

Characteristics of Brain Structure in HIV Male Patients with Syphilis Co-Infection: A Cross-Sectional Study.

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Keywords: HIV, Syphilis, White matter, Diffusion tensor imaging

Posted Date: February 15th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-155540/v1>

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Abstract

Background To investigate the effect of syphilis infection on the microstructure of white matter (WM) in HIV-infected male patients through comparing the differences of WM between HIV-infected male patients with and without syphilitic infection using diffusion tensor imaging (DTI).

Methods 27 HIV-infected male patients with current syphilis or a history of syphilis (HIV+/syphilis+) and 29 HIV-infected male patients without syphilis co-infection history (HIV+/syphilis-) were enrolled. All patients received DTI and comprehensive neuropsychological assessment. Clinical data were compared between the two groups with T-test, Mann-Whitney U Test and Chi-square Test. Tract-based spatial statistics (TBSS) was adopted to analyze the DTI metrics. Multiple linear regression analysis was conducted to investigate the relationships between DTI metrics and clinical variables and cognitive performance.

Results In the HIV+/syphilis+ group, decreased AD was found in the right superior corona radiata (SCR-R) and body of corpus callosum (BCC); increased RD was found in the bilateral posterior corona radiata (PCR), the right posterior thalamic radiation (PTR-R), the left SCR (SCR-L), splenium of corpus callosum (SCC) and BCC; decreased FA was found in multiple regions. AD in BCC was negatively correlated with CD4/CD8 ratios. AD in SCR-R was positively correlated with CD4/CD8 ratios. Patients in HIV+/syphilis+ group had a lower score in complex motor skills (CMS). RD in SCC and SCR-L was negatively correlated with CMS; RD in PTR-R was positively correlated with CMS. AD in SCR-R was positively correlated with CMS.

Conclusions Compared with patients simply infected with HIV, the integrity of WM is more seriously impaired in HIV-infected patients with syphilis co-infection, and it may accelerate the impairment of cognitive function.

1. Background

When the human immunodeficiency virus (HIV) enters the human body, it can invade and destroy the immune system, and can also invade the central nervous system (CNS) at an early stage of infection. One study showed that viral RNA could be detected in the cerebrospinal fluid (CSF) of infected person within as early as eight days of HIV infection^[1]. After invaded, the astrocytes, microglia, oligodendrocytes and other cells can be destroyed by the virus^[2], causing some changes in the microstructure of white matter (WM). Sustained damage caused by HIV can lead to multiple cognitive impairments in patients known as HIV-related neurocognitive disorders (HAND). HAND is classified into three levels according to severity: asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorder (MND) and HIV-associated dementia (HAD)^[3-4]. With the widespread use of antiretroviral therapy (ART), the ratio of MND and HAD decreased while the ratio of ANI increased^[5]. Although the rate of the neurocognitive decline is slow, if the treatment is neglected or not properly controlled, ANI eventually deteriorates into MND and

even into HAD^[6]. Therefore, it is of significance to paying attention to the neurocognitive function of HIV-infected patients.

In recent years, the incidence of syphilis in some European regions has increased^[7-8], which mainly occurs in men who have sex with men (MSM)^[9]. Syphilis, caused by the spirochaete bacterium *Treponema pallidum* has the same group of patients with HIV, the incidence of syphilis in HIV-infected patients is 77 times greater than in the general population^[10-11]. There may be a cooperative relationship between syphilis and HIV: syphilis had a negative impact on the CD4+T cell counts in HIV-positive patients, regardless of treatment^[12]. HIV-infected patients with CD4+T counts <350 μ L were more likely to acquire neurosyphilis^[13], and when immune system is seriously impaired, neurosyphilis tends to progress^[14]. Syphilis co-infection may cause neurocognitive impairment. A study showed that patients with prior syphilis had a greater number of impaired NP test domains and more impaired in the NP learning domain compared with HIV-infected patients without a history of syphilis^[15]; another study showed HIV infected subjects with a history of syphilis had a poor performance in the cognitive domains of memory and learning^[16]. However, the mechanism of cognitive impairment caused by syphilis and HIV co-infection remains unclear. Some scholars believe that increased HIV viral load in CSF of syphilis and HIV co-infection patients may be related to impaired neurocognitive function^[14,17].

The damage of microstructure in WM can reflect the change of cognitive function to some extent. Diffusion tensor imaging (DTI) can reflect the diffusion characteristics of water molecules in WM, and it is extremely sensitive to changes in the microstructure of WM. There are four parameters for DTI: fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD). FA is related to the integrity of the WM, decreased FA indicates that the integrity of WM is impaired^[18-20]. MD can reflect the diffusion rate of water molecules. Decreased FA and increased MD mean the damage of neuronal fiber bundles^[21]. AD reflects the condition of axonal damage, decreased AD indicates acute axonal injury while increased AD suggests chronic axonal injury^[22]. Increased RD indicates the absence of myelin sheath and reflects demyelination^[23]. Several studies have investigated the relationship between the damage to WM and cognitive impairment in HIV-infected patients. Chang^[24] found that for antiretroviral-stable HIV patients, the decline in the global deficit score was related to the increased MD in the genu of callosum and decreased FA in the parietal and frontal WM and putamen. Cysique^[25] studied the HIV-infected patients who were clinically stable with successful viral control and showed that compared to both control group and ANI patients, patients with MND or HAD had lower FA values in cingulum and fornix, higher MD values in the fornix and external capsule. Li^[26] found increased AD and MD in periventricular WM in untreated ANI patients through comparing them with normal controls, the result suggested that the cause of microstructure damage in untreated HIV patients with ANI was axonal injury rather than demyelination.

However, There was no study on the characteristics of its microstructure changes in WM of patients with syphilis and HIV co-infection at present. The incidence of syphilis and HIV co-infection is higher in

males^[27-29], so this study aims to investigate the effect of syphilis infection on the microstructure of WM in HIV-infected male patients through comparing the differences of WM between HIV-infected male patients with and without syphilitic infection. We hypothesized that the degree of damage of microstructure in WM in HIV-infected male patients with syphilis was more severe than in HIV-infected male patients without syphilis. And this study may help us understand the mechanism of cognitive decline in patients with HIV and syphilis co-infection.

2. Methods

2.1 Participant selection

Between June 2015 to June 2017, 27 HIV-infected male patients with current syphilis or a history of syphilis (HIV+/syphilis+) and 29 HIV-infected male patients without syphilis co-infection history (HIV+/syphilis-) were enrolled in this study. This study was conducted in accordance with the guidelines of the Declaration of Helsinki and was approved by the ethics committee of Beijing Youan Hospital, Capital Medical University and informed consent was obtained from all patients or their relatives (guardians). The inclusion criteria were as follows: (1) Patients with HIV was diagnosed by an enzyme-linked immunosorbent assay and western blot analysis; (2) Patients recieved T pallidum particle agglutination (TP-PA) and the Rapid Plasma Reagin (RPR); (3) Male; (4) Age had to be from 18 to 50 years; (5) Patients underwent a comprehensive neuropsychological assessment and had complete clinical and imaging data. The exclusion criteria were as follows: (1) HIV/AIDS patients transmitted by drug abuse or mother-to-child vertical transmission; (2) Anxiety, depression, alcoholism, stimulant use, drug side effects, metabolic encephalopathy, vitamin B12 deficiency and drug interaction; (3) Central nervous system diseases: tumors, cerebrovascular diseases and other visible diseases on MRI (T1WI and T2-fluid attenuated inversion recovery (FLAIR)); (4) Patients with MR contraindications: pacemakers, defibrillators, implanted electronic systems, vascular clips, mechanical heart valves or cochlear implants; (5) Patients with a sudden onset of illness.

To assess the cognitive status, all patients underwent a comprehensive neuropsychological assessment which included six cognitive domains. The neurocognitive evaluation surveys contained: fine motor skills(Grooved Pegboard Test), information processing speed (Trail Marking Test A, TMT-A), memory(Hopkins Verbal Learning Test, HVLT-R; Brief Visuospatial Memory Test, BVM-T-R), abstraction and executive function (Wisconsin Card Sorting Tests, WCST-64), attention and working memory (Continuous Performance Test-Identical Pair, CPT-IP; Wechsler Memory Scale, WMS-III; Paced Auditory Serial Addition Test, PASAT) and verbal/language (Animal Verbal Fluency Test, AFT). Raw scores for each test is converted to T-scores, which is adjusted for age, and education level. T-scores on over one test for one cognitive domain were averaged to get a mean T-scores.

Clinical and demographic data including age, duration of infection, CD4 count, the CD4/CD8 ratios, treatment condition and HIV viral load were collected. The duration of HIV infection was described by the

patient's own account. The recent CD4+ counts and the CD4/CD8 ratios were collected within 2 weeks of the MRI.

All HIV-infected patients received TP-PA and RPR to diagnose the current status of syphilis infection or a history of syphilis. All the patients with current syphilis infection or a history of syphilis were administered with penicillin during diagnosis.

2.2 MRI data acquisition

All patients received MRI scanning using a Siemens Trio 3.0 Tesla scanner. Standard structural imaging were collected using axial T1WI and T2-FLAIR combined fat saturation. DTI data was acquired using a single-shot echo planar imaging sequence. Scanning parameters for T2-FLAIR combined fat saturation: TR=8000ms, TE=2370.9ms, inversion time=97ms, phase encoding directions was AP. Scanning parameters for T1WI: TR=250ms, TE=2.46ms, flip angle=9°, field of vision=256×224, acquisition matrix=256×256, section thickness=1mm, section number=176, phase encoding directions was AP. Scanning parameters for DTI: TR=3300ms, TE=90ms, slice thickness=4mm with 1.2mm gap, number of slices=63, matrix size=128×128, field of view=230×230, number of excitations=3, space resolution=1.8mm×1.8mm×1.8mm, total acquisition time=3.39min, phase encoding directions was AP. Diffusion sensitizing gradients were applied along 20 non-collinear directions with $b=1000\text{s/mm}^2$, and $b=0\text{s/mm}^2$.

2.3 MRI data processing

DTI data were processed using FSL5.0.9(<http://neuro.debian.net/>). There were three steps for data pre-processing. Firstly, eddy current correction with FDT diffusion module was adopted to eliminate head movement and deformation caused by head movement and eddy current during scanning. Secondly, brain mask image was performed using the Brain Extraction Tool, the fractional intensity threshold was 0.2. Finally, the tensor were calculated using the function of DTIFIT with FDT diffusion module in FSL, and the four parameters: FA, MD, AD and RD were obtained. There were four steps for tract-based spatial statistics (TBSS) processing. Firstly, all subjects' FA is registered to a target brain image template (FMRIB58_FA) using nonlinear registration criteria. Secondly, the mean of all FA images was skeletonized to generate a mean FA skeleton image. Then skeletonized FA map of all subjects were constructed by projecting all FA data onto the mean FA skeleton image. The skeletonized maps of other parameters (MD, AD and RD) were obtained similarly. Finally, the skeleton-based statistical analysis was conducted for the four parameters.

2.4 Statistical analysis

Analysis was conducted with IBM SPSS Statistics25.0. All normally distributed variables were reported as mean \pm SD, while non-normally distributed variables were reported as median (25th-75th percentile). T-test was conducted for normally distributed data and Mann-Whitney U Test was conducted for non-normally

distributed data. Chi-square Test was conducted for categorical data. $P < 0.05$ was considered statistically significant.

For TBSS analysis, voxel-wise statistics of the four DTI parameters (FA, MD, AD and RD) between the two groups were compared using general linear model (GLM) module in FSL. Then, randomise in FSL is adopted to conduct the displacement test (5000 random permutations). The threshold-free cluster enhancement (TFCE) approach was adopted for multiple comparison correction. All the results were considered significant with a family-wise error (FWE) correction at the level $p < 0.05$. The Johns Hopkins University (JHU)-ICBM-DTI-81 WM Label Atlas was adopted to identify the differences in white matter fibers.

Multiple linear regression analysis was conducted to investigate the relationships between DTI metrics and clinical variables and cognitive performance.

3. Results

3.1 Clinical and demographic data

This study enrolled 27 HIV+/syphilis+ male patients, 29 HIV+/syphilis- male patients. The clinical and demographic data were listed in Table 1. In our study, there were two kinds of patients in HIV+/syphilis+ group: 11 patients had a history of primary syphilis and 16 patients were diagnosed as primary syphilis. There were no significant differences in age, CD4 count, CD4/CD8 ratios, duration of infection treatment conditions or ratio of target not detected (TND) of HIV viral load.

3.2 Neuropsychological data between the group of HIV+/syphilis+ and HIV+/syphilis-

Table 2 showed the differences in neuropsychological assessment between the group of HIV+/syphilis+ and HIV+/syphilis-. There were no significant differences in verbal fluency (VF), attention/working memory (A/WM), executive function (EF), memory (learning/delayed recall, LDR) and speed of information processing (SIP). But there was significant differences in complex motor skills (CMS) ($p = 0.009$).

3.3 TBSS results

All patients enrolled in this study had finished MRI scanning. After confounding variables, there were no significant differences in MD between HIV+/Syphilis+ group and HIV+/syphilis- group.

Compared with HIV+/syphilis- group, there was a decrease in FA in multiple areas in the HIV+/syphilis+ group: the bilateral anterior corona radiata (ACR), superior corona radiata (SCR), posterior corona radiata (PCR), posterior thalamic radiation (PTR), superior longitudinal fasciculus (SLF), corticospinal tract (CST), anterior limb of internal capsule (ALIC), posterior limb of internal capsule (PLIC), retrolenticular part of internal capsule (RLIC), external capsule (EC), cingulate gyrus (CGC), cerebral peduncle (CP), sagittal

stratum (SS), the left fornix/Stria terminalis (FX/ST), genu of corpus callosum (GCC), body of corpus callosum (BCC) and splenium of corpus callosum (SCC) (Fig. 1).

Compared with HIV+/syphilis-group, there was a decrease in AD in the HIV+/syphilis+ group in these areas: the right SCR (SCR-R) and the BCC. (Fig. 2).

Compared with HIV+/syphilis- group, there was an increase in RD in the HIV+/syphilis+ group in these areas: the bilateral PCR, the right PTR (PTR-R), the left SCR (SCR-L), SCC and BCC. (Fig. 3).

3.4 Correlations between DTI metrics and clinical variables

AD in BCC were negatively correlated with CD4/CD8 ratios($P<0.05$) and SCR-R were positively correlated with CD4/CD8 ratios($p<0.1$). The FA values in different regions have different effects on the clinical data (Fig. 4).

3.5 Correlations between DTI metrics and cognitive performance

RD in SCC and SCR-L was negatively correlated with CMS($P<0.05$); RD in PTR-R was positively correlated with CMS($P<0.1$). AD in SCR-R was positively correlated with CMS($P<0.05$). The FA values in different regions have different effects on the functions of cognitive performance (Fig. 5).

4. Discussion

In our study, we investigate the effects of syphilis infection on brain structural changes in HIV-infected patients and showed that compared with the HIV+/syphilis- group, the FA is widely decreased in the HIV+/syphilis + group. In addition, the HIV+/syphilis + group showed decreased AD in SCR-R and BCC, increased RD in the bilateral PCR, PTR-R, SCR-L, SCC and BCC.

HIV can damage the microstructure of WM in HIV-infected individuals and is more sensitive to WM fibers around the lateral ventricles, such as CC, PCR, PTR, SCR and ACR^[26,30-34], but the exact reason is unclear. One possible reason is that the virus can be present in the CSF of the lateral ventricle, when the blood CSF barrier is broken, the virus can invade adjacent brain tissue^[26,35]. In our study, compared with the HIV+/syphilis- group, widespread decreased FA were found in the area surrounding the lateral ventricle in the HIV+/syphilis + group, the altered areas of AD and RD were also found around the lateral ventricles. The distribution characteristics of abnormal regions are similar to HIV-infected patients. Patients with HIV and syphilis co-infections can have a higher CSF HIV viral load^[17], the CSF HIVRNA was positively correlated with the levels of various inflammatory cytokines^[36], thus a higher CSF HIV viral load may indicate a more active intracranial immune activation. ART introduction can result in reducing CSF HIV viral load but no respond to immune activation^[37]. This may illustrate why the brain tissue around the lateral ventricle are more severely damaged despite treatment.

Factors influencing diffusion anisotropy include pathways of neuronal fiber bundles, diameter of neuraxon, whether the neuraxon are tightly packed, the thickness of myelin sheath and structures other than the axonal fibers^[38]. RD may be the predominant factor contributing to the changes of FA^[26,39-40], both changes in AD and RD can lead to increased in MD^[26,36]. However, our study showed a widespread decreased FA in the whole brain without any differences in MD, the abnormal regions for AD and RD were also relatively smaller. The reason maybe that the destruction of integrity of WM in this group was caused not only by the combined action of demyelination and axonal injury, but also by the damage of the collagenous perivascular fibrous alae^[38]. Widespread decreased FA suggested compared to patients who are simply infected with HIV, the integrity of WM is more seriously impaired in HIV-infected patients with syphilis co-infection. Decreased AD are concentrated in the BCC and SCR and increased RD are concentrated in the SCR, PTR, PCR and SCC, this result may indicate syphilis infection leads to demyelination changes in the posterior region of the lateral ventricles and acute axonal injury in the upper region of the lateral ventricles in this study group, but the exact mechanism is unclear, future studies will be needed to better understand them.

A few studies have explored the relationship between structure of WM and cognitive function, and found that compared to patients without cognitive impairment, patients with cognitive impairment had a decreased FA of whole brain and more extensive increased MD^[41-42]. In our study, decreased FA in different regions of the internal capsule have a negative effect on the function of cognitive performance. The internal capsule connects the cerebral cortex to the brainstem and spinal cord. Damage to this region may result in motor and sensory impairment and then affects cognitive performance. It is worth noting that the increased RD in SCC and SCR-L can affect the ability of CMS, decreased AD in SCR-R can damage the ability of CMS. The SCC connects parts of parietal fibers and may be functionally associated with visual area of the occipital cortex. SCR is part of projection fibers connecting the internal capsule to the cerebral cortex. Damage to these two regions may affect CMS. Furthermore, motor skill learning requires active central myelination, myelin can increase the speed of electrical communication among neurons^[43]. So demyelination may affect motor skills, and this may be the reason why increased RD was correlated with the degradation of CMS in our study.

Our study also showed that CD4 count in HIV+/Syphilis + group was higher than that in HIV+/Syphilis-group, but the difference was not statistically significant. This may be due to the fact that all enrolled syphilis patients were treated with penicillin. Though syphilis had a negative impact on the CD4T cell counts in HIV-positive patients, it can be restored after using penicillin^[12]. We also found AD in BCC was negatively correlated with CD4/CD8 ratios, AD in SCR-R was positively correlated with CD4/CD8 ratios. Lower CD4/CD8 ratios is associated with persistent inflammation and immunosenescence^[41]. Our result demonstrated that immunologic dysfunction may cause axonal injury of WM around the lateral ventricle. More studies needs to be explored in the future to understand the mechanism of immune status affecting brain structure.

Our study has some limitations. Firstly, the limited sample size may result in lower power, thus a study of larger samples should be done in the future; secondly, our study includes only male gender, which may prevent the results applicable to all populations or female patients. thirdly, a longitudinal follow-up study should be done to investigate the dynamic changes of WM between the two groups.

5. Conclusions

This study showed that compared to male patients simply infected with HIV, the integrity of WM is more seriously impaired in HIV-infected male patients with syphilis co-infection, and it may accelerate the impairment of cognitive function, so more attention should be paid to this group and more aggressive measures are needed to delay or halt neurological deterioration in this group. This study may provide important evidence-based medicine value for clinical comprehensive evaluation of condition and formulation of precision treatment plan for patients.

Abbreviations

WM

white matter; DTI:diffusion tensor imaging; TBSS:Tract-based spatial statistics; HIV:human immunodeficiency virus; CNS:central nervous system; CSF:cerebrospinal fluid; HAND:HIV-related neurocognitive disorders; ANI:asymptomatic neurocognitive impairment; MND:mild neurocognitive disorder; HAD:HIV-associated dementia(HAD); ART:antiretroviral therapy; MSM:men who have sex with men; FA:fractional anisotropy; MD:mean diffusivity; AD:axial diffusivity; RD:radial diffusivity; TP-PA:T pallidum particle agglutination; RPR:Rapid Plasma Reagin; FLAIR:T2-fluid attenuated inversion recovery.

Declarations

Ethical approval and consent to participate

This research was approved by the ethics committee of Beijing Youan Hospital. All participants provided written informed consent prior to enrolment.

Consent for publication

Not Applicable.

Availability of data and materials

The datasets used in this manuscript will be available from the corresponding author on reasonable request.

Competing Interests

Authors in this article have no conflicts of interest to declare.

Funding

This work was supported by the National Natural Science Foundation of China [grant number 81771806, 61936013, 81701679], responsible for research design and collection; Capital medical university research and incubation funding [grant number PYZ19162], responsible for data processing and analysis; Beijing Excellent Talent Plan [grant number 2018000021469G290]; Beijing Municipal Health Commission, technology achievements and appropriate technology promotion project [grant no. 2020-TG-002], You'an Medical Development Project of COVID-19 Emergency Prevention and Control Public [grant no. BJYAYY-2020YC-03] and Natural Science Foundation of Tianjin [19JCQNJC09800], responsible for writing and revising the manuscript.

Authors' Contributions

Research design: YQ, RLL, YYW, YFG and HJL. Data collection: RLL, WW, YYW, XL and MML. Data processing and analysis: YQ, XZL, JL, RLL, XDZ, YW, PHM and JJL; Writing and revising the manuscript: YQ and RLL. All authors have read and approved the final manuscript.

Acknowledgements

This article would not have been possible without the valuable reference materials collected by Rui-Li Li, Wei Wang, Yuan-Yuan Wang, and Ming-Ming Liu, data analysis helped by Xu-Ze Liu, Pei-Hong Ma, Xiao-Dong Zhang, Jing-Liu and Jiao-Jiao Liu, insightful guidance and enthusiastic encouragement from my supervisor Hong-Jun Li.

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Tables

Due to technical limitations, table 1,2 is only available as a download in the Supplemental Files section.

Figures

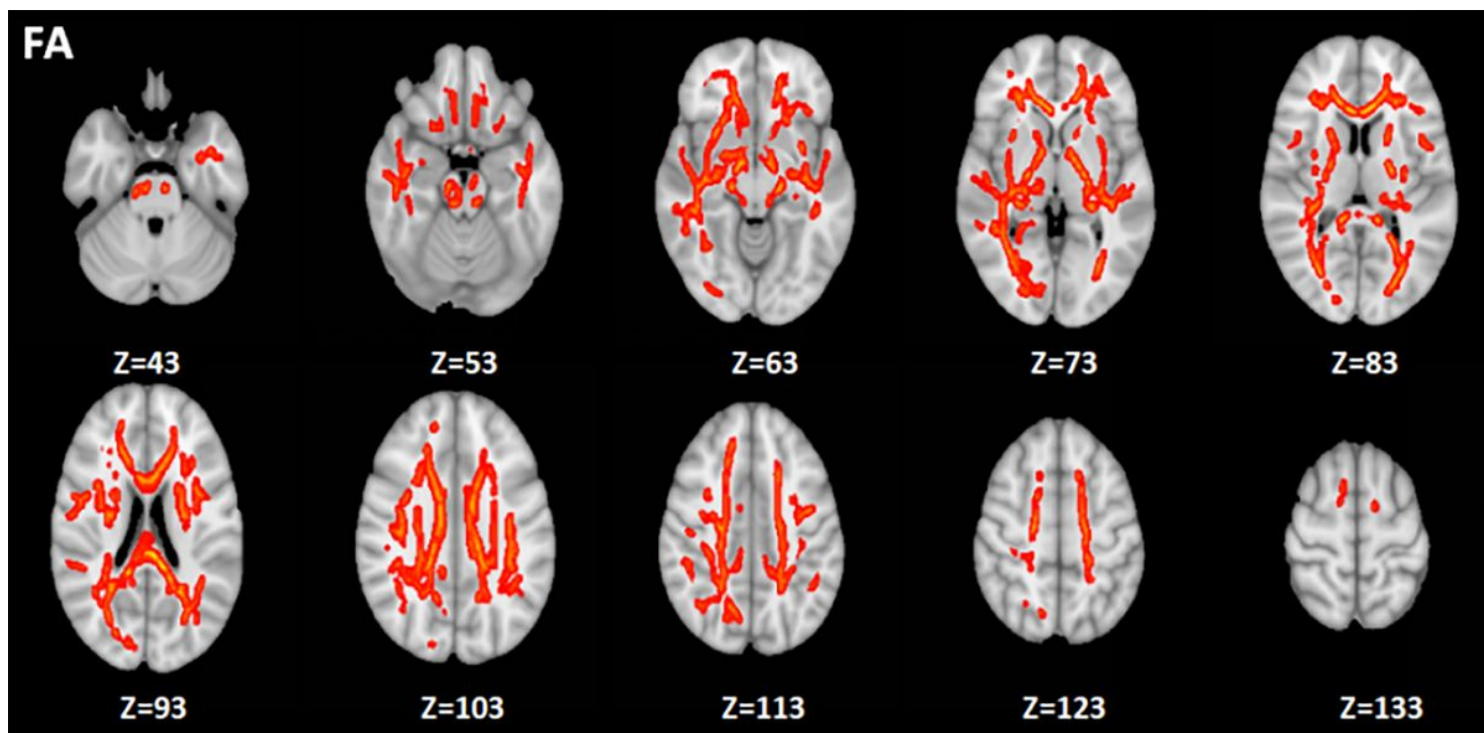


Figure 1

The differences of FA between HIV+/Syphilis+ group and HIV+/syphilis- group. Areas in red regions were significantly increased ($P < 0.05$). The number below each brain image indicates the Z coordinate in the Montreal Neurological Institute (MNI) space.

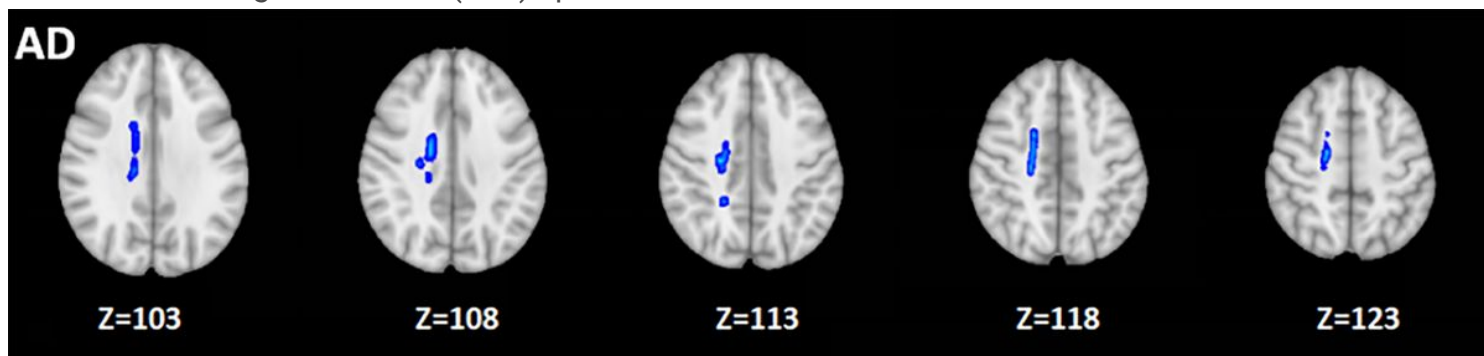


Figure 2

The differences of AD between HIV+/Syphilis+ group and HIV+/syphilis- group. Areas in blue regions were significantly increased ($P < 0.05$). The number below each brain image indicates the Z coordinate in the MNI space.

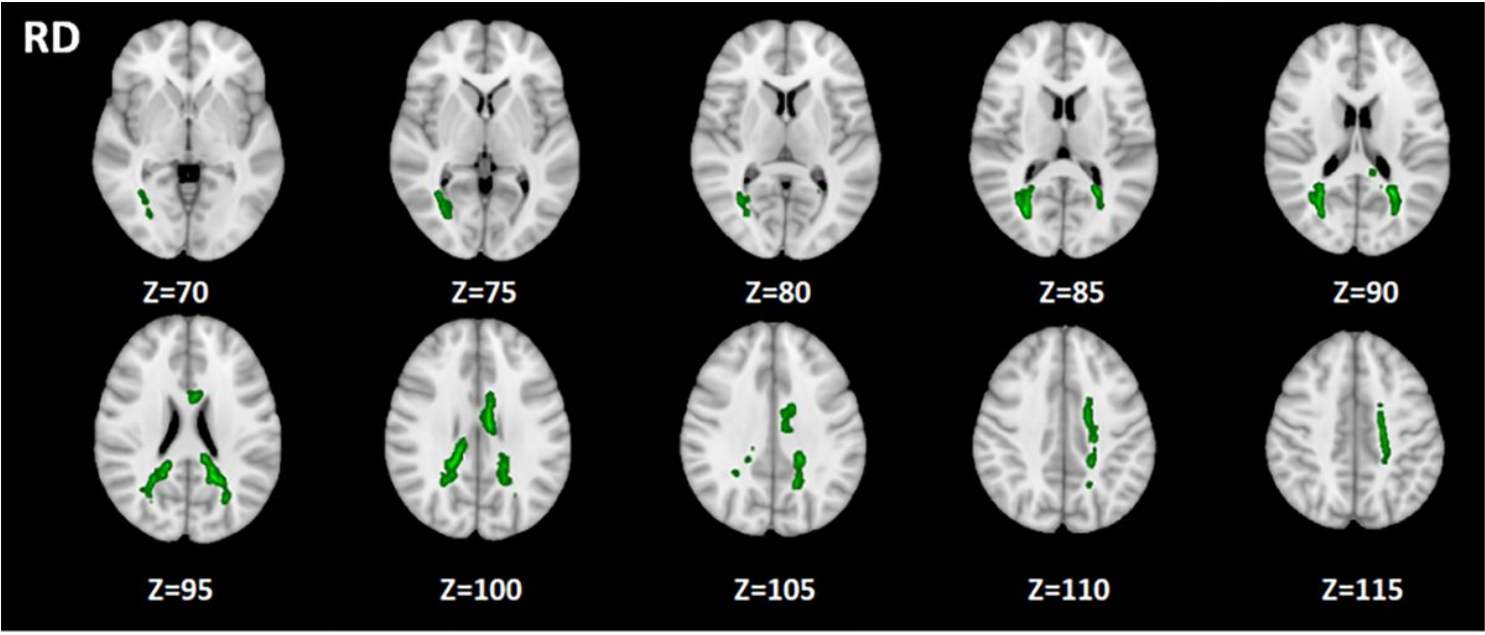


Figure 3

The differences of RD between HIV+/Syphilis+ group and HIV+/syphilis- group. Areas in green regions were significantly increased ($P < 0.05$). The number below each brain image indicates the Z coordinate in the MNI space.

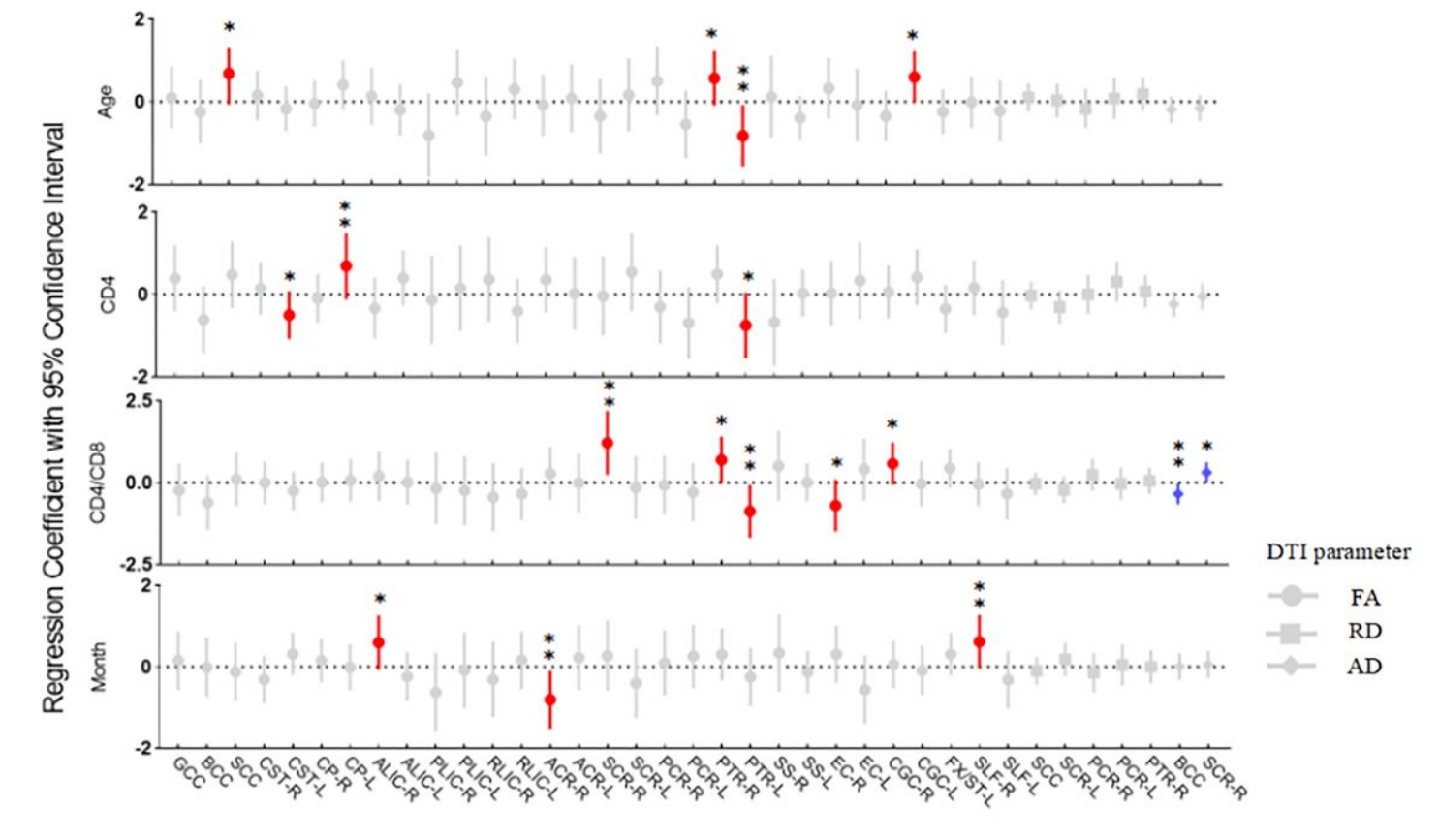


Figure 4

Regression coefficients with 95% confidence interval indicating the effects of clinical variables on fractional anisotropy(FA), radial diffusivity(RD) and axial diffusivity(AD)in white matter. Month duration of infection. GCC: genu of corpus callosum; BCC: body of corpus callosum; SCC: splenium of corpus callosum; CST: corticospinal tract; CP: cerebral peduncle; ALIC: anterior limb of internal capsule; PLIC: posterior limb of internal capsule; RLIC: retrolenticular part of internal capsule; ACR: anterior corona radiata; SCR: superior corona radiata; PCR: posterior corona radiata; PTR: posterior thalamic radiation; SS: sagittal stratum; EC:external capsule; CGC: cingulate gyrus; FX/ST: fornix/Stria terminalis; SLF: superior longitudinal fasciculus; L: left; R: right. Variables showing significant($P<0.1$) are highlighted in red and blue. BCC in RD is automatically excluded for regression because of collinearity. * $P<0.1$, ** $P<0.05$.

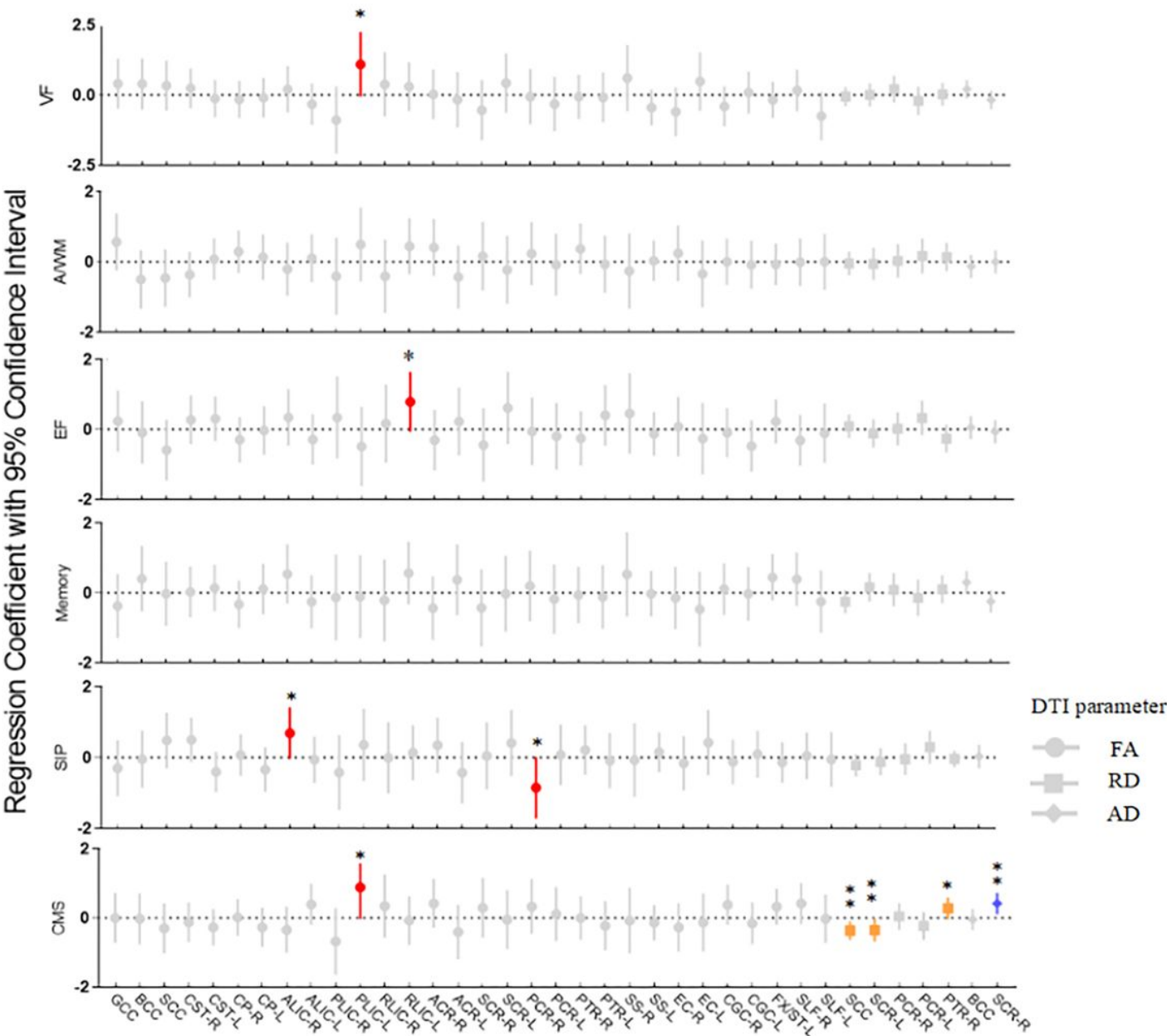


Figure 5

Regression coefficients with 95% confidence interval indicating the effects of cognitive performance on fractional anisotropy(FA), axial diffusivity(AD) and radial diffusivity(RD)in white matter. VF: Verbal Fluency; A/WM: Attention/Working Memory; EF: Executive Functioning; SIP: Speed of Information Processing; CMS: Complex Motor Skills; GCC: genu of corpus callosum; BCC: body of corpus callosum; SCC: splenium of corpus callosum; CST: corticospinal tract; CP: cerebral peduncle; ALIC: anterior limb of internal capsule; PLIC: posterior limb of internal capsule; RLIC: retrolenticular part of internal capsule; ACR: anterior corona radiata; SCR: superior corona radiata; PCR: posterior corona radiata; PTR: posterior thalamic radiation; SS: sagittal stratum; EC:external capsule; CGC: cingulate gyrus; FX/ST: fornix/Stria terminalis; SLF: superior longitudinal fasciculus; L: left; R: right. Variables showing significant($P<0.1$) are highlighted in red, orange and blue. BCC in RD is automatically excluded for regression because of collinearity. * $P<0.1$, ** $P<0.05$.

Supplementary Files

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