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# Graph theory analysis reveals functional brain network alterations in HIV-associated asymptomatic neurocognitive impairment in virally suppressed homosexual males

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## Abstract

**Background** This study aimed to investigate the global and nodal functional network alterations, abnormal connections of brain regions, and potential imaging biomarkers in virally suppressed people living with HIV (PLH) with asymptomatic neurocognitive impairment (ANI) using graph theory analysis.

**Methods** The study included 64 men with ANI (mean age 32.45 years) and 64 healthy controls (HC) (mean age 31.31 years). The functional network was established through the graph theory method and Automated Anatomic Labeling (AAL) 90 atlas, which provides a cerebrum parcellation framework. Moreover, hub regions were identified based on betweenness centrality (Bc). Functional connectivity (FC) differences were investigated between the two groups, these connections were located in the resting-state network (RSN). Neuropsychological (NP) tests were performed, and relationships between graph theory measures, clinical data, and NP tests were analyzed. Multiple comparisons were used to correct for false-positive findings.

**Results** On the global level, small-worldness, global efficiency (Eg), and local efficiency (Eloc) were significantly decreased in ANI subjects. On a nodal level, brain regions in the frontal and subcortical regions showed significantly decreased nodal measures, while regions in the parietal, temporal, and occipital lobes showed increased nodal measures. Increased FCs were found between brain regions in the visual, frontoparietal, and somatomotor networks. Hub regions overlapped highly between the two groups. Age was negatively correlated with graph theory measures.

**Conclusion** Our findings demonstrate the global and nodal alterations in the functional network of virally suppressed homosexual males in the ANI stage. Frontal and subcortical brain regions may be important for finding the imaging biomarkers for HIV-associated neurocognitive disorder.

**Keywords** HIV, Functional connectivity, Asymptomatic neurocognitive impairment, Graph theory, Homosexual male

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## Background

As of 2021, there were 38.4 million people globally living with the Human Immunodeficiency Virus (HIV), of which 6 million were in Asia. Homosexual men and other men who have sex with men (MSM) accounted for the largest source of HIV infection in Asia (46%), while males aged between 25 and 49 accounted for 42% of cases. It is encouraging to note that 86% of people living with HIV (PLH) were aware of their HIV status. The advent of combination antiretroviral therapy (cART) has been successful, with 28.7 (75%) million patients under treatment, among whom 92% were virally suppressed (UNAIDS data 2022| UNAIDS) [1].

HIV can induce encephalitis and synaptic damage in the central nervous system (CNS) after breaching the blood-brain barrier during the early phase of infection [2], resulting in cognitive impairment known as HIV-associated neurocognitive disorders (HAND), with approximately half of the PLH at risk of developing HAND [3]. The widespread availability of cART has not only reduced the mortality rate but also transformed HIV infection into a chronic condition and decreased the incidence of dementia and motor deficits in PLH. However, mild forms of cognitive impairment, such as asymptomatic neurocognitive impairment (ANI), still prevail. ANI denotes the early stage of impaired cognitive function, yet it does not influence the daily lives of PLH [4]. Therefore, early diagnosis and intervention of ANI could minimize or reverse the impact of severe cognitive impairment (e.g., memory loss, fine motor function decline) on their daily life [5, 6].

Although neuropsychological (NP) testing is the classic method for detecting HAND. It is ineffective in assessing ANI due to the insignificance of clinical symptoms. Therefore, research has focused on blood, cerebrospinal fluid, and neuroimaging biomarkers to complement HAND diagnoses. Neuroimaging techniques could provide objective and quantified data on the brain, and it has identified neuroimaging abnormalities in different dementia types as well as the prodromal stage of dementia [7].

Resting-state functional magnetic resonance imaging (rs-fMRI) is a sensitive tool for detecting large-scale brain network alterations in HIV + individuals [8]. In recent years, functional connectivity analysis has been applied to HAND subjects, with studies showing increased posterior cingulate cortex efficiency [9] in those with ANI, as well as increased connectivity in visual and frontoparietal networks [10]. Virally suppressed subjects, on the other hand, showed decreased functional connectivity in the salience and executive networks [11]. Research has suggested that rs-fMRI can predict and monitor cognitive impairment in PLH [12, 13]. Graph theory analysis, which uses rs-fMRI to study the brain as a complex network, with each brain region represented as a node and functional connectivity of brain regions represented as edges, has provided new insights into how brain regions and connections change in brain networks of subjects with cognitive impairment [14]. This approach has been used successfully in other diseases, such as Alzheimer's disease, Parkinson's disease, and schizophrenia [15–17]. Research of graph theory analysis on PLH has been increasing in recent years. PLH has shown decreased functional network features both at global and nodal levels [11, 18, 19]. Moreover, Wismüller and his group have focused on topology alterations in HAND subjects, their studies showed that global measures such as modularity and small-worldness were deceased, nodal measures were decreased in the occipital cortex and the cingulate cortex, and suggested there were subtle reorganization in brain networks in HAND [20, 21]. Brain regions in the default mode network and basal ganglia could be important in distinguishing HAND [22]. Brain structural and functional features were reported to be different in males and females [23]; furthermore, different sexual orientations, such as homosexual and heterosexual, showed certain differences in rs-fMRI [24, 25]. Although previous studies have included homosexual males and ANI subjects, they mainly focused on network features in general PLH and HAND subjects. However, the network features of virally suppressed homosexual males in the ANI stage are not fully clear. We believe that this is the first study that focuses on functional network features in virally suppressed homosexual males in the ANI stage.

We performed graph theory analysis in resting-state functional MRI on a cohort of virally suppressed homosexual male subjects in the ANI stage. We explored graph theory measures both on global and nodal levels. We also investigated functional connectivity (FC) changes between brain regions. Moreover, we identified hub regions in the brain. Finally, we examined the relationship between graph theory measures, clinical data, and neuropsychological tests.

## Materials and methods

### Participants

This study included 143 participants recruited from clinics in Beijing Youan Hospital, Capital Medical University, China. All participants were right-handed and native Chinese-speaking males. In order to control the sex differences and sexual orientation as confounding factors, all PLH in this study were infected through homosexual intercourse, which is based on the self-reports of their risk behaviors. The inclusion criteria: age between 18 and 40 years, duration of stable cART over 6 months, and plasma HIV RNA levels of < 20 copies per ml (details of cART schemes are shown in Supplementary Table 1); full clinical records; educational background of at least

9 years; and without contraindications to MRI. Healthy controls were recruited within the same urban regions as the PLH and matched to PLH by age, gender, and educational level. The exclusion criteria for PLH and HC: history of psychiatric conditions that could affect cognition (e.g., schizophrenia, autism, depression, and anxiety); metabolic diseases (e.g., diabetes, heart conditions, kidney failure, and liver failure); complications from the perinatal period (e.g., anemia, depression, diabetes, heart conditions, hyperemesis gravidarum); other central nervous system (CNS) diseases or opportunistic CNS infections; substance user (e.g., nicotine, marijuana); nontraumatic brain injury (e.g., brain tumor, infection, stroke, epilepsy, and aneurysm) and previous traumatic brain injury with consciousness loss for at least 30 min. For PLH, in order to exclude HIV-associated mild neurocognitive disorder (MND) and HIV-associated dementia (HAD), subjects with self-reported everyday functioning impairment were excluded as well. All participants signed written informed consent forms before participation, and the research protocol was approved by the Beijing Youan Hospital Ethics Committee.

2.5 h before the MRI, participants underwent a standard battery of neuropsychological tests within six cognitive domains: (1) Wechsler Memory Scale (WMS-III), Continuous Performance Test-Identical Pair (CPT-IP), and Paced Auditory Serial Addition Test (PASAT) for attention/working memory; (2) Verbal Fluency Test (AFT) for verbal fluency; (3) grooved pegboard for fine motor skills of both the dominant and non-dominant hand [26] (4) Hopkins Verbal Learning Test (HVLT-R) and Brief Visuospatial Memory Test (BVMT-R) for memory, specifically, learning and delayed recall; (5); Trail Marking Test A (TMT- A) for information processing speed; and (6) Wisconsin Card Sorting Tests (WCST-64) for executive function. Additionally, participants were given a short Activities of Daily Living scale as a self-assessed questionnaire to evaluate cognitive difficulties in their daily lives [27]. Average T-scores were calculated by adjusting for age and educational level [28, 29]. A diagnosis of ANI was made by using the Frascati criteria if neuropsychological test scores were at least 1 standard deviation below the mean in two or more cognitive domains, there were no cognitive difficulties in daily life [30]; furthermore, subjects should not have preexisting cause for the ANI, and do not belong to delirium dementia. Of the 143 participants, 72 were diagnosed with ANI and 71 were age-matched healthy controls (HC). 3 ANI participants were excluded due to extreme head motion (>3 mm in deposition or 3° in rotation), 2 were excluded because they did not complete the NP tests, and 3 were excluded because of a lack of clinical data. Among 71 HC subjects, 4 were excluded due to extreme head motion, 1 was excluded because the subject did not complete the NP tests, and 2 subjects aborted the MR imaging and could not finish. The final study sample included 64 ANI patients (mean age 32.45 ± 6.61 years) and 64 HC subjects (mean age 31.31 ± 6.37 years).

#### Image acquisition

Neuroimaging data were obtained using a 3.0T MR scanner (Tim-Trio, Siemens, Erlangen, Germany) with a 32-channel head coil. Whole brain rs-fMRI data were acquired using a gradient echo planar imaging (EPI) sequence with the following parameters: TR, 2,000ms; TE, 30ms; flip angle, 90°; FOV, 224 × 224 mm; resolution matrix, 64 × 64; section thickness, 3.5 mm; the number of sections, 35; and voxel size = 3.5 × 3.5 × 3.5 $mm^3$. 35 axial slices and 240 time points were acquired. A sagittal magnetization prepared gradient-echo (MPRAGE) sequence was also acquired with the following parameters: TR/TE/TI = 1,900/2.52/900ms; FOV = 250 × 250; acquisition matrix = 256 × 246; flip angle = 9 ; voxel size = 1 mm × 1 mm × 1 mm.

#### Preprocessing

Preprocessing was performed using the Data Processing and Analysis for Brain Imaging (DPABI V6.1) pipeline based on Matlab 2016b (Mathworks, Natick, MA, USA) [31]. DICOM images were converted to four-dimensional NIFTI format, and the first 10 time points were removed to ensure signal stability. Slice timing correction was performed using the middle slice as a reference. Each time series was then realigned using a rigid body linear transformation with a two-pass procedure. T1-weighted imaging(T1WI)was coregistered to mean functional images before being segmented into gray matter, white matter, and cerebrospinal fluid. Computed transformations from individual native space to MNI space using DARTEL. The Friston 24-parameter head motion model was employed to eliminate motion effects [32]. Linear trends signals were regressed to minimize signal drift. Global signal regression (GSR) was used to limit redundant global confounds and improve the coherence between anatomy and resting-state correlations [33, 34]. The results remain constant without applying GSR. The low-frequency drifts and high-frequency noise were removed using the temporal bandpass filter (0.01∼0.1 Hz) [35]. We did not apply the smoothing to avoid blurring signals from voxels outside the region into the region.

#### Network construction

Functional brain networks were constructed using the graph theoretical network analysis toolbox GRETNA ( www.nitrc.org/projects/gretna/). GRETNA is a sophisticated and convenient rs-fMRI toolbox for preprocessing and network analysis. The network analysis module

is based on the Brain Connectivity Toolbox in MATLAB [35]. In line with previous studies, we defined a total of 90 ROIs, excluding the brain stem and cerebellar regions, using the AAL90 template (Supplementary Table 2) [20–22, 36]. Time series were calculated by averaging the time series of all voxels. FC between nodes was considered as the edges of the network. Pearson's correlation coefficients of each node pair were constructed, establishing a correlation matrix for each subject. To confirm normal distribution, Fisher's r-to-z transformation was applied. A binary connection matrix was constructed.

### Network analysis

We utilized a range of sparsity thresholds ($0.05 \leq \text{sparsity} \leq 0.4$, interval = 0.05) to analyze the number of edges [37] using the GRETNA, the minimum sparsity was set to ensure that there were no isolated nodes in the network. The maximum sparsity was set to ensure that the small-world index was larger than 1 for all healthy subjects, and the results were calculated as the average across the thresholds. We computed several global measures, including global efficiency (Eg), local efficiency (Eloc), and small-worldness, as well as nodal measures, such as nodal clustering coefficient, nodal shortest path length, nodal efficiency (Ne), nodal local efficiency (Nle), nodal degree centrality (Dc), and nodal betweenness centrality (Bc), details of graph theory measures are shown in Supplementary material (Supplementary 1) [35]. To compare network connectivity between the two groups, we used the GRETNA software package and overlaid the AAL template onto the resting-state network (RSN) to locate the brain regions in the RSN, the RSN template came from the Group ICA of fMRI toolbox (GIFT) software (http://mialab.mrn.org/software/gift/index.html) [38]. Nodes with higher Bc values were considered hub regions [39]. We computed the mean Bc of each node in each group and identified 15 nodes with Bc values above one standard deviation as hub regions [18, 20, 40].

**Table 1** Demographic and clinical variables of study participants

| Variable | ANI ($n=64$) | HC($n=64$) | $p$-value |
|---|---|---|---|
| Age (years) | 32.45 ± 6.61 | 31.31 ± 6.37 | 0.994 |
| Education (year) | 14.80 ± 2.87 | 15.08 ± 2.64 | 0.577 |
| Male Sex (%) | 100 | 100 | - |
| CD4+ | 571.68 ± 222.68 | NA | - |
| CD4+/CD8 + ratio | 0.88 ± 0.39 | NA | - |
| Undetectable HIV RNA (Plasma VL) (%) | 100 | NA | - |
| Transmission category (MSM) (%) | 100 | NA | - |
| Disease course (months) | 60.95 ± 40.04 | NA | - |
| Duration on cART (median) (IQR) (year) | 3(2.5) | NA | - |
| Neurocognitive performance T score | | | |
| Speed of information processing | 46.19 ± 8.88 | 49.88 ± 6.93 | 0.0099* |
| Memory (learning and recall) | 38.56 ± 8.37 | 44.67 ± 7.44 | < 0.0001* |
| Attention/working memory | 41.73 ± 6.75 | 44.82 ± 5.21 | 0.0043* |
| Abstraction/executive | 51.88 ± 8.49 | 54.20 ± 8.54 | 0.1245 |
| Fine motor skills | 48.36 ± 9.32 | 50.73 ± 6.89 | 0.1036 |
| Verbal and language | 38.58 ± 8.49 | 41.52 ± 6.12 | 0.0265* |

### Statistical analysis

GraphPad Prism 9 (San Diego, CA, USA; https://www.graphpad.com/ scientific-software/prism) was used to analyze the demographic and clinical characteristics using independent two-sample t-tests ($P < 0.05$). D'Agostino & Pearson test was used for testing data normality. Continuous variables with normal distribution were presented as mean ± standard deviation (SD). Group-wise differences in global and nodal graph theory measures, as well as FC of nodes were studied using two-sample t-tests in GRETNA [35], and the results were calculated as the average across the sparsity range. We took into account the possible effects of age and education, which have been included in the statistical model of GRETNA as confounding factors. We applied FDR and Bonferroni correction and set a significance level of $P < 0.05$ for all tests. In order to show the most significant results, Bonferroni correction was applied to all group comparisons; if the data did not survive Bonferroni correction, they were presented with FDR correction. We performed Pearson's correlations to assess the relationship between graph theory measures, clinical data, and NP tests ($P < 0.05$). We used the BrainNet Viewer toolbox [41] and Circos [42] to visualize the results.

## Results

### Participants

There was no statistical significance in age ($p = 0.994$) and education ($p = 0.577$) between the two groups. However, ANI subjects showed lower scores on NP tests, particularly in the domains of speed of information processing, memory (learning and recall), attention/working memory, and Verbal and language skills, compared to the HC group. The demographics and clinical characteristics of the participants are summarized in Table 1.

Table 1: Continuous data presented as mean ± standard deviation. Significant differences in age and education between groups were determined by an independent t-test. Significance was set as $p < 0.05$. Abbreviations: ANI, asymptomatic neurocognitive impairment; HC, healthy control; MSM, Men who have sex with men; VL, viral load; IQR, interquartile range.

### Global and nodal alterations

We observed significant alterations in global and nodal measures in ANI subjects compared to HC (FDR corrected). In terms of global measures (Fig. 1; Supplementary Table 3), ANI subjects showed a significant reduction in global efficiency, local efficiency, and small-worldness ($p < 0.001$).

In nodal measures (Fig. 2; Supplementary Table 4; Figs. 1, 2, 3 and 4), ANI subjects showed both increased and decreased alterations. Betweenness centrality (captures the number of shortest paths that pass through a node), degree centrality (measurement of connectivity between a node with other nodes), nodal efficiency (measurement of connectivity efficiency of a node within a network), nodal clustering coefficient (represents the presence of clustered connectivity around individual nodes), and nodal local efficiency (average global efficiency of the subgraph induced by neighbors of the node) were altered substantially [43]. Specifically, the nodal measures of brain regions in the frontal lobe and subcortical regions were significantly reduced, and those of brain regions in the parietal, temporal, and occipital lobes were significantly increased. There was no significant difference in nodal shortest path length. Details of nodal measures alterations are presented in the Supplementary material (Fig. 2; Supplementary Table 4; Figs. 1, 2, 3 and 4). Furthermore, we identified 15 hub regions in both groups (Fig. 3). These hub regions were mainly located in the parietal and temporal lobes. However, some hub nodes such as the supplementary motor area and precentral gyrus were only present in the ANI group, while Heschl's gyrus, superior temporal gyrus, and fusiform gyrus were only present in the HC group.

### Connections of brain network

ANI subjects showed increased FC compared to the HC group. We identified 15 increased connections in ANI subjects (Fig. 4 left) between the frontoparietal, temporal, and occipital brain regions. As most functional connectivity studies were reported within the RSN template by using Independent Component Analysis (ICA), we tried to locate brain regions in the AAL template into the RSN template [38] (http://mialab.mrn.org/software/gift/index.html) by overlaying the two templates for a better understanding of the connections between different functional networks. After locating the brain regions in RSN, primarily located in the visual, frontoparietal, and somatomotor networks (Fig. 4 right) ($p < 0.05$, Bonferroni corrected).

### Correlation between graph theory measures, clinical variables, and NP tests

We found negative correlations between age and global local efficiency, as well as nodal efficiency in the anterior cingulate and paracingulate gyri, amygdala, and nodal local efficiency in the putamen, all FDR corrected (Fig. 5). We also observed several correlations between graph theory measures and NP tests, however, none of these associations were robust enough to survive multiple comparisons (Supplementary Fig. 5). Unfortunately, we did not observe any correlation between clinical HIV markers (e.g. CD4; CD4/CD8) and graph theory measures.

## Discussion

In this study, we utilized graph theory to investigate the functional network alterations in virally suppressed HIV + homosexual males in the ANI stage. We found that ANI subjects had significantly decreased small-worldness, global efficiency, and local efficiency at the global level (Fig. 1; Supplementary Table 3). At the nodal level,

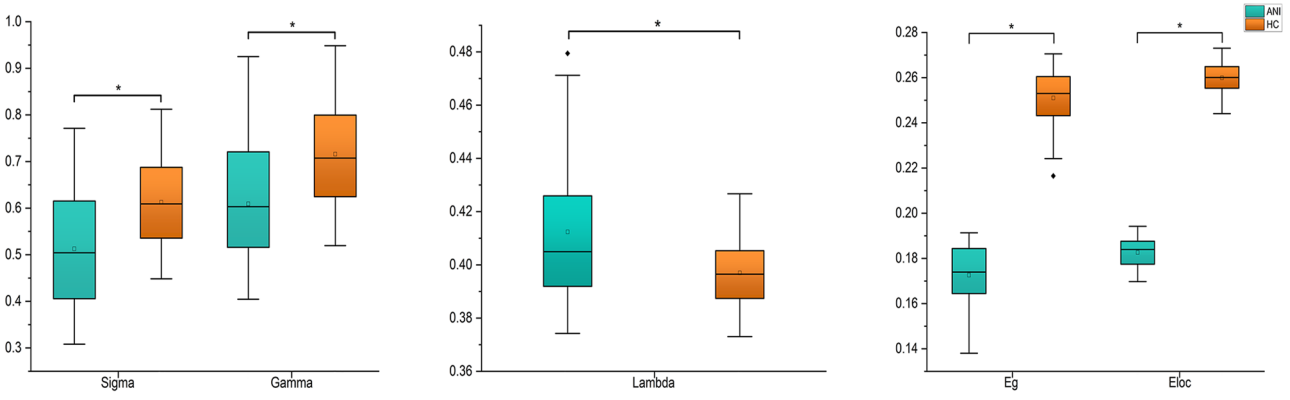


**Fig. 1** Group differences of global measures between ANI and HC subjects based on the two-sample t-test. Results were presented as mean ± standard deviation. *$p < 0.001$ is considered statistically significant. The hollow box inside the boxes represents the mean value of the data. The black rhombus represents outliers. Small-worldness and small-worldness relating measures were decreased significantly in ANI subjects (**a**, and **b**). global efficiency and local efficiency were significantly deceased as well (**c**). Sigma, small-worldness; Gamma, normalized clustering coefficient; Lambda, normalized shortest path length. Sparsity, 0.05–0.40. Abbreviations: e.g., Eg, global efficiency; Eloc, local efficiency

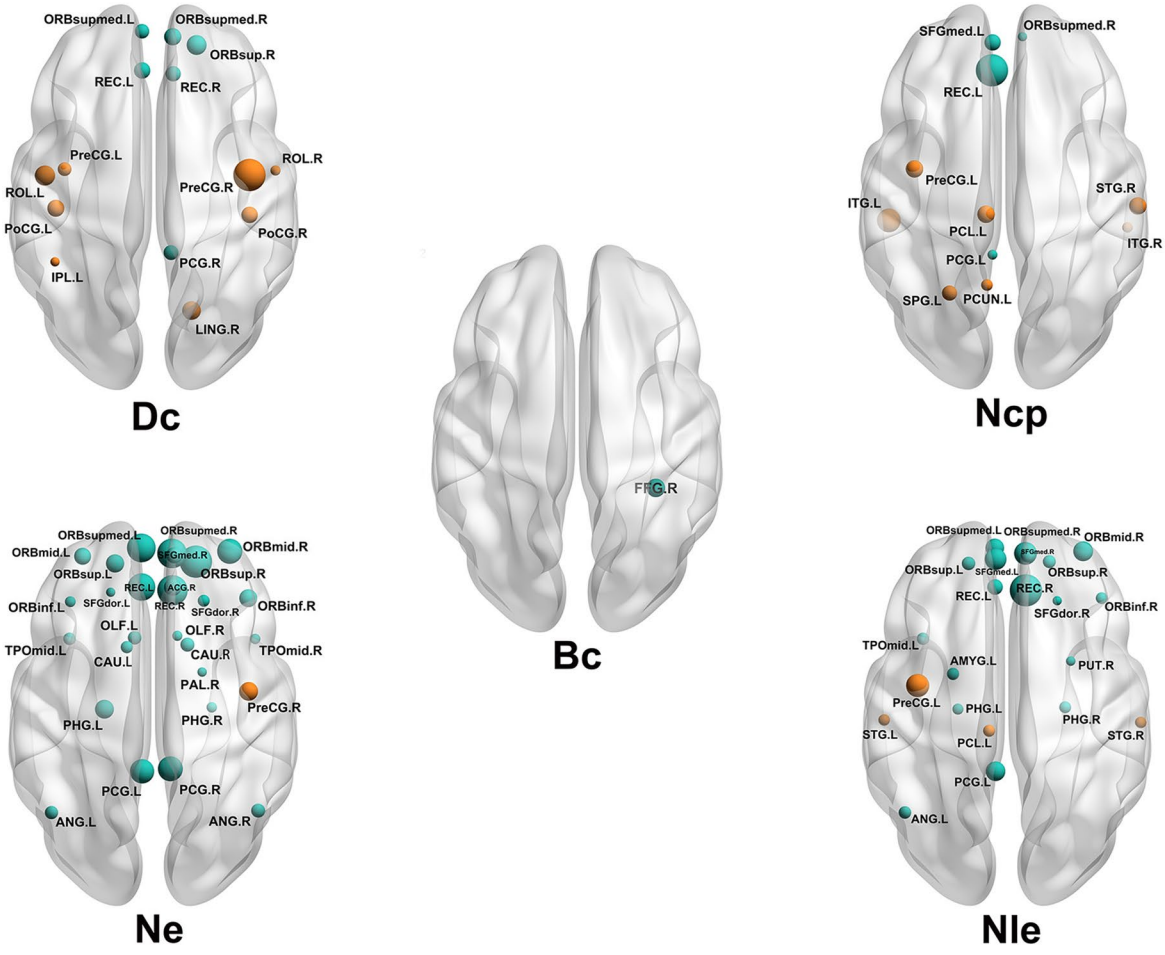


**Fig. 2** The nodal alterations in ANI subjects by two-sample t-test with FDR correction. Dark cyan represents brain regions that had significantly reduced nodal measures compared to HC. Orange represents brain regions that had significantly increased nodal measures. Different size represents the t-value of the two-sample t-test. Details of the abbreviation labels are provided in the Supplementary material (Supplementary Table 2). Dc, degree centrality; Bc, betweenness centrality; Ncp, nodal clustering coefficient; Ne, nodal efficiency; Nle, nodal local efficiency

decreased nodal measures were observed in frontal brain regions, whereas increased nodal measures were seen in brain regions of the parietal, temporal, and occipital lobes (Fig. 2; Supplementary Table 4; Figs. 1, 2, 3 and 4). Compared to HC, ANI subjects showed higher functional connectivity among the frontoparietal, temporal, and occipital brain regions, which were mainly located in visual, somatomotor, and frontoparietal networks, as determined by locating the brain regions into RSN (Fig. 4). Furthermore, we identified hub regions in ANI subjects (Fig. 3). We also observed a negative correlation between age and graph theory measures (Fig. 5; Supplementary Fig. 5).

### Global-level alterations

Small-worldness represents the balance of integration and segregation in a network, which optimizes processing costs to provide high function. Global efficiency represents the functional integration of the whole brain and the efficiency of information integration between distant brain regions, while local efficiency indicates the efficiency of a node with its neighboring areas [14, 44]. Few studies have reported global alterations in the functional network among PLH, but our results align with studies that reported a significant reduction in small-worldness and network efficiency in PLH [19, 21], half of whom were ANI. The decreased small-worldness, global efficiency, and local efficiency in ANI subjects (Fig. 1; Supplementary Table 3) indicated that the whole-brain network shifted towards a random graph, reducing functional network efficiency and regional neighborhood communication. After controlling the gender and viral load in this study, which could be confounding factors [23, 45]. Functional integration and segregation are still be disrupted, indicating that the functional whole-brain network topology could be reorganized soon after HIV infection and persisting along with disease course

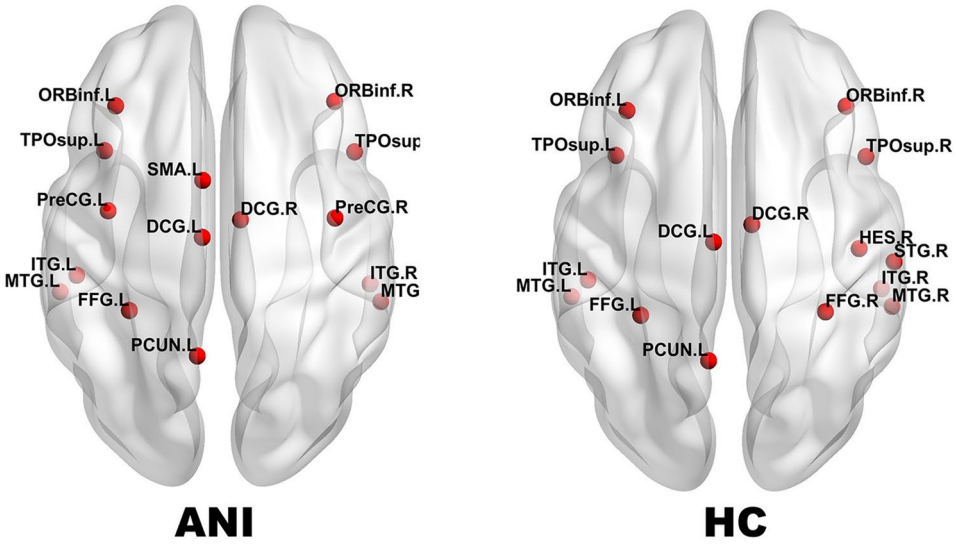


**Fig. 3** Hub regions in two groups were identified based on betweenness centrality. Hub regions were highly overlapped between the two groups. Supplementary motor area and precentral gyrus were presented only in the ANI group, Heschl's gyrus, superior temporal gyrus, and fusiform gyrus were presented only in the HC group. Details of the abbreviation labels are provided in the Supplementary material (Supplementary Table 2)

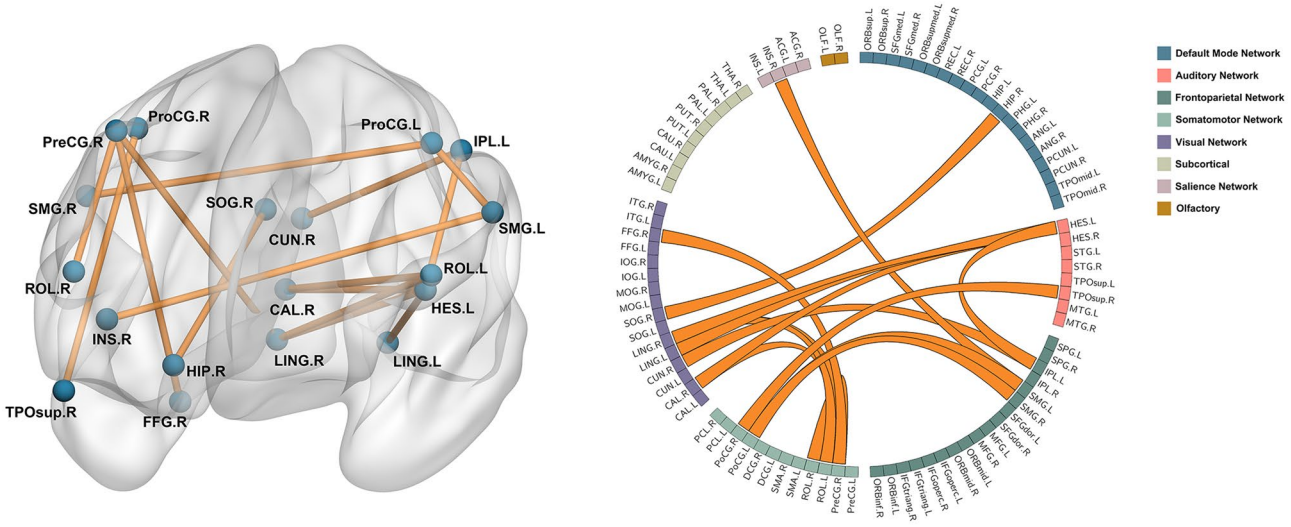


**Fig. 4** The abnormal connections in ANI subjects compared to HC. Blue nodes on the left represent brain regions that have abnormal connections. The orange line represents the positive connections between different nodes. Brain regions of the AAL template were identified in RSN. Details of the abbreviation labels are provided in the Supplementary material (Supplementary Table 2)

extension and age growth, although PLH were under successful cART with undetectable viral load.

### Nodal-level alterations and hub distribution

We found significant nodal changes in ANI subjects. Brain regions in the frontal lobe and subcortical area showed a significant reduction in most nodal measures (Fig. 2; Supplementary Table 4; Figs. 1, 2, 3 and 4). Among these frontal lobe brain regions, the rectus gyrus, frontal gyrus, orbital part, and superior frontal gyrus were affected substantially, Interestingly, these regions are located in Brodmann area 9–12, which is involved in higher functions of cognition (information integration, associational, memory, and recall) [46]. We also found reductions in nodal measures in subcortical areas, specifically in the limbic system (posterior cingulate gyrus, amygdala, parahippocampal gyrus) and the basal ganglia (caudate nucleus, putamen, pallidum) (Fig. 2; Supplementary Table 4; Figs. 1, 2, 3 and 4). Cognitive impairment in HIV + patients was previously associated with subcortical impairment in the pre-cART era, specifically related to working memory, emotion, and motor control [47]. In the pre-cART era, HAND was considered subcortical dementia [48], however, research suggested

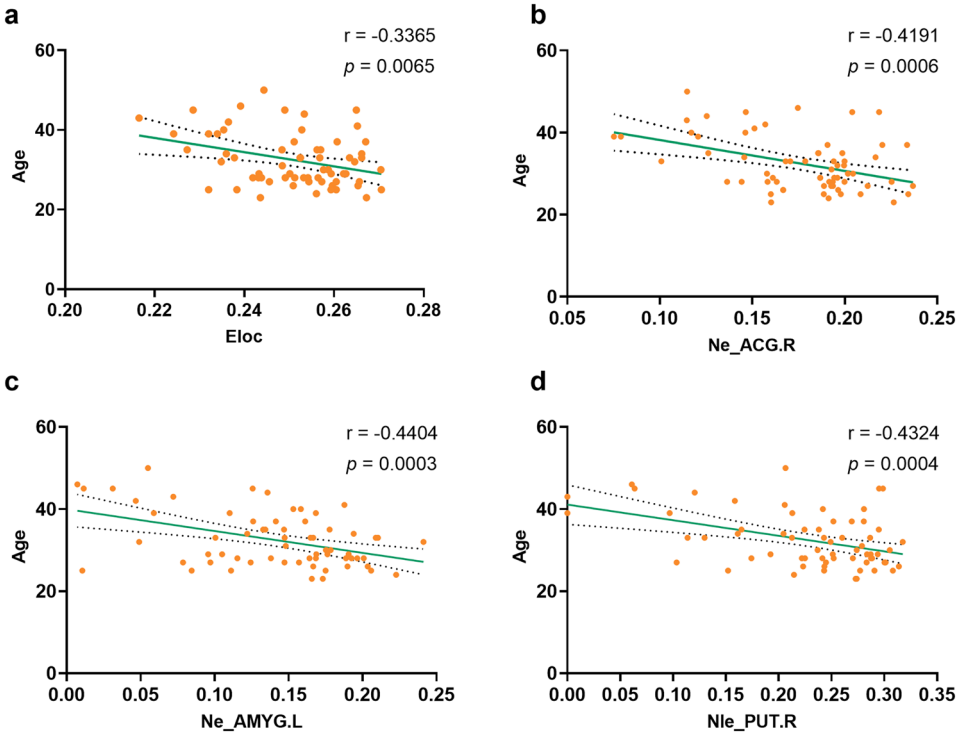


**Fig. 5** Correlation results between clinical data and graph theory measures by Pearson correlation analysis with FDR correction. Age was negatively correlated with local efficiency, nodal efficiency of anterior cingulate and paracingulate gyri (right) and amygdala (left), and nodal local efficiency of the putamen (right)

that in the cART era, cognitive impairment is shifting to cover higher dysfunction such as executive functioning [10]. Several studies reported frontal and subcortical volume loss [49–51], and structural and functional imaging also suggests frontal and subcortical damage [9, 52–54]. Moreover, previous graph theory analysis on PLH also showed decreased nodal measures in frontal and subcortical regions [18, 19, 21, 55], and our previous structural network research on PLH and HAND subjects showed nodal alterations in these brain regions as well [56–58]. This study extends previous studies on demonstrating the functional network alterations in virally suppressed homosexual males in the ANI stage, decreased nodal measures in this study suggest functional communications between brain regions were affected, which could lead to deterioration of cognitive impairment. ANI subjects in this study showed significantly lower NP test scores in memory and recall, which supported this theory. We assume frontal and subcortical regions were damaged soon after HIV infection. Although cART has a positive effect on HAND, these brain regions remain as important targets of HIV and affect the functional abilities and brain structure. Moreover, we found a strong negative correlation between age and nodal level alterations (e.g., global efficiency; nodal efficiency; nodal local efficiency) (FDR corrected) (Fig. 5). Previous studies have also demonstrated the significance of age in cognitive impairments [59, 60]. Additionally, nodal-level changes were correlated with the NP test (Supplementary Fig. 5), although these results did not survive FDR correction. Therefore, we believe that during the ANI stage, and as the disease's course and age progress, continuous attention should be paid to the functional brain network alterations in nodal measures such as BC, Ne, and Nle, which may enable earlier detection of ANI and monitoring of the long-term changes in HAND. We imagine longitudinal research for graph theory analysis on frontal and subcortical regions may reflect the progression of HAND and may be important for finding imaging biomarkers.

We observed significantly increased nodal measures in brain regions of ANI subjects located in the parietal lobe (precentral gyrus, postcentral gyrus, paracentral lobule, Rolandic operculum, superior parietal gyrus, angular gyrus, precuneus), temporal lobe (superior temporal gyrus, inferior temporal gyrus), and occipital lobe (lingual gyrus) (Fig. 2; Supplementary Table 4; Figs. 1, 2, 3 and 4). Previous studies have shown reduced grey and white matter integrity in the parietal, temporal, and frontoparietal lobes in ANI and virally suppressed subjects [52, 61]. Nevertheless, a recent study showed increased ALFF in sensorimotor and temporal amplitudes in aging PLH [62]. Recent graph theory research on PLH demonstrated inconsistent results within the structural network

in the inferior parietal lobule, postcentral gyrus, and precuneus [63].

We acknowledge betweenness centrality as a measure of the importance of nodes in a network, based on the number of shortest paths that pass through the node. Brain regions with high betweenness centrality are considered associating hubs of the functional network [43, 64]. Following previous graph theory studies [20, 39], we identified 15 brain regions as hubs in each group (Fig. 3). We found a strong overlap between the ANI and HC groups, although each group had several unique hub regions. In this study, hub regions were mostly located in the temporal and parietal lobes, with few hub regions in the occipital and frontal lobes. In contrast, previous studies on PLH showed hub regions were mainly in the prefrontal, somatosensory cortex, subcortical, and occipital regions [18, 20]. Hub regions are crucial for efficient communication between brain regions and functional networks [14]. We assume that along with growing age and long disease course, and nodal alterations in each brain region, this may lead to a redistribution of hub regions. As far as we know, this is the first study that reveals the hub distribution of virally suppressed homosexuals with the ANI stage. By revealing different stages of HAND and different groups of PLH, we could understand the network topology of PLH, hence it is beneficial for finding the imaging biomarker for HAND.

#### Increased functional network connections in the ANI stage

Compared to the HC, individuals with ANI exhibited greater functional connectivity between the frontoparietal, temporal, and occipital brain regions (Fig. 4). We found that most of the abnormal connections were located in the visual, frontoparietal, and somatomotor networks. Previous studies demonstrated declined functional connectivity mostly located in the default mode network (DMN) and brain regions in the prefrontal, and parietal lobes [65, 66]. Other studies showed increased connectivity in frontoparietal and sensorimotor networks [10, 67]. Virally suppressed PLH showed increased FC in visual and frontoparietal networks [68]; furthermore, homosexual males displayed increased FC and increased functional activity in the visual network [25], we also found increased FC in visual and frontoparietal networks, and our results are consistent with these previous studies that focused on similar subjects. Moreover, at the early stages of Alzheimer's disease, regional functional abnormalities and FC abnormalities were also shown in temporal and occipitoparietal regions [69, 70]. This may indicate that regional and FC alterations in these brain regions could be important at the early stage of cognitive impairment. Interestingly, while the DMN has been suggested to play an important role in HAND and other cognitive impairment diseases [71], we found that the AAL90 DMN alterations were not as significant as in previous studies [11, 72]. Nevertheless, the alterations observed in these brain regions and FC changes are inconsistent in PLH. The studies that we have mentioned above reported both increased and decreased FC. However, ANI subjects in this study did not demonstrate significantly decreased FC compared to HC. We suspect that increased nodal measures and FC in the parietal, temporal, and occipital are compensatory effects resulting from the impairment of the frontal lobe and aimed at maintaining normal cognition, and functional ability, along with long-term HIV affection to the brain and deterioration of cognitive functions, decreased FC could be shown. Therefore, a longitudinal study should be employed to monitor the FC alterations of HAND.

There are some limitations in this study that need to be acknowledged. Our sample size is relatively small, larger cohorts could help us understand better the functional network topology of homosexual males within the ANI stage. Subjects in the control group were not all homosexual, future studies should include more healthy homosexual males as a control group, as it will help demonstrate the brain network features of homosexual males with HIV. We defined brain regions using the AAL90 template because it has been largely used in research, using other brain templates such as Power 264 [73] and Schaefer templates [74] could broaden our understanding of functional segregation and integration changes and graph theory alterations in more refined brain parcellation in PLH. We did not focus on brain regions in the cerebellum in this study, although studies have found certain changes in the cerebellum [55, 75]. We demonstrated the alterations in the functional network using the most common features of graph theory, however, more features such as modularity and structural-functional coupling should be going into. Using the functional network template and combining structural data to understand more about the integration and segregation changes in the brain network of HAND. Additionally, our study did not include cognitive normal, MND, and HAD subjects, comparing functional network alterations in different HAND stages could benefit us in obtaining HAND progression. Although PLH in this study were all virally suppressed, some antiretroviral drugs are neurotoxic and may affect cognitive impairment [76]. Even though we avoided the influences of sex differences on functional network alterations, we believe it is important to reveal functional network features of different genders and people with different sex orientations. We included young PLH in this study, however, the population of older PLH is growing as well in the cART era, future research should include HAND subjects in different age ranges, and it is valuable for understanding the network features in long disease courses. Another limitation is that participants in

this study were all recruited in mainland China, so results may not be generalizable to a global population. Lastly, this is a cross-sectional study, which may introduce inherent bias. Our group is collecting longitudinal data to produce more robust and definitive results.

In conclusion, we demonstrated the resting state functional network alterations in the virally suppressed homosexual males in the ANI stage using graph theory analysis. We have observed network small-worldness and efficiency decreased in ANI subjects. Nodal measures were decreased in frontal and subcortical brain regions. On the other hand, we found not only increased nodal measures but also increased functional connectivity in temporal, parietal, and occipital brain regions. Furthermore, we have identified hub regions of ANI subjects. We assume network alterations in frontal and subcortical brain regions could be important in finding imaging biomarkers for HAND. Future research should be using graph theory analysis with large sample sizes and longitudinal design, it will provide more comprehensive knowledge about network alterations of HAND.

#### Abbreviations

| | |
|---|---|
| AAL | Automated Anatomic Labeling |
| ANI | Asymptomatic Neurocognitive Impairment |
| Bc | Betweenness Centrality |
| cART | combination Antiretroviral Therapy |
| Eg | Global Efficiency |
| Eloc | Local Efficiency |
| FC | Functional Connectivity |
| HAND | HIV-associated Neurocognitive Disorders |
| HC | Healthy Controls |
| HIV | Human Immunodeficiency Virus |
| ICA | Independent Component Analysis |
| NP | Neuropsychological Tests |
| PLH | People Living With HIV |
| rs-fMRI | resting-state Functional Magnetic Resonance Imaging |
| RSN | Resting-state Network |

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12879-025-10780-2.

Supplementary Material 1

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#### Author contributions

Conceptualization: RLL, HJL. Data curation: SH, JMM. Formal analysis: XRAL, SH. Funding acquisition: RLL, HJL. Investigation: JJL, HXL, FX. Methodology: RLL, XRAL. Project administration: HJL, RLL. Resources: WW, JJL. Software: XRAL, WW, CKH. Supervision: RLL, HJL. Validation: RLL, HJL. Visualization: XRAL, XYJ. Writing-original draft: XRAL. Writing-review & language help & editing: XRAL, RLL, HJL.

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#### Data availability

The datasets analysed during the current study are available from the corresponding author upon reasonable request.

### Declarations

#### Ethics approval and consent to participate

All procedures performed in studies involving human participants were under the ethical standards of the institutional and national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. 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.

#### Competing interests

The authors declare no competing interests.

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## Publisher's note