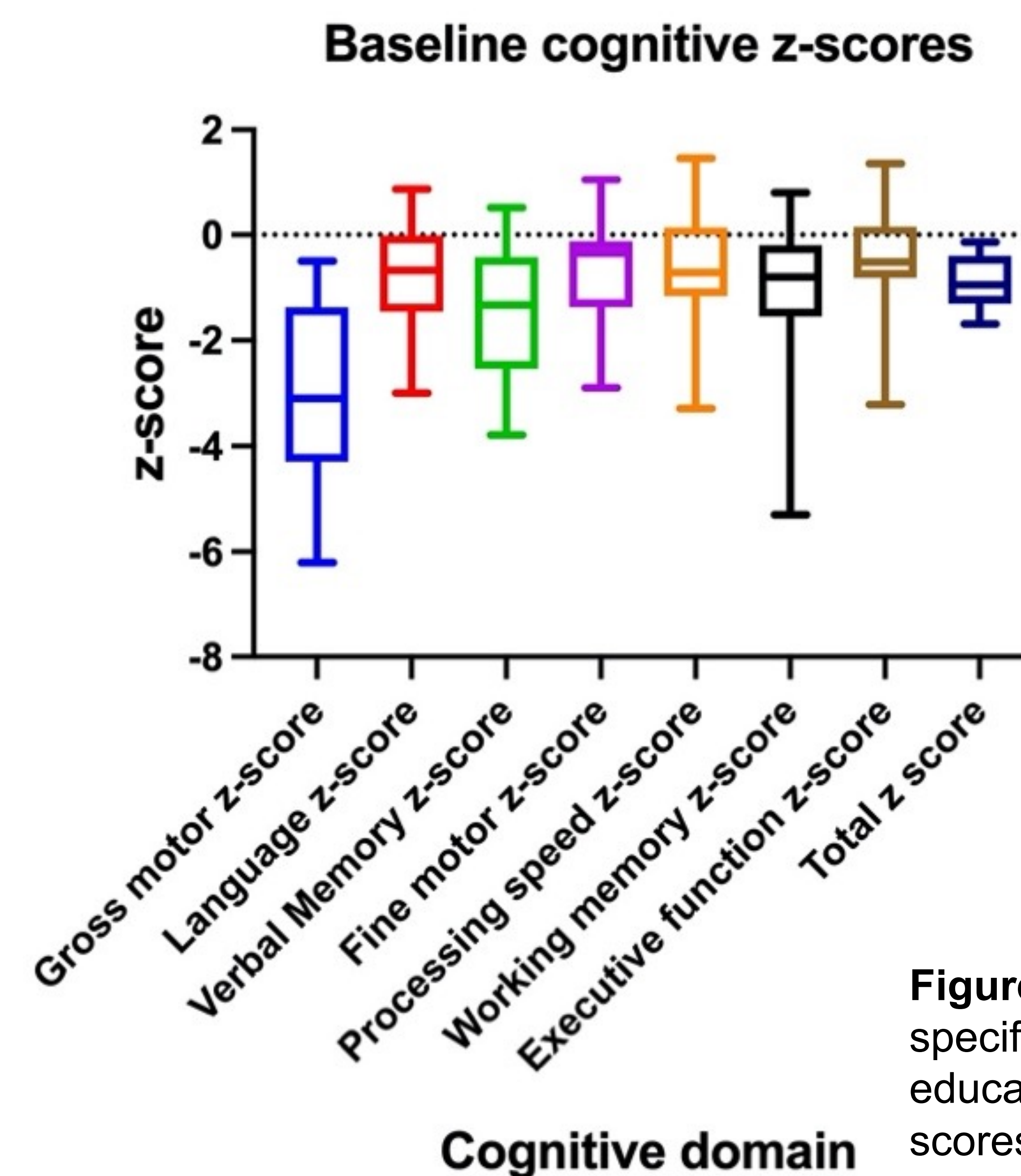


Figure 2. Baseline standardized cognitive z-scores, domain specific and total z-score. Scores are adjusted for age, sex, education level, and race/ethnicity as appropriate. Lowest scores occur in the gross motor domain (average z-score: -2.9).

RESULTS

Participants with pHIV differed in education level completed compared to our age and sex matched historical controls (12.6 years vs 17.5 years, $p < 0.001$). Ten (58%) adults living with pHIV were cognitively impaired with the lowest scores in the gross motor (average z-score: -2.9) and verbal memory (average z-score: -1.5) domains (Figure 2). Global and frontal lobe MWF were lower in the pHIV cohort compared to matched uninfected controls (mean global and frontal MWF: pHIV: 0.071, 0.051; controls: 0.095, 0.081; $p < 0.0001$) (Figure 3). Lower global MWF correlated with worse performance in the executive function domain in adults living with pHIV (Spearman r : 0.762, p : 0.037) (Figure 4).

CONCLUSIONS

Cognitive impairment is common among our cohort of adults living with virally suppressed pHIV, particularly in the gross motor domain. This may be due to a legacy effect on motor development as individuals in this cohort were born during a period when access to ART was limited. Our pilot imaging data suggest that decreased axonal myelination may occur in individuals living with virally suppressed pHIV on ART. Given the strong correlation between MWF and executive function scores, this reduction in myelination may be a pathologic substrate of pHIV-related cognitive impairment. MWF may be a relevant biomarker for clinical prognostication and therapeutic trials in HIV-related cognitive impairment. Future studies will evaluate longitudinal changes in MWF in young persons living with HIV compared to demographically matched controls, particularly matching for education level as this variable is a known predictor of MWF.

Myelin Water Fraction Values for HIV+ and HIV- groups

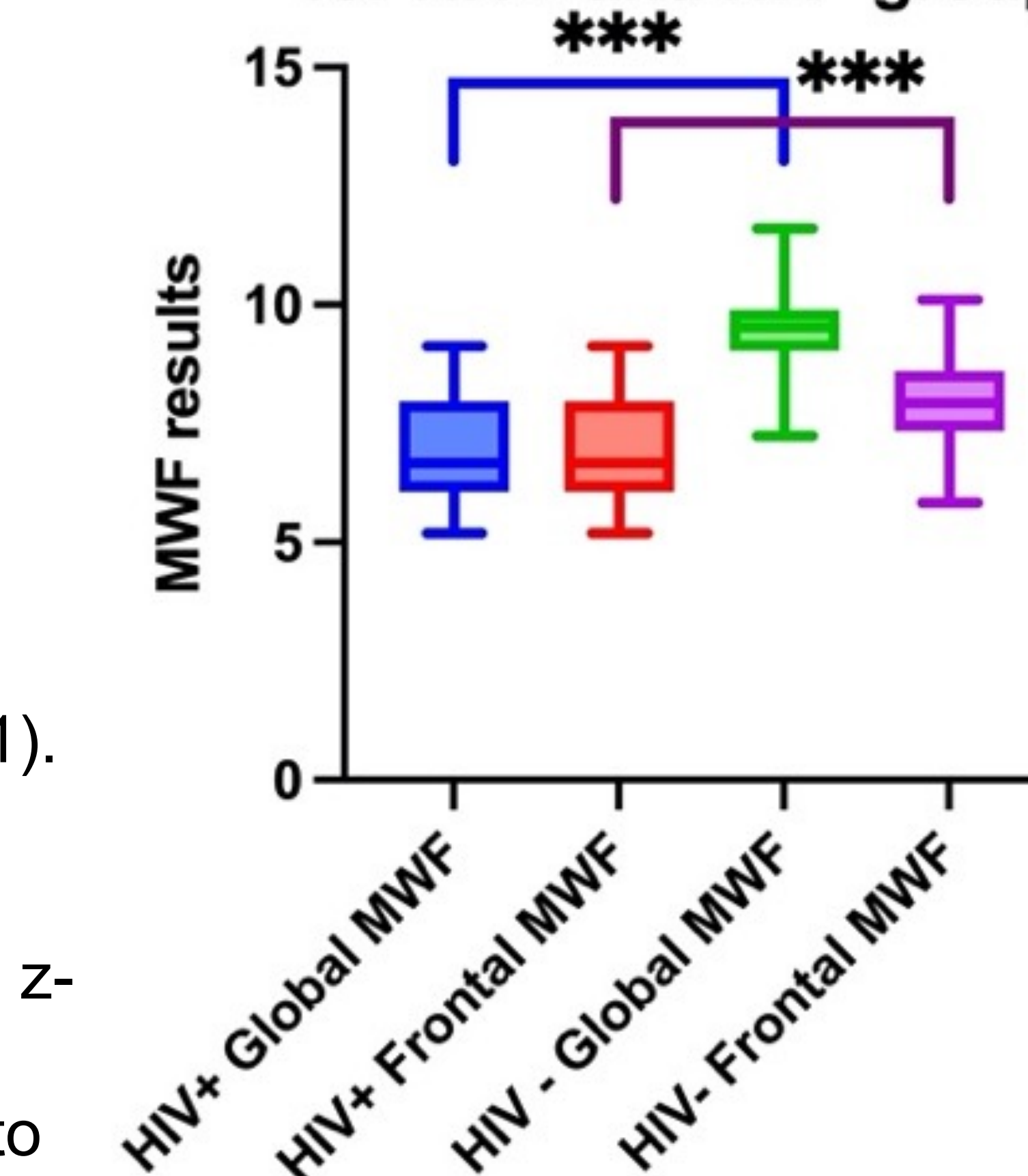


Figure 3. Global and frontal lobe myelin water fraction (MWF) values between perinatal HIV+ group and sex and age matched controls. Significant differences were found in regional and global MWF values between groups ($p < 0.001$).

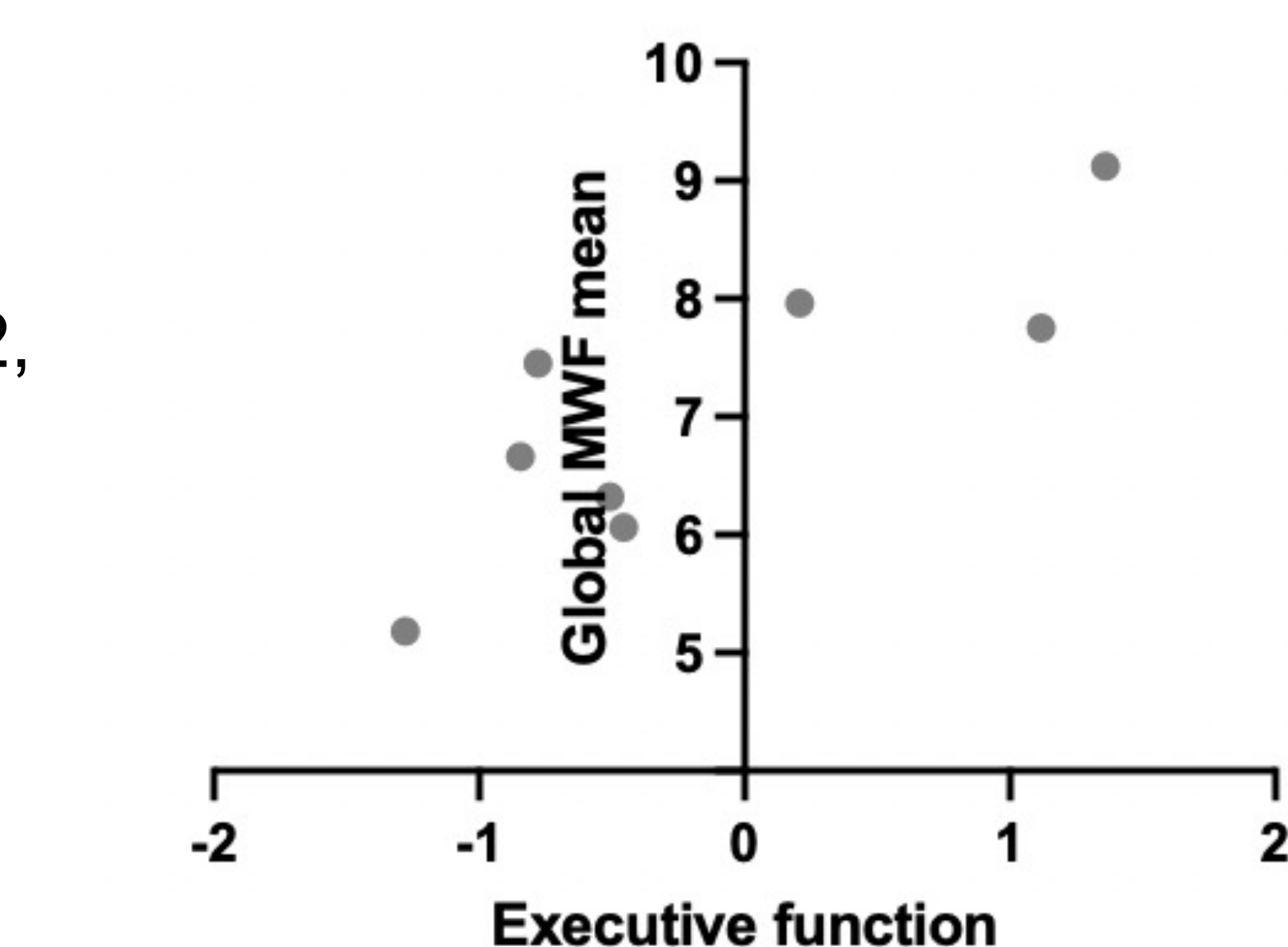


Figure 4. Correlation matrix of global myelin water fraction and executive function z-scores in our cohort of adults living with well-controlled perinatally acquired HIV ($p=0.037$).