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The impacts of HIV infection, age, and education on functional brain networks in adults with HIV

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Abstract
HIV-associated neurocognitive disorders (HAND) remain highly prevalent in people with HIV (PWH). Studies suggested that certain sociodemographic factors are associated with the risk of HAND in PWH. Here we investigated the impact of HIV infection and demographics on functional brain networks. One run of 8.5 min resting state functional MRI (fMRI) data was collected from 101 PWH (41–70 years old) and 40 demographically comparable controls. Functional connectivity (FC) was calculated using average wavelet coherence. The impact of demographic factors on FCs was investigated using canonical correlation analysis (CCA). Wavelet coherence analysis revealed a reduced within-network connectivity in the dorsal somatomotor network (dSMN), along with a reduced between-network connectivity between dSMN and medial temporal lobe (MTL) in PWH (compared to controls). Across all participants, CCA revealed that older age and HIV infection had negative impacts on network connectivity measures (mainly reduced within- and between-network FCs), whereas education had an opposite effect. In addition, being female at birth or a member of a minority ethnic/racial group was also associated with network disruptions. Our data suggested that advanced age and HIV infection are risk factors for functional brain network disruptions, whereas higher educational attainment was linked to better preserved functional network connectivity.

Keywords HIV · MRI · Network connectivity · Age · Education

Introduction

In the post-era of combination antiretroviral therapy (cART), HIV-associated neurocognitive disorders (HAND) remain highly prevalent and impactful in people with HIV (PWH). Many factors can contribute to neurocognitive impairment in PWH (Saylor et al. 2016), including HIV disease severity (e.g., low CD4 nadir counts (Valcour et al. 2006)) and comorbidities (e.g., cardiovascular disease (Wright et al. 2010)). In addition, certain sociodemographic factors are associated with greater risks of neurocognitive impairment in PWH, including advanced age (Morgan et al. 2012) and lower levels of education (Bonnet et al. 2013). Neuroimaging studies have shown that advanced age is associated with greater neural injury in PWH, including brain volume reduction (Guha et al. 2016; Saloner et al. 2019) and disruptions to structural and functional brain networks (Thomas et al. 2013; Kuhn et al. 2018). However, few neuroimaging studies have investigated the impact of other sociodemographic factors on brain structure and function in PWH, including education, which, as a proxy for cognitive reserve in adults, is known to affect brain structure and function (EClipSE Collaborative Members et al. 2010).

Alterations in patterns of functional connectivity (FC), measured by noninvasive functional magnetic resonance imaging (fMRI) (especially resting state fMRI), have been widely used to study cognitive impairment and alterations in clinical populations (e.g., PWH) and nonclinical populations (e.g., healthy older adults) (Stam 2014). For instance, cognitive aging studies have shown that advanced age is associated with reduced FC in several main brain networks and the reduction in FC correlates with cognitive decline (Sala-Llonch et al. 2015). By contrast, education is shown to have an opposite

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effect, i.e., with higher number of years of education being associated with higher FCs (Perry et al. 2017; Shen et al. 2018), implicating an education-related preservation of "normal" functional network connectivity.

In HIV, several previous studies have shown that HIV infection leads to abnormalities in FC within several cortical functional networks, such as the default mode network (DMN), control network (CON), and salience network (SAL) (Wang et al. 2011; Thomas et al. 2013). In addition to these cortical connections, recent studies found that both cortico-striatal and cortical-cerebellar connections play important roles in HIV and HAND (Ortega et al. 2015), suggesting that subcortical regions are as important as cortical regions and should be taken into account in HIV studies.

Here, we systematically investigated the effect of HIV and sociodemographic factors on functional brain networks, using a recently developed brain parcellation that characterized whole-brain functional network organization with improved representation of subcortical regions and previously established cortical regions (Seitzman et al. 2020). There were two main aims:

First, we investigated whether HIV affects system-level network connectivity in whole-brain functional networks using wavelet coherence analysis (Chang and Glover 2010; Zhang et al. 2016; Mohanty et al. 2020), which measures the relationship between two signals in the time–frequency domain. Studies suggested that wavelet-based approaches might have the advantages of denoising, being robust to outliers, and capturing the "true" synchronized long memory neuronal oscillations (Gu et al. 2015; Mohanty et al. 2020). We hypothesized that certain aspects/components of brain networks were disrupted in PWH (compared to HIV-uninfected controls).

Second, we used canonical correlation analysis (CCA) to quantify the multivariate association between patterns of network connectivity measures and demographics (including age, education, race, sex at birth, and HIV infection). CCA is a powerful multivariate approach that seeks maximal correlation between linear combinations of variables in two different sets, i.e., functional connectivity and behavioral test scores (Smith et al. 2015; Drysdale et al. 2017; Yu et al. 2019). A recent study used a combination of CCA and multimodal MRI techniques to investigate the impact of HIV on brain structure and networks (Sui et al. 2020). We hypothesized that both advanced age and HIV infection were associated with disruptions to functional brain networks, whereas higher educational attainment (measured as number of years of formal education) had an opposite effect.

Methods

Participants

Participants were recruited from the greater Washington, D.C., metropolitan area. One hundred and four PWH and forty demographically matched HIV negative controls were enrolled after a telephone-screening and a subsequent onsite-screening visit using the following criteria: 41–70 years old; speak and understand English; more than 7 years of education; no MRI contraindications; no illicit substance use within the past 3 months (mandatory urine toxicology test was performed during each visit); and no other major neurological and psychiatric disorders. The study protocol was approved by Georgetown University's Institutional Review Board and written informed consent from each participant was obtained prior to enrollment. Three PWH were excluded from data analysis due to visible brain anomalies ($n = 2$) or had poor signals ($n = 1$, see below). Hence, the final dataset reported here includes a total of 101 PWH and 40 matched controls. Disease-related information for the 101 PWH included: current CD4 count 680 (498) (median, interquartile range (IQR)); CD4 nadir 199, 297.25 (median, IQR); disease duration 28 (14) years (median, IQR); 87.3% of PWH with successful viral suppression (plasma viral load < 50 copies/ml).

Neuropsychological testing

A neuropsychological test battery including tests of seven cognitive domains was administered (for details, see Yang et al. 2021a). For each participant, a *T*-score for each cognitive domain was calculated separately using a normative database then a global mean *T*-score (GMT, a global cognitive measure) was obtained by averaging the *T*-scores from each of the seven domains. In addition, a global deficit score (GDS) was calculated based on neuropsychological tests (Carey et al. 2004; Blackstone et al. 2012) and the Lawton and Brody Activities of Daily Living (Lawton and Brody 1969) index was computed to diagnose HAND using the standard Frascati guideline (Antinori et al. 2007).

MRI acquisition and preprocessing

Structural MRI and resting-state functional MRI were scanned at the Center for Functional and Molecular Imaging at Georgetown University Medical Center using a 3-T Siemens Magnetom Trio with a 12-channel head coil or Prisma-Fit scanner with a 20-channel head coil. As in our previous studies (Yang et al. 2021a), the potential effects of data acquisition from different scanners were controlled using the ComBat method (Johnson et al. 2007; Yu et al. 2018).

High-resolution T1-weighted images were acquired with 3D-MPRAGE using the following parameters: $1 \times 1 \times 1$ mm^3 resolution, TR/TE = 1900/2.52 ms, flip angle = 9°, 160 contiguous 1-mm sagittal slices, FoV = 256 × 256 matrix.

One run of resting state fMRI images was acquired with an echo-planar sequence using the following parameters: flip angle = 90°, TR/TE = 2040/29 ms, FoV = 64 × 64 matrix, 35 interleaved axial slices (4 mm thick, no gap; $3.2 \times 3.2 mm^2$ in plane resolution). There were 264 acquisitions, and the first 5 acquisitions were discarded to allow for magnetization stabilization.

The Computational Anatomy Toolbox (CAT, version 12.6) (www.neuro.uni-jena.de/cat/) and the CONN functional connectivity toolbox (https://www.nitrc.org/projects/conn/) were used for preprocessing and analyzing structural and functional MRI data, respectively. Default preprocessing procedures in the CAT and CONN software were applied. Standard structural MRI preprocessing in CAT consisted of correction for bias-field inhomogeneities, denoising, skull-stripping, segmentation, and corrections for partial volume estimation. Resting-state functional images were first preprocessed in SPM12 (https://www.fil.ion.ucl.ac.uk/spm/). The preprocessing of functional MRI data included slice-timing correction, realignment, coregistration to structural volume, normalization based on structural normalization parameters obtained from CAT12, outlier identification, and smoothing with an 8-mm FWHM. Normalized images were then processed following the standard CONN pipeline (Whitfield-Gabrieli and Nieto-Castanon 2012). The temporal processing in CONN included removal of 36 regressors (9 confounding factors: six movement parameters + signals from CSF/white matter/gray matter, as well as their temporal derivative, quadratic term, and temporal derivatives of each quadratic term), band passing [0.01 0.1] Hz, detrending. Instead of using global signal as a nuisance regressor, signals from gray matter, white matter, and CSF were each modeled in separate nuisance regressors in the current study.

Quality Control (QC) of MRI images

All the MRI images, including T1 images in native space, normalized T1 images, resting-state BOLD images in native space, and normalized resting-state BOLD images, were visually inspected by F.N.Y. A binary quality rating for each image was created (0: fail, 1: pass). For T1 images, an additional quality assurance rating generated by CAT12 was used: the overall rating had to be higher than 3.5 (i.e., higher than the satisfactory quality). For resting-state BOLD images, maximum movement in any direction or maximum rotation had to be lower than 1 mm or 1° (additional scrubbing process was applied to volumes that did not meet this criterion), respectively. Two PWH participants were excluded due to failure to pass QC, i.e., with visible brain anomalies. A third PWH participant was excluded due to poor signal in 13 out of 300 ROIs (i.e., no GM signal in these ROIs).

Functional network analysis

The atlas we used has 300 functionally defined cortical, subcortical, and cerebellar areas (Seitzman et al. 2020). Functional connectivity between all pairs of regions from this atlas was calculated using average wavelet coherence (http://grinsted.github.io/wavelet-coherence/) between 0.01 and 0.1 Hz (Gu et al. 2015; Zhang et al. 2016; Yu et al. 2019). We excluded 5 ROIs due to poor signal quality (i.e., no GM signal) and signal dropout and 12 more ROIs that were not assigned to a specific network, which resulted in 282 ROIs for the subsequent analyses. There 282 ROIs were grouped into 13 well-defined brain networks, including default mode network (DMN), visual network (VIS), frontoparietal network (FPN), reward network (REW), dorsal attention network (DAN), ventral attention network (VAN), salience network (SAL), cingulo opercular network (CON), dorsal somatomotor network (dSMN), lateral somatomotor network (lSMN), auditory network (AUD), parietomedial network (PMN), and medial temporal lobe (MTL). Within- and between-network connectivities were defined by previous studies (Gu et al. 2015; Yu et al. 2019). Within-network connectivity was calculated as the average functional connectivity within all ROIs in each of 13 brain networks. Two types of between-network connectivity were defined as follows: pairwise between-network connectivity between all pairs of the 13 brain networks (average functional connectivity between ROIs in one network and ROIs in another network), and one-versus-all-others between-network connectivity between each brain network and all other brain networks (average functional connectivity between ROIs in one network and ROIs in all other networks).

Group comparisons of network connectivity

Each network connectivity (within-, one-versus-all-others-, and pairwise between-network connectivity) was compared across groups using generalized linear model (GLM) analysis, adjusting for age, education, sex, and race as covariates. All p values were adjusted for multiple comparisons (13 within-network metrics + 13 one-versus-all-others between-network metrics + 78 pairwise between-network metrics = 104 comparisons) by controlling the false discovery rate (FDR).

Canonical Correlation Analysis (CCA)

To better characterize the multivariate relationship between demographics (including HIV infection) and network connectivity, CCA was performed in the combined sample of PWH and controls. CCA seeks maximal correlations between

combinations of variables in both sets (demographics and network connectivity). To reduce dimensionality, a principal component analysis (PCA) was conducted on 91 network connectivity measures (13 within-network connectivity and 78 pairwise between-network connectivity) (Fig. 1). We chose the first 23 components that explained more than 90% of the total variance. These 23 principal components of network connectivity were used as one set of variables in CCA. The other set consisted of each patient's demographics, including age (years), education years, sex (1 = male at birth, 0 = female at birth), race (1 = African American, 0 = not African American), and HIV infection (1 = PWH, 0 = healthy controls) (similar results were found if we normalized these two sets of variables before running CCA). A schematic illustration of the CCA analysis is provided in Fig. 2. The CCA provided 5 pairs of modes that maximally correlated the network variables and the demographics. For each pair of CCA modes, a permutation testing procedure with 10,000 permutations was performed to test the significance (one set of variables was randomly shuffled across rows, then CCA analysis was rerun). In addition, a more strict statistical analysis Bartlett's χ^2 statistic was performed. Only if both tests rejected the null hypothesis of no association at the level of $p < 0.05$, was a CCA mode pair considered significant in this study. Given a significant CCA mode pair, Pearson's correlations between each CCA mode and the corresponding set of network connectivity or demographics were performed (FDR-corrected for multiple comparisons). These tests were conducted to quantify the strength of the contribution of the individual network connectivity and demographics to the corresponding CCA mode.

Statistical analyses

The statistical analyses were conducted in SPSS 27.0 (Chicago, IL), and MATLAB 2018b (Math Works, Natick, MA). All statistical analyses were two-tailed.

Contingency χ^2 tests and ANCOVA were used to examine group differences in demographics between PWH and controls (see Table 1). As our sample of participants was predominantly African American (AA), race was defined as a dichotomous variable: AA (1), non-AA (0).

PCA and CCA were conducted using the functions *pca* and *canoncorr* in MATLAB, respectively. Point-biserial correlation was used to calculate associations between dichotomous variables and continuous variables, in a way similar to Pearson's correlation.

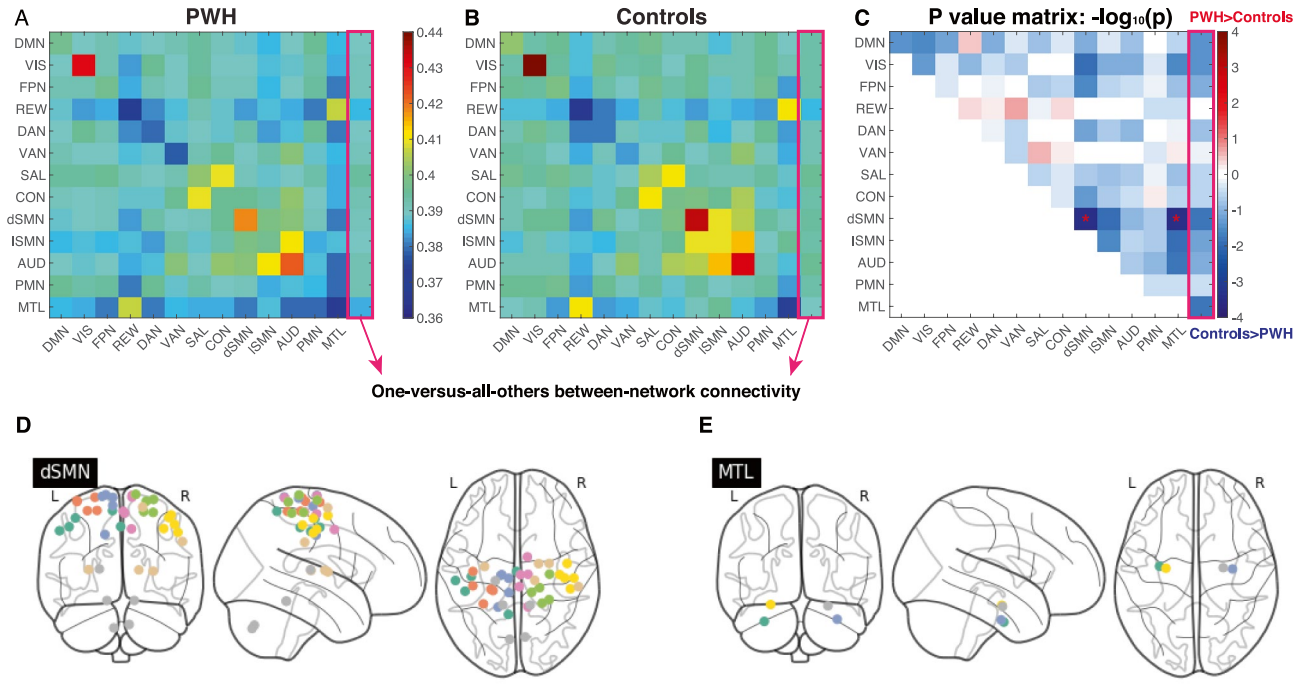

Fig. 1 Functional connectivity (FC) of within- and between-networks. Network connectivity metrics, including 13 within-network connectivity, 78 pairwise between-network connectivity, and 13 one-versus-all-others between-network connectivity (outlined in red rectangle), of **A** PWH and **B** controls. **C** Differences between PWH and controls in those 104 network connectivity measures, depicting as $-\log_{10}(p)$ values. Red star represents p values that survived FDR correction. Red means PWH had higher network connectivity values than controls, while blue denotes controls had higher network connectivity values than PWH. Brain regions (center MNI coordinates) that belong to **D** dSMN and **E** MTL, respectively

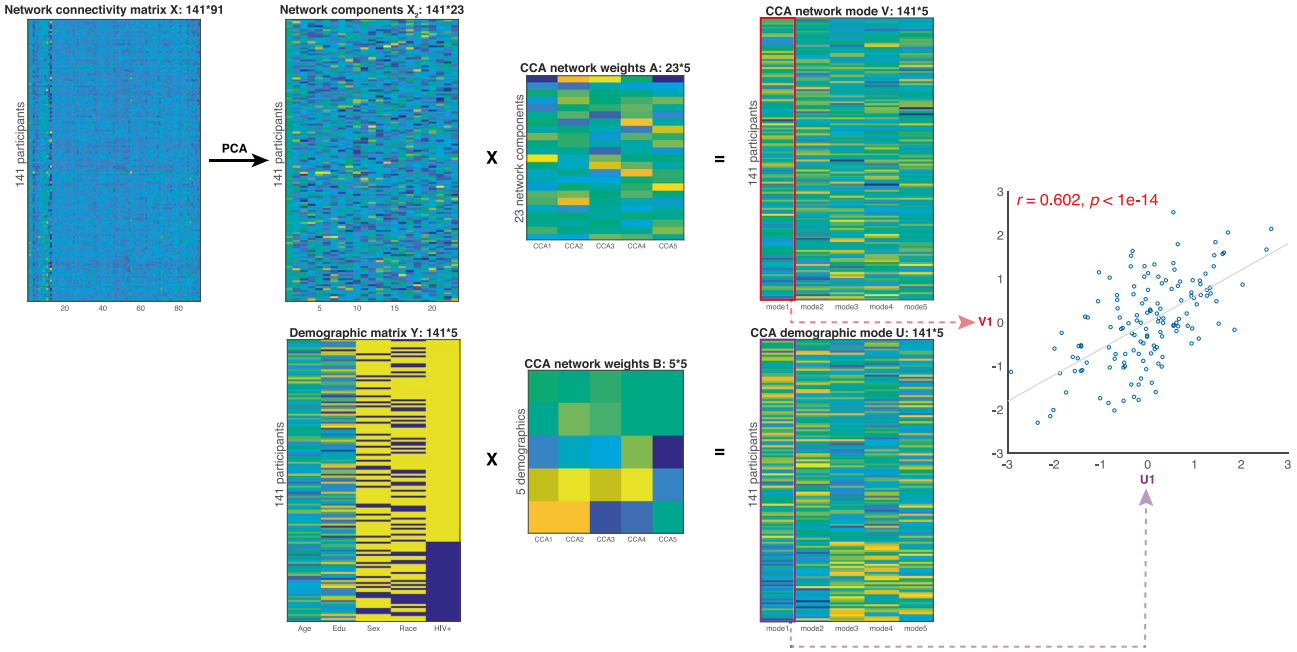

Fig. 2 Schematic illustration of the CCA. First, PCA was performed on network connectivity matrix X (141 participants * 91 network connectivity measures). This resulted in network component matrix X_2: (141 participants * 23 network components). CCA was conducted on X_2 (141*23) and Y (141 participants * 5 demographics (including HIV infection status, age, sex, race, and education)) by applying calculated weight *A* and *B* to X_2 and Y, respectively. The products of CCA were CCA network mode V (141*5) and CCA demographic mode U (141*5). Only the first mode pair V1 and U1 reached statistical significance in both nonparametric tests. The scatter plot of the correlation between V1 and U1 is shown on the right side of this figure. V1 and U1 were highly correlated ($r = 0.602$, $p < 1e^{-14}$)

Results

Participants

There were no significant differences in demographics, GDS, and GMT between PWH and controls (Table 1).

Differences of network connectivity between PWH and controls

Mean network connectivity in PWH and controls is shown in Fig. 1A, B, respectively. Overall patterns of network connectivity were comparable between PWH and controls (2d correlation coefficient = 0.948, measured by *corr2* in MATLAB). However, PWH have decreased network connectivity compared to controls in general. Specifically, PWH have significantly lower within-network connectivity in dSMN ($F_{(1,135)} = 13.39$, $p = 0.018$ FDR-corrected), and reduced between-network connectivity in dSMN-MTL ($F_{(1,135)} = 13.44$, $p = 0.018$ FDR-corrected), after controlling for age, education, sex, and race. Figure 1D, E depict network nodes of dSMN and MTL, respectively.

In addition, both within-network connectivity in dSMN and between-network connectivity in dSMN-MTL were not significantly correlated with HIV markers (CD4 nadir, current CD4, and disease duration) and *T*-scores in seven cognitive domains.

Correlation patterns of network connectivity with demographics

To further investigate the multivariate relationship between network connectivity and demographics (including HIV infection), CCA was performed between these two sets

Table 1 Demographics, GDS, and GMT of PWH and controls

Demographics	PWH	Controls	*p* values
Age	56.3 (6.4)	54.6 (7.1)	n.s
Edu	14.3 (3.0)	14.6 (2.7)	n.s
Sex (female%)	24.8%	35.0%	n.s
Race (AA%)	64.4%	60.0%	n.s
GDS	0.33 (0.40)	0.39 (0.47)	n.s
GMT	48.84 (6.39)	49.57 (7.54)	n.s
# participants	101	40	

Note: Data depicted as mean (standard deviation)

PWH people with HIV, *n.s.* non-significant, *Edu* education (the number of years of formal education), *Sex* sex at birth, *AA* African Americans, *GDS* global deficit score, *GMT* global mean *T*-score

of variables in 141 participants (101 PWH + 40 controls). The first CCA mode pair reached statistical significance under two different non-parametric tests (permutational $p = 0.023$, Bartlett's χ^2 test $p = 0.021$). Next, we examined the relationship between demographics and the identified demographic CCA mode. All five demographics were significantly correlated with the demographic mode (all $p < 1 \times 10^{-7}$, FDR-corrected, see Fig. 3A, B). The associations between 91 network connectivity measures and the network CCA mode were also investigated. The majority of network connectivity measures were negatively correlated with the network CCA mode (see Fig. 3C). Seventeen out of 91 network connectivity measures were significantly correlated with the network CCA mode ($p < 0.05$, FDR-corrected, see Fig. 3D), including within-network connectivity in the DMN, VIS, FPN, DAN, VAN, dSMN, lSMN, AUD, and PMN.

To better understand the association between demographics and network connectivity, we did a post hoc correlation analysis between demographics and the 17 network connectivity measures (correlation coefficients are depicted in Fig. 3E). In general, years of education and being male at birth (male at birth was coded as 1) were positively correlated with network connectivity, while age, being minority (AA was coded as 1), and HIV infection were negatively correlated with network connectivity.

Discussion

In this study, we investigated the effects of HIV and demographics on the architecture of whole-brain functional networks. After controlling for age, years of education, sex, and race, wavelet coherence analysis revealed that compared to demographically comparable controls, PWH had lower within-network connectivity in dorsal somatosensory network as well as lower between-network connectivity (between the dorsal somatosensory network and medial temporal lobe). We further explored the combined effects of demographics and HIV infection status on the multivariate patterns of network connectivity. The result suggested that age, being minority, being female at birth, and HIV infection might be risk factors for abnormalities in 17 functional network connectivity measures, while higher levels of education might be beneficial for maintaining normal functional network connectivity.

Despite the fact that most PWH in the current study were on stable cART and had successful peripheral viral suppression and there was no difference in global cognitive function between PWH and controls (Table 1), disrupted network connectivities in dSMN and between dSMN-MTL were prominent in PWH. These results converge with previous magnetoencephalography (MEG) studies, which showed that PWH had decreased activity in both postcentral gyrus and supplementary motor area (Becker et al. 2013; Wilson

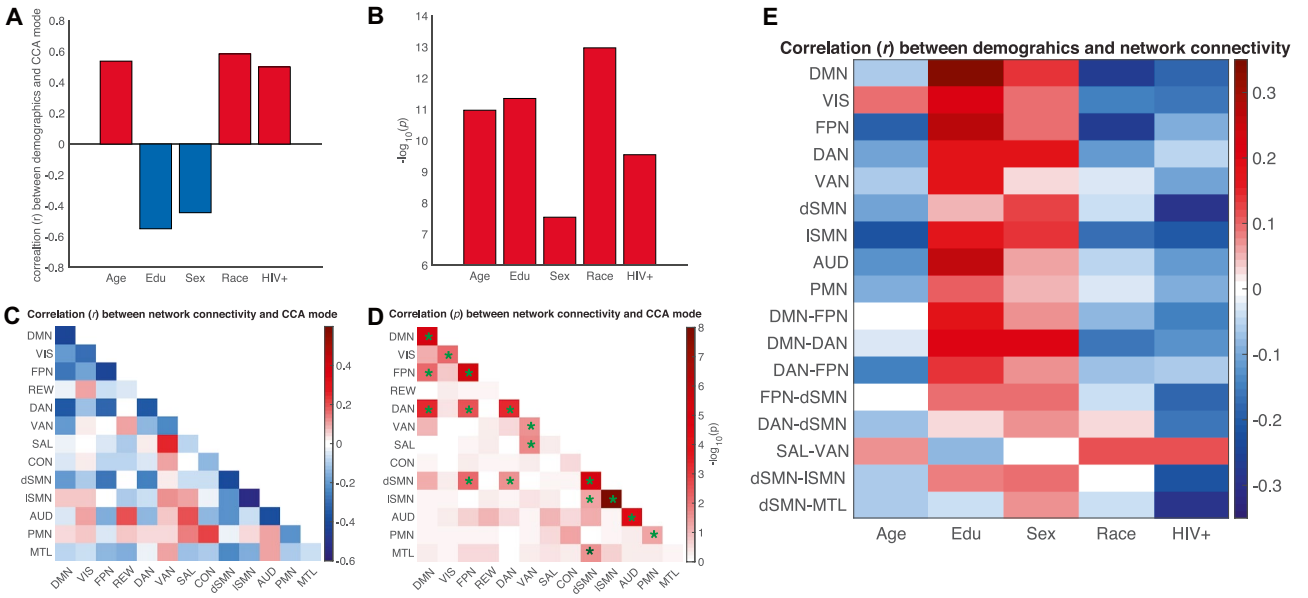

Fig. 3 Results of CCA. **A** Correlations between demographics and CCA demographic mode U1. FDR corrected p values of those correlations are shown in **B**. Similarly, correlations between network connectivity and CCA network mode V1 are shown in **C**. FDR-corrected p values of those correlations are shown in **D**. Green stars indicate $p < 0.05$. **E** Post hoc correlation between demographics and network connectivity. Red represents positive correlation coefficients, and blue denotes negative correlation coefficients. Results were based on all participants

et al. 2015) (both belong to dSMN, see Fig. 1D) compared to controls. Furthermore, Wilson et al. (2015) reported that PWH had smaller left postcentral gyrus than controls, and more interestingly, the gray matter volume reduction in the left postcentral gyrus correlated with MEG anomaly (but only in PWH) (Wilson et al. 2015). Taken together, it is notable that PWH have shown various dSMN deficits using different imaging modalities, suggesting the neural injury to the dSMN might be prevalent in PWH, which in turn might underlie the prevalent injury in the motor and related neurocognitive domains (Heaton et al. 2011). Although MTL, consisting of bilateral anterior hippocampus and entorhinal cortex in the current study, has been involved in various neurodegenerative diseases including HAND (Moore et al. 2006), few studies have investigated the association between dSMN and MTL. Additional studies are needed to further examine the role of dSMN-MTL relationship in HIV pathology.

Of note, previous FC studies with resting state fMRI data did not find an effect of HIV on the sensorimotor network (Thomas et al. 2013; Cole et al. 2018). Several factors might contribute to this discrepancy. First, the regions involved in the sensorimotor network in the previous studies (Thomas et al. 2013; Cole et al. 2018) were different from dSMN used in the current study, which was based on a recently developed brain parcellation atlas (Seitzman et al. 2020) and included subcortical regions (putamen and thalamus) and cerebellar regions (cerebellar lobes 4, 7, 8). Both subcortical and cerebellar structures are known to be vulnerable to HIV pathology (Israel et al. 2019). Second, wavelet coherence, instead of Pearson correlation, was used to quantify FC in the current study. Wavelet coherence has several benefits over Pearson correlation, such as robustness to outliers (Gu et al. 2015; Mohanty et al. 2020). Third, most PWH in the current study are on stable cART and virally suppressed. Fourth, difference in demographics among studies might contribute to the inconsistent findings, as suggested by the present study, in which we found that all four demographic factors had strong impacts on brain networks (Fig. 3).

The current study did not directly investigate the difference in functional connectivity between PWH with HAND and PWH without HAND. However, using a different approach (Shen et al. 2017), our previous study revealed that the functional connectivity associated with the right post-central gyrus, the right putamen, and the cerebellum lobe VIII may have the potential to differentiate cognitively impaired PWH from controls and cognitively normal PWH (Yang et al. 2021b). Importantly, these regions are part of the dSMN in the current study, providing converging evidence suggesting that alterations in the dSMN may play an important role in HAND status.

The CCA results have several important implications. First, advanced age and HIV showed similar detrimental effects on a multivariate pattern of network connectivity, especially on within-network connectivity in DMN, FPN, and lSMN. This is consistent with a previous study that found additive effects of HIV and aging on the DMN (Thomas et al. 2013), suggesting that older PWH may be at an elevated risk of neural injury, which in turn may put them at a greater risk of neurocognitive impairment (Morgan et al. 2012). Second, we found that being female at birth was associated with increased network disruptions in these middle- to advanced-age participants. The increased network disruptions might reflect/underlie the higher risk of cognitive impairment (Maki et al. 2018; Sundermann et al. 2018; Duarte et al. 2021; Liang et al. 2021) and neural injury (Liang et al. 2021) in women with HIV than men with HIV. However, this result should be taken with caution: (i) the study sample was imbalanced with regard to sex at birth, with 25 female PWH versus 76 male PWH; (ii) the small sample size might also limit our capability to explicitly test this prediction with PWH only, which produced an insignificant model. Third, the data suggested that being minority was associated with worse network disruptions, which is in line with a higher risk of cognitive impairment in African Americans living with HIV (McCombe et al. 2013; Cross et al. 2013). The greater impairment in African Americans is likely due to a combination of multiple and complicated factors, including socioeconomic status (SES) (Arentoft et al. 2015) and associated comorbidities (e.g., type 2 diabetes (Signorello et al. 2007))— all of them have known impacts on brain health and brain functions. Last but certainly not the least, the CCA results revealed that education acted in the opposite direction of age and HIV infection in affecting functional brain networks, with higher number of years of formal education associated with less disruptions to the functional networks (mainly higher within- and between-network FCs, Fig. 3). This is in line with studies examining healthy adults and reporting higher educational achievement is beneficial for different measurements of functional connectivity (Marques et al. 2016; Perry et al. 2017; Hausman et al. 2020), suggesting education might act as a protective factor against neural injury (i.e., disruptions to functional brain networks) due to advanced age and HIV infection, which in turn might underlie (at least partially) the association between education levels and risks of neurocognitive impairment in PWH (Bonnet et al. 2013). Furthermore, these data suggested that, in addition to using demographically comparable controls, the usage of covariates is justified, and the impact of covariates on the results should be investigated (Hyatt et al. 2020).

This study has several limitations. First, consistent with several other studies (e.g., Thomas et al. 2013), we also did not find any correlations between network connectivity and NP scores and HIV markers. This might be due to a

relatively young sample (41–70 years old) and/or relatively normal cognitive performance in our sample of PWH. Second, there was a significant correlation between race and GMT across all participants ($p = 0.0006$) in this study, with African Americans living with HIV had lower GMT scores, suggesting a potential bias in study sampling. Even though there were no correlations between network connectivity and GMT scores, the difference in GMT scores might still contribute to the CCA results, i.e., the observed negative impact of being a member of a minority ethnic/racial group on brain networks was driven by difference in global neurocognitive function in the current study sample, at least partially. Third, due to a small sample size with female participants and a lack of socioeconomic data (such as household income), we were not able to fully investigate the mechanisms underlying the association between network connectivity and race or sex in the present study. Future studies with a large sample size, more balanced participant groups (i.e., more female participants, and comparable global cognitive function between ethnic/racial groups), and detailed info on SES status are warranted to address these questions. Fourth, PWH with higher educational attainment tend to have better cART adherence, which may lead to longer duration of successful viral suppression that might contribute to the impact of education on functional connectivity in the current study. However, the current study did not have the data to accurately quantify the duration of viral suppression. Future studies with longitudinal cohorts may help to directly address this important question.

In summary, we found a systemic reduction in functional connectivity of within- and between-networks in PWH (compared to controls). In addition, while advanced age and HIV infection negatively affected functional network connectivity, the opposite relationship was identified for education, suggesting that higher educational attainment may ameliorate the detrimental impact of age and HIV infection on functional brain networks.

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Author contribution Statistical analysis conducted by Fan Nils Yang.

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Declarations

Conflict of interest The authors declare no competing interests.

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