Original Article

Distance-specific functional connectivity strength alterations in human immunodeficiency virus asymptomatic neurocognitive impairment patients: a cross-sectional study

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Background: Asymptomatic neurocognitive impairment (ANI) is the mildest form of human immunodeficiency virus (HIV)-associated neurocognitive disorders (HANDs), and functional connectivity strength (FCS) alternations have been observed in the ANI stage. However, it is not clear whether the FCS alterations are influenced by the anatomical distance. This study sought to investigate distance-specific FCS changes in HIV ANI patients.

Methods: In total, 29 patients with HAND and 32 healthy controls (HCs) were enrolled in the study. Between-group differences were detected for short, middle and long range anatomical distance FCS. A correlation analysis was performed to examine the relationship between distance-specific FCS and immunological parameters and neuropsychological tests. A receiver operating characteristic (ROC) analysis was conducted to examine the discriminative performance for HIV ANI patients.

Results: In comparison to the HCs, the HAND patients showed increased short-range FCS in the left inferior parietal lobule (IPL), middle-range FCS in the superior temporal gyrus (STG), long-range FCS in the left precuneus (PCC), and decreased FCS in the right postcentral gyrus (PCG) (cluster $P<0.05$, voxel significance $P<0.001$). Further, the long-range FCS in the right PCG was negatively correlated with the CD4/CD8 ratio ($r=-0.479$, 95% confidence interval (CI): −0.735 to −0.104, $P=0.015$), and the distance-specific FCS also showed good classification performance between the HAND patients and HCs. The left IPL, left STG, right PCG, and left PCC had areas under the curve (AUCs) of 0.875 [95% confidence interval (CI): 0.758–0.949, $P<0.0001$], 0.806 (95% CI: 0.677–0.900, $P<0.0001$), 0.855 (95% CI: 0.734–0.935, $P<0.0001$), and 0.852 (95% CI: 0.754–0.950, $P<0.0001$), respectively. There was no significant relationship between the distance-specific FCS and the neuropsychological tests.

Conclusions: Distance-specific FCS could be used to examine subtle alternations in HIV-infected patients in the ANI stage and help to explain the possible neurophysiological mechanism of HAND.

Keywords: Human immunodeficiency virus (HIV); asymptomatic neurocognitive impairments (ANIs); functional connectivity strength (FCS); anatomical distance

Submitted Aug 17, 2023. Accepted for publication Dec 20, 2023. Published online Jan 22, 2024.
doi: 10.21037/qims-23-1161
View this article at: https://dx.doi.org/10.21037/qims-23-1161

Introduction

Human immunodeficiency virus (HIV)-associated neurocognitive disorder (HAND) can be divided into the following three stages according to the Frascati criteria (1): asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorder, and HIV-associated dementia. Even among patients treated with antiretroviral therapy, the mild form of HAND is still the main cause of neuronal dysfunction (2), and HIV infection is a global burden. In the Asia-Pacific region, the effect of HAND has been underestimated, and in India, subtle subclinical asymptomatic deficits have been reported in almost 61% of HIV-positive patients (3). In a previous study, patients with ANI were found to be at high risk of developing symptomatic neurocognitive disorders (4). Thus, it is imperative to investigate early brain changes in HIV-infected patients in the ANI stage.

In past decades, resting-state functional magnetic resonance imaging (rs-fMRI) has been widely used to evaluate the intrinsic patterns of the brain. It has been reported that HIV infection disrupts the functional connectivity (FC) of the attention network, default mode network (DMN), and sensorimotor network (5). Most studies of HIV-infected patients in the ANI stage have focused on white-matter tracts, and very few studies have examined the FC between brain nodes. ANI is commonly classified by neurocognitive tests, but there is a lack of clinically diagnostic biomarkers for monitoring the neurocognitive dysfunction progression (6). In virally suppressed HIV-infected patients, atrophy of frontal white matter and lower CD4/CD8 were predictors of brain changes (7) for ANI. In a multicenter study, compared with a neurocognitively unpaired group, an ANI group showed magnetic resonance spectroscopy signal changes in subcortical brain regions, but their structural volume was not altered (8). Han *et al.* pointed out that increased FC of the visual network was present in ANI patients and was correlated with verbal and language function (9). FC strength (FCS) is defined as node degree centrality, which is calculated using the Pearson's correlation coefficients between each voxel and every other voxel. However, little is known about FCS alterations in ANI patients.

The human brain is a complex and economic trade-off topological system of network embedded in an anatomical structure. Thus, distance is a key element in depicting the Euclidean distance between any pair of nodes, which reflects the anatomical distance of the connective edge in the Montreal Neurological Institute (MNI) coordinates. A short-distance connection between brain regions has minimal costs, while a long-distance connection has high costs but is good for information processing (10). A well-organized brain depends on a balance between long and short-distance FC (11). Many studies have shown that abnormalities in distance-specific FCS are associated with cognitive function in schizophrenia, major depressive disorder, and obsessive-compulsive disorder (12,13). However, little research has been conducted to determine whether the anatomical distance affects early-stage HANDs.

In this study, we used rs-fMRI to investigate the distance-specific FCS in three defined distance thresholds based on the anatomical distance. We further examined whether the abnormality of FCS could be used to discriminate between ANI-stage HIV-infected individuals and healthy controls (HCs). Moreover, the correlations between the FCS alterations and clinical variables were also analyzed. We present this article in accordance with the STROBE reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-23-1161/rc).

Methods

Participants

In total, 29 HIV-infected patients (mean age: 29.6± 5.6 years; all males) and 32 HC (mean age: 31.7± 4.2 years; all males) were enrolled in this study. Individuals with neurological disorders, a history of coinfection with hepatitis B or C, opportunistic central nervous system infection, substance or alcohol abuse, and traumatic brain injury were excluded from the study. All the HIV-infected patients were examined using clinical and laboratory tests, including tests to determine the $CD4^+$ T cell count and the ratio of CD4 to $CD8^+$ T cells. Among the patients, 27 HIV-infected patients were receiving stable highly active antiretroviral treatment medication, and two were receiving

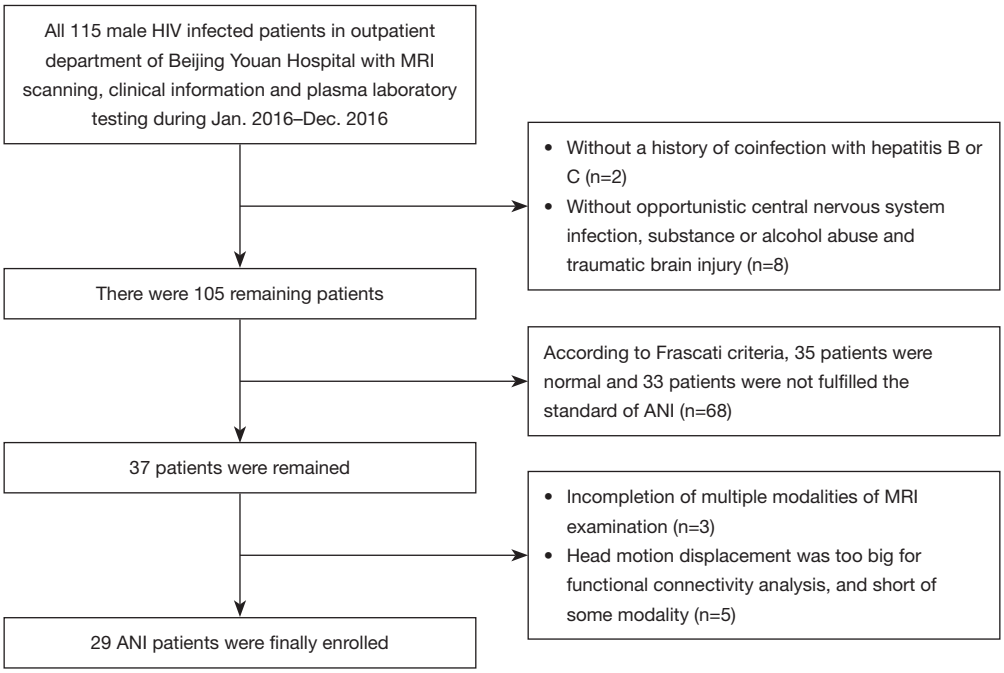

Figure 1 The flow diagram shows the enrollment process of ANI patients with HIV infection. HIV, human immunodeficiency virus; MRI, magnetic resonance imaging; ANI, asymptomatic neurocognitive impairment.

no such medication. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the Research Ethics Review Board of Beijing Youan Hospital, Capital Medical University. All the participating individuals were recruited at the Beijing Youan Hospital and provided written informed consent.

All the participants underwent an extensive standard battery of neuropsychological tests covering the following six domains: language fluency (which was assessed by the Animal Verbal Fluency Test) (14); attention (which was assessed by the Continuous Performance Test-Identical Pair, Wechsler Memory Scale, and Paced Auditory Serial Addition Test) (15); executive function (which was assessed by the Wisconsin Card Sorting Test-64) (16); memory (which was assessed by the Hopkins Verbal Learning Test and Brief Visuospatial Memory Test) (17,18), speed of information processing (which was assessed by Trail Marking Test A) (19); and motor function (which was assessed by the Grooved Pegboard test, dominant and non-dominant) (20). All the tests were administered by an experienced neurologist.

ANI stage was diagnosed according to the Frascati criteria (1). The criteria were as follows: (I) a result at least 1.0 standard deviation (SD) below the mean for age-education adjustive norms on standardized neuropsychological tests in at least two cognitive areas; (II) unimpaired daily function; and (III) impairment that was not part of the delirium. The process for enrolling ANI-stage HIV-infected patients in the study is shown in *Figure 1*. In total, 115 patients were initially identified in the outpatient department. After exclusion, 29 ANI-stage patients were included in the study.

Magnetic resonance imaging (MRI) acquisition

All the participants underwent MRI scanning using a Siemens 3T Trio whole-body scanner (Siemens, Erlangen, Germany) with a 32-channel head coil at the Beijing Youan Hospital. A T1-weighted three-dimensional magnetization prepared rapid acquisition gradient echo sequence was acquired with the following parameters: repetition time: 1,900 ms; echo time: 2.52 ms; isotropic voxel size: 1 mm; and flip angle: 9°. Functional images were collected by echo planar imaging (EPI) sequencing with the following parameters: repetition time: 2,000 ms; echo time: 30 ms; flip angle: 90°; matrix: 64×64; and voxel size: 3.5×3.5×3.5 mm^3. Data were collected at 240 time points over a scan time of 8 minutes and 6 seconds. All the participants were instructed

to remain still, close their eyes, and remain awake during the scan.

Data pre-processing

All the rs-fMRI scans were pre-processed using the Statistical Parametric Mapping (SPM12) (www.fil.ion.ucl.ac.uk/spm/) and Data Processing and Analysis for Brain Imaging (DPABI) software (21). First, the first 10 volumes of data were removed for signal stabilization. Second, the slice-time difference and the head motions were subsequently corrected. Third, all the processed images were normalized to the MNI space with the EPI template and re-sampled into 3×3×3 mm^3. Fourth, the images were smoothed by a Gaussian kernel with a 4-mm full-width at the half-maximum. Moreover, some key covariates were regressed out from the time course of each voxel, including linear trend, Friston 24 head-motion parameters, global signal, cerebrospinal fluid, and white-matter signals. Finally, band-pass filtering (0.001–0.1 Hz) was applied to each voxel signal to reduce the drift and noise.

Distance-specific FCS analysis

FCS was determined by the voxel-based whole-brain correlation analysis. First, we computed whole-brain full-range FCS by summarizing the Pearson's correlation coefficients between each voxel and other voxel's time series within the gray-matter mask to construct a correlation matrix (22,23). The gray-matter mask was generated using a cut-off threshold (>0.2) on a gray-matter probability template. Second, the processed data were normalized by Z-score transformation. Finally, in relation to the anatomical distance of the FCS, we divided the whole-brain FCS into the following three subgroups based on their Euclidean distances: short-range FCS (0–25 mm), middle-range FCS (25–75 mm), and long-range FCS (>75 mm) (24). Thus, we calculated a distance-specific FCS matrix for each ANI-stage HIV-infected patient and HC.

Statistical analysis

The demographic information of the HIV-infected patients and HCs was compared using a two-sample *t*-test. The sample size was estimated using G*power software (www.gpower.hhu.de) with the following parameters: power =0.8, $D \geq 0.75$, and $\alpha = 0.05$. The distance-specific FCS between the two groups was also compared using a two-sample two-sided *t*-test after Gaussian random field correction (P<0.05, voxel significance P<0.001) with age and gender as the covariates. Moreover, the distance-specific abnormal FCS was used to examine the relationship with the neurocognitive scores and immunological tests by a correlation analysis and to explore the discriminative ability between the HIV-infected patients and HCs by a receiver operating characteristic (ROC) analysis.

Results

There were no significant differences between the ANI-stage HIV-infected patients and HCs in terms of age and education. The demographic and neuropsychological information of the participants is presented in *Table 1*. The ANI group had a stable viral load and CD4/CD8 ratio. There was no significant head-motion difference in the Jenkinson frame-wise displacement between the two groups (P=0.07). As *Figure 2* shows, compared with the HCs, the HIV-infected patients showed increased short-distance FCS in the left inferior parietal lobule (IPL), and middle-distance FCS in the superior temporal gyrus (STG). Additionally, the long-distance FCS was increased in the left precuneus (PCC) and decreased in the right postcentral gyrus (PCG).

The correlation analysis showed that the long-distance FCS in the right PCG was negatively correlated with the CD4/CD8 ratio [r=–0.479, 95% confidence interval (CI): –0.735 to –0.104, P=0.015], which is a key immunological marker of HIV (see *Figure 3A*). There was no significant correlation between the distance-specific FCS and neuropsychological tests. Four abnormal FCS brain regions (i.e., left IPL, left STG, right PCG, and left PCC) were found to be effective in distinguishing between ANI-stage HIV-infected patients and the HCs, and had corresponding areas under the curve (AUCs) of 0.875 (95% CI: 0.758–0.949, P<0.0001), 0.806 (95% CI: 0.677–0.900, P<0.0001), 0.855 (95% CI: 0.734–0.935, P<0.0001). and 0.852 (95% CI: 0.754–0.950, P<0.0001) (see *Figure 3B*).

Discussion

In this study, we investigated distance-specific FCS alterations in ANI-stage HIV-infected patients in comparison to HCs. We found that the HAND patients displayed higher FCS in the left IPL (short-distance), left STG (middle-distance), and left PCC (long-distance), and lower FCS in the right PCG (long-distance). Moreover, the CD4/CD8 ratio of the plasma sample was negatively

Table 1 Demographic and neuropsychological information of all subjects

Variables	HIV+ patients (ANI stage)	Healthy controls	P value
Number	29	32	–
Age (years)	29.7±5.6	32.0±4.9	0.10
Gender (male)	29	32	–
$FD_{Jenkinson}$	0.13±0.05	0.16±0.08	0.07
$CD4^+$ count (cells/μL)	537.5±180.3	–	–
CD4/CD8 ratio	0.69±0.52	–	–
Language fluency	39.4±9.15	–	–
Attention	36.2±5.7	–	–
Executive function	50.0±7.8	–	–
Memory	38.6±7.4	–	–
Speed of information processing	40.5±8.8	–	–
Motor function	42.2±9.7	–	–

Data are presented as the number or mean ± standard deviation. HIV, human immunodeficiency virus; ANI, asymptomatic neurocognitive impairment; FD, frame-wise displacement.

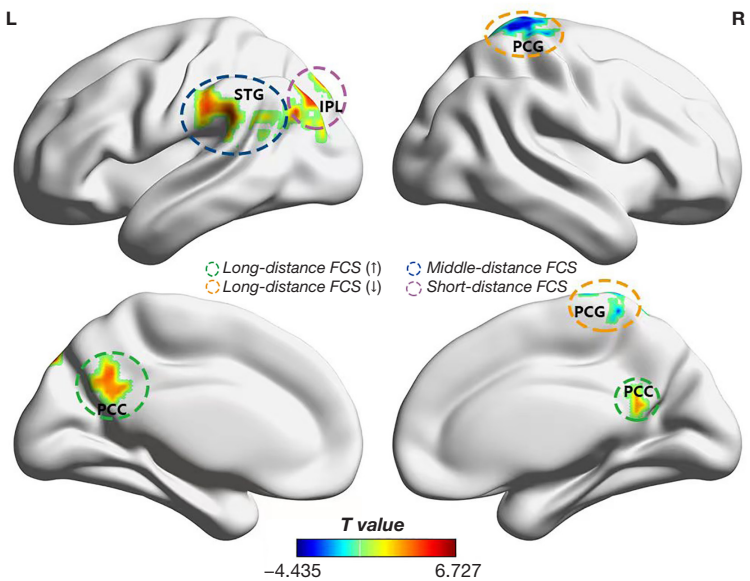

Figure 2 Group comparisons of short, middle and long distance FCS between the HIV-infected patients in the ANI stage and HCs (multiple comparison corrected: P<0.05, voxel significance P<0.001). The purple and blue colored circles represent the short- and middle-distance FCS in the left IPL and STG. Moreover, long-distance FCS revealed an increased strength in the left PCC as represented by the green colored circle, and decreased strength in the right PCG as represented by the orange circle. L, left; R, right; STG, superior temporal gyrus; IPL, inferior parietal lobule; PCG, postcentral gyrus; FCS, functional connectivity strength; PCC, precuneus; HIV, human immunodeficiency virus; ANI, asymptomatic neurocognitive impairment; HC, healthy control.

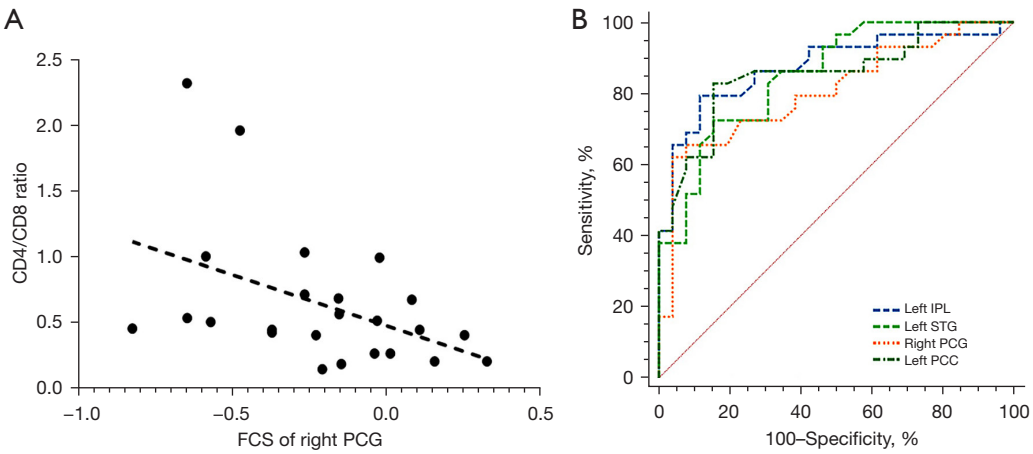

Figure 3 Correlational and ROC analysis results. (A) Correlation between the plasma CD4/CD8 ratio and long-range FCS of the PCG (>75 mm) in ANI-stage patients. (B) ROC analysis of FCS in four abnormal brain regions. FCS, functional connectivity strength; PCG, postcentral gyrus; IPL, inferior parietal lobule; STG, superior temporal gyrus; PCC, precuneus; ROC, receiver operating characteristic; ANI, asymptomatic neurocognitive impairment.

correlated with the long-distance FCS of the right PCG. The ROC analysis found that the short-distance FCS of the left IPL had the best discriminative ability for HAND patients with an AUC of 0.875. The left IPL is involved in sensorimotor processing, movement control, memory, etc. (25,26). The ANI-stage HIV-infected patients displayed increased FCS in the left IPL and STG, which may be due to the dysfunction of sensorimotor integrity and cooperation. The role of the STG is to transform audio information into motor behavior, and we predicted that the IPL and STG cooperate with each other. Even in asymptomatic HIV-positive patients, balance and gait disturbance have been observed using a series of motor-related tests (27). Thus, sensorimotor function may first be impaired during the progression of HIV neurocognitive disorders. In addition, IPL is an important node of the DMN, and HIV could lead to decreased intra-/inter-network FC alternations in the DMN, salience, and control networks (28). It has been reported that the FC between the DMN and salience network was increased in HIV-infected groups compared to HIV uninfected groups (29). It may be that after the HIV enters the central nervous system, it leads to the disruption of short-distance connectivity of the IPL and thus reduces the efficiency of motor and memory function (30).

The ANI patients had higher FCS in the PCC and lower FCS in the PCG in the long-range distance FC than the HCs. Long-range distance FCS means a high metabolic cost to maintain normal function (10). In one side, long-range FC enables information to be transferred more efficiently among several connectors. It was consistently reported in some brain disorder diseases, like Alzheimer's disease, in which the long-range connection in the network is easily attacked. Additionally, as a functional hub of the DMN, the PCC is involved in high-order cognitive tasks, such as memory, visuospatial imagery, and integrating perception. In primates with the simian immunodeficiency virus, we previously confirmed that the amplitude of low-frequency fluctuation increased in the PCC and PCG. Taken together, these results indicate that the PCC may be the key vulnerable region in the early stage of HAND.

Interestingly, the CD4/CD8 ratio was negatively correlated with long-range FCS in the right PCG. The lower CD4 nadir was associated with reduced FC in the memory network and might reflect a history of immunosuppression (31). However, it is difficult to obtain the CD4 nadir at the correct time point, and thus it cannot be used in daily clinical diagnosis. The plasma CD4/CD8 ratio is an important marker of HIV care and disease progression management. In early HIV infection, the trajectory of the CD4/CD8 ratio was found to be correlated with motor speed function over time through neuropsychological performance (32). Our results showed that a lower CD4/CD8 ratio was related to higher FCS in the PCG, which indicates that the motor circuit changes during the initial stage of HIV neurocognitive impairments. Some other factors, including nadir $CD4^+$ T cells and the duration of infection, influence FC alternations in HIV-

positive patients. For example, nadir $CD4^+$ T cells are related to reduced FC in HIV-infected patients who are apolipoprotein E (ApoE) carriers (31), and acute infection shows some subtle fMRI alterations (33). However, nadir CD4 is not easy to obtain in clinical outpatient departments and the infection times were self-reported. Thus, our study focused mainly on clinical plasma parameters, including the $CD4^+$ T cell count and the ratio of CD4 and $CD8^+$ T cells. Further, we investigated the relationship between the duration of infection and functional brain changes through the ideal simian immunodeficiency virus-infected macaque model, as the animal model was well controlled from no infection to several time points after inoculation (34,35).

This study had some limitations. First, the sample size of the HIV-positive patients in the ANI stage was relatively small, which might have influenced the statistical effect. Second, the neurocognitive testing of the ANI stage was affected by participants' situations, including sleep quality, which needs to be examined more carefully in the future. Third, this study was a cross-sectional study of HIV-positive patients and HCs, and longitudinal studies need to be conducted to prove the distance-specific FCS changes in the future.

Conclusions

In this study, we used distance-specific FCS (short, middle, and long range) to examine alternations in HIV-infected patients in the ANI stage. Higher short- and middle-distance FCS in the left IPL and STG were found in ANI patients, whereas higher long-distance FCS was also detected in the left PCC, and lower FCS was also detected in the PCG. The ROC analysis showed that distance-specific FCS was effective in distinguishing between these two groups with high accuracy. In addition, the plasma CD4/CD8 ratio was significantly correlated with the FCS of the right PCG. The findings emphasize that motor sensory function and the DMN may be altered during the early stage of HIV infection, which provides insights into the mechanism of HAND.

Acknowledgments

Funding: The work was supported by Beijing hospital Authority Clinical medicine Development special funding support (No. ZLRK202333), the Open Fund Project of the Beijing Key Laboratory of Fundamental Research on Biomechanics in Clinical Application (No. 2023KF05) and China's National Natural Science Foundation (No. 61936013).

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://qims.amegroups.com/article/view/10.21037/qims-23-1161/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-23-1161/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013), and it was approved by the Research Ethics Review Board of Beijing Youan Hospital, Capital Medical University. All the participating individuals were recruited at the Beijing Youan Hospital and provided written informed consent.

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Cite this article as: Zhao J, Wu Y, Chen F, Zhao H, Chen J, Jing B, Li H. Distance-specific functional connectivity strength alterations in human immunodeficiency virus asymptomatic neurocognitive impairment patients: a cross-sectional study. Quant Imaging Med Surg 2024;14(2):1835-1843. doi: 10.21037/qims-23-1161

