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Resting-state functional magnetic resonance imaging in clade C HIV: within-group association with neurocognitive function

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Abstract Neuroimaging abnormalities are common in chronically infected HIV-positive individuals. The majority of studies have focused on structural or functional brain outcomes in samples infected with clade B HIV. While preliminary work reveals a similar structural imaging phenotype in patients infected with clade C HIV, no study has examined functional connectivity (FC) using resting-state functional magnetic resonance imaging (rs-fMRI) in clade C HIV. In particular, we were interested to explore HIV-only effects on neurocognitive function using associations with rs-fMRI. In the present study, 56 treatment-naïve, clade C HIV-infected participants (age 32.27 ± 5.53 years, education 10.02 ± 1.72 years, 46 female) underwent rs-fMRI and cognitive testing. Individual resting-state networks were correlated with global deficit scores (GDS) in order to explore associations between them within an HIV-positive sample. Results revealed ten regions in six resting-state networks where FC inversely correlated with GDS scores (worse performance). The networks affected included three independent attention networks: the default mode network (DMN), sensorimotor network, and basal ganglia. Connectivity in these regions did not correlate with plasma viral load or CD4 cell count. The design of this study is unique and has not been previously reported in clade B. The abnormalities related to neurocognitive performance reported in this study of clade C may reflect late disease stage and/or unique host/viral dynamics. Longitudinal studies will help to clarify the clinical significance of resting-state alterations in clade C HIV.

Keywords Human immunodeficiency virus (HIV) · Neurocognitive deficits · Resting-state functional magnetic resonance imaging · Resting-state functional connectivity (RSFC) · Global deficit scores (GDS)

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Introduction

HIV-associated neurocognitive disorders (HAND) are a common sequel of HIV infection and persist despite the use of combination antiretroviral therapy (cART) (Heaton et al. 2010). In HIV-infected individuals, the relative contribution of HIV disease mechanisms, cART, and host variables to the expression of cognitive impairment remains unclear. The diagnosis of HIV-associated cognitive impairment requires testing of multiple neurocognitive domains, including attention, information processing, language, complex perceptual motor skills (or psychomotor processing), learning, memory, and simple motor skills (McArthur 2004; Gartner 2000; De Francesco et al. 2016). The incidence of severe forms of HAND has declined through the effects of cART, but milder

forms remain persistent, and may be increasing in prevalence. It is unclear whether these milder forms are a precursor of more severe disorder; or whether the frequency is inflated by limitations in the diagnostic process (Gisslen et al. 2011). A valid imaging biomarker in neuropsychologically impaired individuals would help to clarify some of these concerns through a more direct link to HIV neuropathology.

Prior studies reveal variability in the reported prevalence of HAND. These may be the result of differences in the adaptation and use of neuropsychological testing across sites, cART-experience and regimen, HIV disease stage and degree of viral suppression, and demographic characteristics of the study samples (such as gender, age, and pre-morbid cognitive reserve) (Bouwman et al. 1998; Antinori et al. 2007). The net effect is limited insight into the association between neuropathological HIV effects and clinical impairment. HIV genotype has also been proposed as a source of variability in HAND since the subtypes of HIV are not equally distributed on a global basis. While HIV-B is prevalent in North America and Europe, HIV-C is dominant in Sub-Saharan Africa and Southeast Asia (Rotta and Almeida 2011). Most of the neuroimaging work conducted to date in HIV has focused on structural and functional markers of HAND in HIV-B. Structural neuroimaging of HIV-C in South Africa confirm neurovirulence, with smaller volumes in the total gray matter (GM), white matter (WM), and thalamus in HIV-infected participants compared to healthy controls (Heaps et al. 2012). A further study comparing volumes between HIV-B and HIV-C samples with respect to local controls revealed no effect of HIV subtype (Ortega et al. 2013). Again, there are limited data linking neuroimaging signature of HIV-C and cognitive abilities. Specifically, there are no studies exploring the resting-state functional properties of the brain in HIV-C individuals. Resting-state functional magnetic resonance imaging (rs-fMRI) is a non-invasive imaging technique that permits investigation of resting-state functional connectivity (RSFC), which adds additional information to existing structural imaging modalities. Previous studies indicate high sensitivity of RSFC to impaired brain function across multiple clinical disorders (Van den Heuvel and Pol 2010; Wang et al. 2013; Zhou et al. 2013).

HIV-B infected individuals exhibit altered connectivity in the attention network (Ortega et al. 2015), thalamus (Qiu et al. 2011), and the default mode network (DMN) (Thomas et al. 2013; Wang et al. 2011), when compared to HIV- controls. Only Wang et al. (2011) identified a link between connectivity and cognitive performance in HIV-B where connectivity in the lateral occipital cortex network was correlated with a task involving visual-motor coordination. While these previous studies focused on between group effects, Ann et al. (2016) focused on RSFC between HAND and non-HAND participants using a seed-based analysis centered in the bilateral precuneus. They found reduced connectivity between the bilateral precuneus and prefrontal cortex in the HAND participants compared to cognitively intact HIV+ individuals. Additionally, increased connectivity in the DMN correlated with better performance on tests of learning and memory. While informative, these studies included mixed samples of cART-naïve individuals, and the methodological approach did not examine whole-brain correlations between RSFC and cognitive function.

We designed our study to identify HIV-specific effects on RSFC in a cohort of treatment-naïve HIV-infected individuals by inserting Global Deficit Scores into the general linear model (GLM). Our research further adds to the literature by specifically investigating these effects in HIV-C, for which there are limited data. We hypothesized that worse cognitive function would correlate with altered connectivity through a range of resting-state networks, and that these patterns would correspond to the typical cognitive phenotype of treatment-naïve HIV.

Methods

Participants

We included 61 HIV+ and 50 HIV- demographically similar control participants from a larger study (Paul et al. 2014), for the purposes of neurocognitive ascertainment. Data from only the HIV+ participants were then used to explore the associations between RSFC and cognition. All participants provided consent to participate in the study as prescribed by the Human Research Ethics Committee at the University of Cape Town. Exclusion criteria included schizophrenia and bipolar mood disorder, neurological disorders such as multiple sclerosis and other central nervous system (CNS) conditions, head injury with more than 30 min loss of consciousness, clinical evidence of opportunistic CNS infections, and substance use disorder as defined by the Mini-International Neuropsychiatric Interview (MINI-Plus) (Lecrubier et al. 1997). Additionally, participants with possible pregnancy, claustrophobia, or metal implants were disqualified from participation in the study as these factors would affect scanning.

Participants were recruited from two primary care HIV clinics in Cape Town, South Africa, prior to cART initiation. As such, all were cART-naïve at the time of participation. Inclusion criteria included an age range of 18 to 45 years, and Xhosa as the primary language. HIV status was determined by an enzyme-linked immune assay (ELISA) and confirmed by either a Western blot, plasma HIV RNA, or a second antibody test. HIV subtype was determined by polymerase chain reaction (PCR) of the tat exon 1 region (HXB2 position 5831–6045), using the Promega GoTaq Flexi Kit (Promega, Madison, WI). This approach has been described in Paul et al. (2014, 2017).

Neuroimaging scans were acquired and blood samples were taken during a separate visit 1 week after neuropsychological testing and prior to commencing cART.

Neuropsychological assessment

All cognitive tests were performed by a psychometrist fluent in both Xhosa and English. Tests included grooved pegboard test, the Hopkins Verbal Learning Test-Revised (HVLT-R) (Brandt and Benedict 1991), Rey Complex Figure Test (RFC) (Knight and Kaplan 2003), Brief Visuospatial Memory Test-Revised (BVMT-R) (Benedict et al. 1996), Mental Alternation Test (MAT) (Salib and McCarthy 2002), Wechsler Memory Scale III (WMS III) (Wechsler 1997), Trail Making Test A (TMTA) (Corrigan and Hinkeldey 1987), Color Trails Test (CTT) (D'Elia and Satz 1996), Stroop Color Word Test (Golden 1978), Wisconsin Card Sorting Test (WCST) (Grant and Berg 1948), and the Wechsler Abbreviated Scale of Intelligence (WASI) (Wechsler 1999).

Cognitive performances recorded for the HIV-infected group were converted to *T* scores based on comparisons to the HIV-negative sample. T scores were then converted to global deficit scores (GDS) as described previously (Carey et al. 2004). The GDS, within the HIV+ group only, were then used to explore the resting-state signature of HIV infection.

MRI scanning protocol

A 3T Allegra MRI scanner (Siemens, Erlangen, Germany) located at the Cape Universities Brain Imaging Centre (CUBIC), in Cape Town, South Africa, was utilized for all scans. For each subject, a gradient echo planar imaging (EPI) sequence was used to acquire rs-fMRI data: voxel resolution = $4 \times 4 \times 4$ mm^3; FOV = $256 \times 256 \times 144$ mm^3; 36 slices; 164 volumes; TR/TE = 2200/27 ms; flip angle = 90^o. Additionally, T1-weighted (T1w) structural images were acquired using an MPRAGE sequence for each subject: voxel resolution = $1 \times 1 \times 1$ mm^3; FOV = $256 \times 256 \times 176$ mm^3; 176 slices; TR/TE = 2400/2.38 ms; TI = 1000 ms; flip angle = 8^o.

Pre-processing

Processing and analyses of all imaging data were performed using tools in AFNI (Cox 1996) and FSL (v5.0) (Smith et al. 2004), as well as in-house scripts. Prior to processing of the functional data, each subject's T1w volume was skull-stripped by means of in-house scripts and AFNI's *3dSkullStrip*, for later use in alignment and registration. Each subject's skull-stripped anatomical was visually checked to ensure the quality of the processing, with adjustments performed as necessary.

The main processing of each subject's rs-fMRI data was implemented using a set of procedures specified with AFNI's *afni_proc.py* tool as follows. First, the first four time points were removed from each EPI time series, spikes were truncated, and slice timing correction was applied to adjust for the temporal offset between slice acquisitions. The EPI volumes were coregistered using 6 degrees of freedom (3 translation and 3 rotation) to adjust for motion during scanning and aligned to the T1w anatomical image. Volumes exceeding 0.3 mm of bulk motion were excluded from further analyses. The average subject motion for the remainder of the volumes was found to be 0.10 ± 0.05 mm. Linear affine alignment of each subject's motion-adjusted EPI volumes to their T1w volumes was performed, which was nonlinearly warped to the standard Talairach-Tournoux template; these transforms were concatenated with the motion adjustment, and a single transform was applied to map the EPI data into standard space, maintaining their initial spatial resolution. Visual inspection of the alignment between the rs-fMRI data and the Talairach template was performed for each subject as an additional measure of quality control.

The T1w volumes were segmented into tissue masks of gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF). Signals from eroded maps of both WM and CSF were regressed out from the EPI time series along with motion, motion derivatives, and linear and quadratic trends. The EPI data were then spatially smoothed using a 6-mm full-width at half-maximum (FWHM) Gaussian kernel. Low-frequency fluctuations (LFFs) were calculated by bandpass filtering the time series in the standard interval 0.01–0.1 Hz, in order to reduce contributions of physiological processes in the BOLD signal.

Group independent component analysis (ICA) was preformed using FSL's MELODIC tool (Smith et al. 2004), in order to decompose the 4D time series data and to identify resting-state networks (RSNs) of high temporal correlation. A standard size of dimension reduction was used, producing 20 independent components (ICs). The ICs were compared with a standard set of RSN template maps from the Functional Connectome Project (Biswal et al. 2010) using *3dMatch* in FATCAT (Taylor and Saad 2013), with results also inspected visually. In this case, 14 ICs were identified as known functional networks, and these were thresholded at $Z > 4$ to provide network spatial masks of high RSFC. The remaining components (representing mainly non-GM tissue, edge alignment artifacts, small motion effects, etc.) were not included in further analyses.

Statistical analyses

General linear modeling (GLM) was implemented with non-parametric permutation testing in FSL to examine the association between the RSFC and GDS. The design matrix was set up to evaluate correlations between the connectivity measures of each RSN and participant GDS, while controlling for possible confounders. In this study, subject age, gender, and

Table 1 Sample characteristics of HIV-positive participants included in imaging analysis

Demographic variables	HIV positive
N	56
Age (years)	32.27 ± 5.53
Gender (male/female)	10/46
Education (years)	10.02 ± 1.72
GDS[a]	0.60 ± 0.59
Clinical measures	
CD4 count (cells/mm^3) at time of scan	185.39 ± 147.37
Average plasma viral load, RNA copies/mL (logged)	4.59 ± 1.02

[a] GDS values for the HIV-positive sample were calculated from *T* scores with respect to control group scores

education (number of years) were considered as potential confounders. Voxelwise connectivity *Z* scores were estimated for each subject and each network using FSL's *dual_regression* function (Beckmann et al. 2009). FSL's *randomize* function (Winkler et al. 2014) was then used to perform permutation tests for voxelwise GLMs using the specified design matrix, resulting in test statistic maps. AFNI's *AlphaSim* tool was used to determine the minimum cluster size of significant regions within the respective RSN with a corrected $p < 0.05/N$, where N is the number of networks identified, and alpha = 0.01. Significant clusters were then identified and extracted using FATCAT's *3dROIMaker*.

For each participant, an average RSFC value (i.e., *Z* score) was calculated for each significant cluster. SPSS (version 20; IBM, Armonk, NY) was used to determine Pearson correlation coefficients between the RSFC and GDS. Outliers, defined as the mean ± 3 times the standard deviation (SD), was removed from these calculations.

Results

Sample characteristics

Fifty-six participants were included in the subsequent analyses as excessive motion eliminated five participants (Table 1).

Resting-state networks

A total of 14 ICs were identified as standard RSNs. The IC number, network, and corresponding functional connectome project map are provided in Table 2. The RSNs were thresholded at a $Z > 4$ and binarized to form network masks (Fig. 1).

Resting-state connectivity correlations with GDS

Analyses revealed regions in 6 of the 14 identified networks where RSFC was significantly associated with cognitive impairment in HIV-infected participants. In all cases, the functional connectivity (FC) of the significant clusters was inversely related to GDS. Table 3 shows the peak coordinates

Table 2 Identified RSNs with network name, abbreviation, independent component number (IC no.) and corresponding network in the Functional Connectome Project (FCP) (Biswal et al. 2010) templates

Network name	Abbreviation	IC no.	Corresponding FCP no.
Visual occipital lobe	Vis1	00	02
Dorsal attention	dAtt	01	09
Right executive control	R-Exec	02	08
Default mode network	DMN	03	13
Dorsal default mode network	dDMN	04	06
Salience	Sal	05	16
Visual lingual gyrus	Vis2	06	01
Sensorimotor	SenMot	07	15
Ventral attention	vAtt	08	18
Left executive control	L-Exec	09	11
Attention	Att	10	20
Auditory	Aud	11	18
Cerebellum	Cer	12	07
Basal ganglia	Bas	13	12

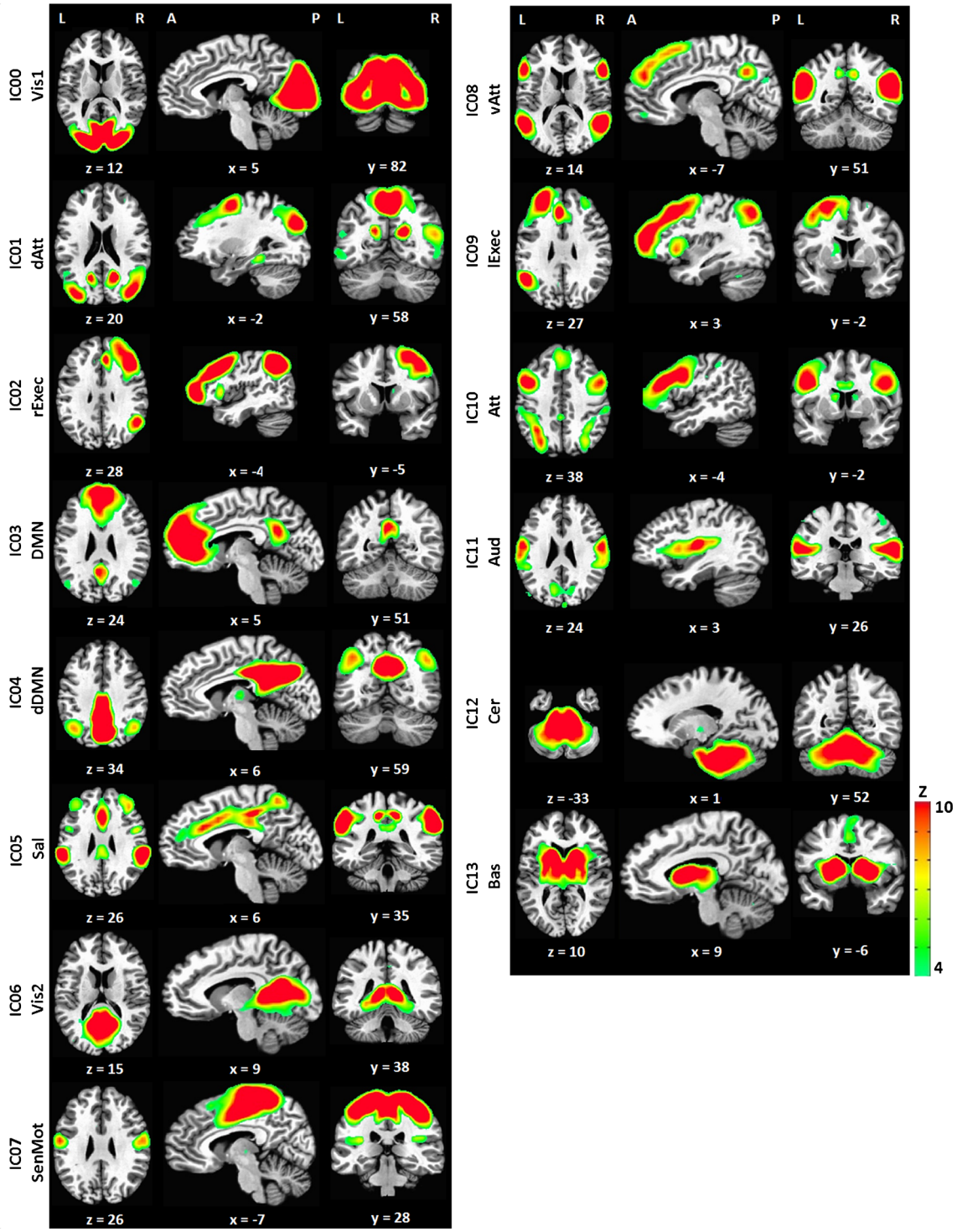

Fig. 1 *Z* score maps (thresholded $Z > 4$) representing the 14 RSNs identified by the ICA for 56 HIV+ subjects: visual occipital lobe (Vis1), dorsal attention (dAtt), right executive (R-Exec), default mode network (DMN), dorsal DMN (dDMN), salience (Sal), visual lingual gyrus (Vis2), sensorimotor (SenMot), ventral attention (vAtt), left executive (L-Exec), attention (Att), auditory (Aud), cerebellum (Cer), and basal ganglia (Bas)

of these regions of interest (ROIs) in each RSN, as well as the anatomical structure at the peak. Several networks contained more than one significant cluster.

Figures 2 and 3 show the cluster locations (blue) within the networks (hot colors). Additionally, the scatterplots of the RSFC-GDS correlations are shown for each cluster.

Table 3 Volumes, peak Talairach coordinates, and anatomical location of clusters showing significant association between resting state functional connectivity (RSFC) with global deficit scores (GDS). Also shown are the correlation (Pearson *r*) and significance values. In each case, reduced RSFC was associated with increased GDS. Figures 2 and 3 show region locations and scatterplots

Network	Size (mm^3)	Peak (mm)			*r*	*p*	Anatomical locations of peak
		x	*y*	*z*			
IC01 – Dorsal attention (dAtt) attention	2173	34	− 5	52	− 0.53	<0.001	Right precentral gyrus
IC03 – DMN	1920	18	47	36	− 0.40	0.003	Right superior frontal gyrus
IC07 - Sensorimotor (SenMot)	2176	− 42	− 29	36	− 0.32	0.016	Left postcentral gyrus
	2368	34	− 9	52	− 0.37	0.005	Right precentral gyrus
	4608	10	− 9	60	− 0.39	0.003	Right medial frontal gyrus
IC08 – Ventral attention (vAtt)	1984	58	− 17	− 20	− 0.39	0.003	Right inferior temporal gyrus
	2112	10	51	36	− 0.51	<0.001	Right superior frontal gyrus
IC10 – Attention (Att)	1920	54	23	20	− 0.36	0.007	Right inferior frontal gyrus
	2304	34	− 41	40	− 0.45	0.001	Right inferior parietal lobule
IC13 – Basal ganglia (Bas)	2816	6	− 5	8	− 0.36	0.007	Right thalamus

Discussion

We describe a unique association between neurocognitive function and RSFC in treatment-naïve HIV-C-infected adults. We found that reduced RSFC was correlated with cognitive deficits in the attention and sensorimotor networks, DMN, and basal ganglia. Our study is unique in the fact that no previous rs-fMRI studies identified regions of altered connectivity by inserting measures of cognition into the GLM analysis—even in the frequent clade B studies. As such, the present study is the first to report global cognitive function as a predictor of differences in resting-state network activation. In this way, rs-fMRI may hold promise as a sensitive biomarker of neurocognitive status.

The fact that RSFC was significantly affected in the attention networks is to be expected as impaired attention in HIV-infected individuals is common (Berger and Arendt 2000; Selnes 2005; Watkins and Treisman 2015; Cysique and Brew 2009; Nath et al. 2008; Heaton et al. 2004). Of the previous rs-fMRI studies, only one (Ortega et al. 2015) reported reduced RSFC between HIV-infected individuals and healthy controls in attention networks. However, they did not find any correlations between RSFC and neurocognitive impairment. In contrast, our results show reduced RSFC with increased cognitive impairment in five regions of the attention networks. These differences might be explained by methods, the absence of cART use in our samples, or the clinical and demographic composition of the samples.

We also found that cognitive deficits correlated with reduced RSFC in the thalamus, a structure known to be affected in several motor disorders, such Parkinson's disease and Huntington's chorea, (Mink 1996; Groenewegen 2003). The basal ganglia also play a role in emotional processing (Cancelliere and Kertesz 1990; Paulmann et al. 2008), learning and memory (Graybiel 2005; Packard and Knowlton 2002), and executive function (Graybiel 2000). Structural MRI has frequently shown that reduced subcortical volumes in HIV-infected individuals are related to neurocognitive impairment (Dal Pan et al. 1992; Aylward et al. 1993; Paul et al. 2002; Ances et al. 2006). The findings reported by Qiu et al. (2011) support our results. Specifically, Qiu et al. (2011) reported reduced regional homogeneity in the thalamus. Again, thalamic involvement may reflect a subcortical pattern commonly seen in untreated HIV.

Reduced RSFC in the sensorimotor network also correlated with worse global cognition. Juengst et al. (2007) performed task-based fMRI requiring simple sensorimotor activity in a between-group study of HIV-infected individuals with a range of HAND severity and healthy controls. While group differences were not identified, the hemodynamic response was delayed in the HIV-infected participants with minor neurocognitive

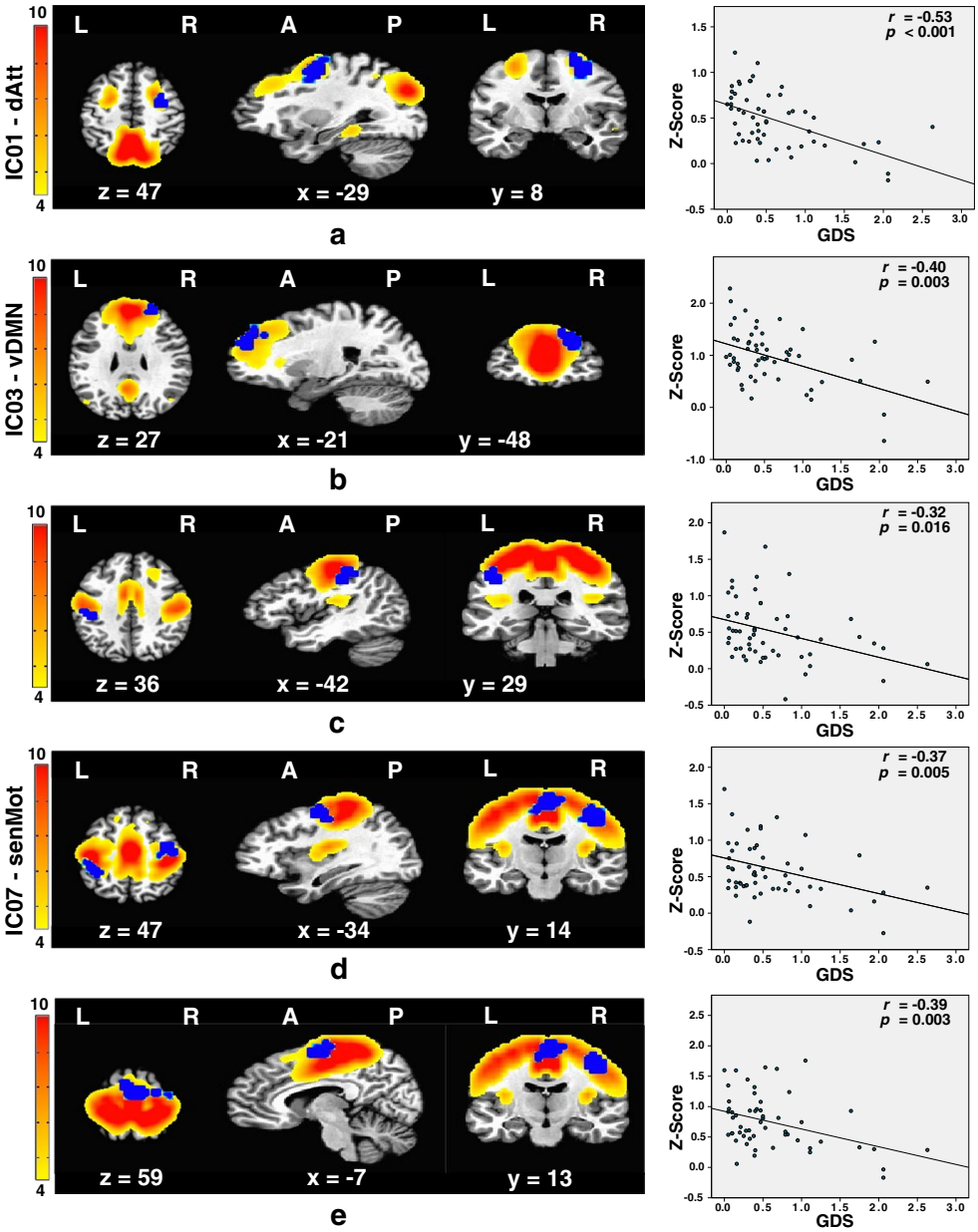

Fig. 2 (Left) Brain maps of clusters that exhibited significant associations between resting state connectivity (blue) in the dorsal attention network (hotter colors) for 56 HIV+ subjects. Peak is situated in **a** the right precentral gyrus of the dAtt network, **b** the right superior frontal gyrus of the DMN, **c**–**e** the left postcentral gyrus, right precentral gyrus, and right medial frontal gyrus of the SenMot network. (Right) Correlation graphs show relationships between average *Z* scores and GDS with *r* and corrected *p* values

disorder (MNCD) and HIV-associated dementia (HAD), which is consistent with alterations in neuronal functioning. By contrast, other rs-fMRI studies have not revealed altered RSFC in the sensorimotor network in HIV-infected patients. The absence of cognitive performance in the analytic models may account for these outcomes.

Our results of reduced RSFC in the DMN are supported by other studies focused on RSFC (Thomas et al. 2013) and regional homogeneity (Wang et al. 2011). Additionally, Ann et al. (2016) found positive correlations between the right inferior operculum and superior frontal gyrus, the specific region of the DMN identified in our study, with the memory and learning neuropsychiatric domains.

While the aforementioned studies did not specifically mention clade, they were performed in higher-income countries where clade B is prevalent. However, the different designs of these reports make it difficult to definitively ascribe altered RSFC findings to clade effects. In spite of this, our findings of altered connectivity with GDS in the attention network, thalamus, and DMN are reflected in these studies, irrespective of design and clade. In contrast, only our study found that

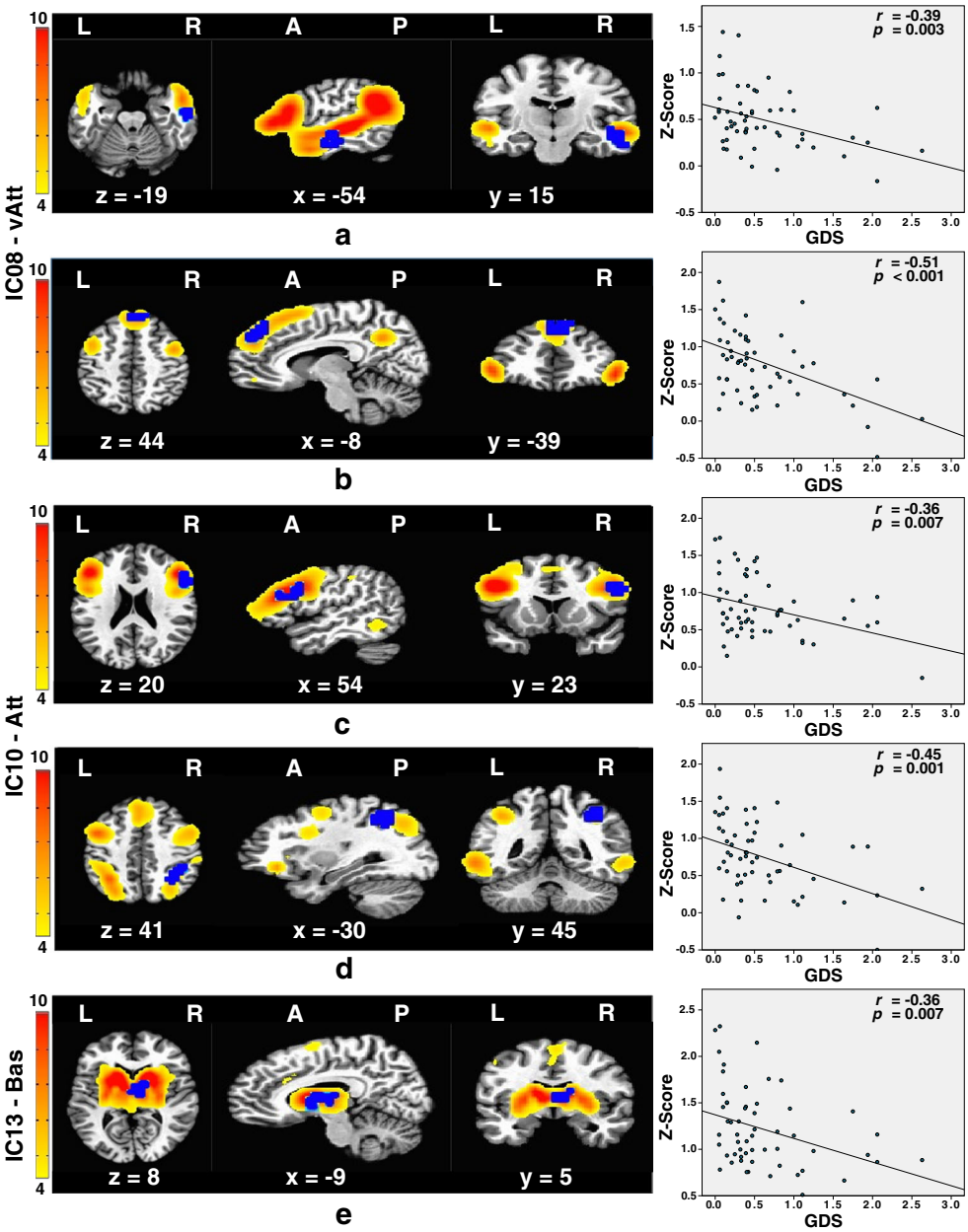

Fig. 3 (Left) Brain maps of clusters that exhibited significant associations between resting state connectivity (blue) in the dorsal attention network (hotter colors) for 56 HIV+ subjects. Peak is situated in the right inferior temporal gyrus and right superior frontal gyrus in the vAtt network (**a**—**b**), the right inferior frontal gyrus and right inferior parietal lobule in the Att network(**c**–**d**), and the right thalamus in the Bas (**e**). (Right) Correlation graphs show relationships between average *Z* scores and GDS with *r* and corrected *p* values

RSFC in the sensorimotor network was affected. Table 4 summarizes the methodologies, demographics, and major findings of the cited articles. Firstly, there are several demographic differences between these studies and our own, namely that most of the participants in our sample were female with fewer years of education than the prior studies. Secondly, our sample only included treatment-naïve individuals, as compared to the other studies mostly including cART-experienced samples. These differences may account for the level of RSFC disruption observed in the present study. Thirdly, viral clade differences may be present. Previous work from our team confirms that HIV-C is neurovirulent, despite earlier preclinical evidence suggesting lower neurotoxicity of clade C due to a polymorphism in the Tat C31 dicysteine motif. We have previously reported outcomes from the sample included in this study demonstrating no differences in cognition or structural neuroimaging when individuals with the Tat C31S substitution are compared to individuals without the Tat defect (Paul et al. 2014). Results from the present study align with the general conclusion that clade C is neurovirulent.

In conclusion, this is the first rs-fMRI to investigate RSFC in relation to neurocognitive deficits in treatment-naïve clade C HIV. We found that reduced RSFC was associated with increased global cognitive deficits in the attention and sensorimotor networks, the DMN, and the thalamus. Neurocognitive functions controlled by these networks are involved in the

Table 4 Comparison of demographics, methodologies, and results of referenced articles

Study	HIV					Control			Study design	Findings
	N	Age	Gender % male	Years of education	Number of patients on treatment	*N* Age	Gender (% male)	Education (years)		
Wang et al. 2011	15	29.5 ± 6.3	73	15.5 ± 2.0	8	15 29.5 ± 6.1	87	14.5 ± 2.1	HIV-infected vs control participants group analysis Correlation with NP measures of regions identified in group analysis	Decreased coactivation in lateral occipital network (DMN) in HIV compared to control Inverse correlation between RSFC and GP Dominant in LOC (HIV only) Positive correlation between RSFC and RFC in LOC (HIV only)
Ortega et al. 2015	CART−: 49 CART+: 82	CART−: 34.9 ± 15.4 CART+: 41.5 ± 14.5	CART−: 86 CART+: 63	CART−: 13.4 ± 2.3 CART+: 12.9 ± 3.	82	45 31.7 ± 10.9	58	13.4 ± 2.7	Group analysis between HIV CART+, HIV CART−, and controls	Reduced connectivity in striatum and DMN, and ventral attention network of HIV+ compared to control. HIV+ CART + had higher RSFC between striatum and DMN than HIV+ CART- subjects
Qiu et al. 2011	13	45.5 ± 5.4	46	Not mentioned	Not mentioned	13 43.4 ± 3.4	46	Not mentioned	HIV-infected vs control participants group analysis using Regional homogeneity method	Reduced regional homogeneity in HIV+ participants compared to controls mainly in DMN and limbic system
Thomas et al. 2013	52	41 ± 14	90	14 ± 2	23	52 44 ± 14	51	15 ± 3	HIV-infected vs control participants group analysis	Reduced connectivity in DMN, control and salience network of HIV+ compared to control.
Ann et al. 2016	HAND: 10 non-HAND: 13	HAND: 56.0 ± 8.2 non-HAND: 52.8 ± 6.2	HAND: 100 non-HAND: 100	HAND: 13.1 ± 4.4 non-HAND: 12.7 ± 3.3	HAND: 10 non-HAND: 13	11 54.7 ± 4.2	100	12.7 ± 1.6	Seed-based rs-fMRI study with seed region placed in bilateral precuneus.	Reduced RSFC between bilateral precuneus and prefrontal cortex in HAND compared to non-HAND participants Positive correlations between RSFC and memory and learning ability in right inferior operculum and right superior frontal gyrus

clinical expression of HAND. Future studies using longitudinal designs are needed to better establish whether RSFC is a dynamic biomarker of neuronal well-being and function in HIV.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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