Cerebral regional and network abnormalities in HIV-infected with neurocognitive impairments: An fMRI study

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Article

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Abstract

Although the combination antiretroviral treatment (cART) has considerably lowered the risk of HIV associated dementia (HAD), the incidence of neurocognitive impairments(NCI) have not decreased likely due to the insidious and slow progressive nature of HIV infection. Recent studies show that the rest state functional magnetic resonance imaging (rs-fMRI) is a prominent technique in helping the non-invasive analysis of neucognitive impairment. Our study is to explore the neuroimaging characteristics among people living with HIV(PLW-HIV) with or without NCI in terms of cerebral regional and neural network by rs-fMRI, based on the hypothesis that HIV patients with and without NCI have independent brain imaging characteristics. 33 HIV subjects with NCI and 33 HIV subjects without NCI, classified into HIV-NCI group and HIV-control group respectively according to Mini-Mental State Examination(MMSE) results. The fraction amplitude of low-frequency fluctuation (fALFF) and functional connectivity (FC) were calculated to characterize the cerebral regional and neural network alterations. Finally, the correlation among fALFF/FC values in certain cerebral regions and clinical characteristics were calculated. Compared to the HIV-control group, the fALFF values of bilateral calcarine gyrus, bilateral superior occipital gyrus, left middle occipital gyrus, left cuneus in the HIV-NCI group were increased. The FC values between right superior occipital gyrus and right olfactory cortex, bilateral gyrus rectus, right orbital part of middle frontal gyrus in the HIV-NCI group were increased. The FC values between left hippocampus and bilateral medial prefrontal gyrus, bilateral superior frontal gyrus were decreased. The fALFF values of left cuneus in both two groups was negatively correlated with international HIV dementia scale scores (IHDS) (R=-0.255, P=0.037) ; The fALFF values of left calcarine gyrus in both two groups was negatively correlated with MMSE scores (R=-0.316, P=0.009) ; The FC values between right superior occipital gyrus and right olfactory cortex (R=-0.396, P=0.001) in both two groups was negatively correlated with MMSE scores. Our study showed that the abnormal fMRI patterns in specific brain regions of the occipital cortex, while the defects in brain network mostly associated with prefrontal cortex, were associated with HIV-related cognitive impairment. The variation of fALFF and FC in given brain regions can be used to distinguish HIV subjects with and without cognitive impairment.

1. Introduction

As of 2021, more than 38.4 million people are living with Human Immunodeficiency Virus (HIV)[1]. Often one of the most common clinical features of HIV was neurocognitive impairment known as HIV-associated neurocognitive disorder (HAND). At least half of the HIV-infected cases were observed to have HAND-related symptoms, which included the disturbance of executive functions, episodic learning and memory, attention, working memory, and psychomotor speed and coordination[2]. Although the combination antiretroviral treatment (cART) has considerably lowered the risk of HIV associated dementia (HAD) , the most severe form[3], the incidence of HAND have not decreased likely due to the insidious and slow progressive nature of the disease. Previous studies have stressed the importance of monitoring the cognitive performance of HIV infected individuals and showed that severe forms of HAND such as HAD could be prevented with aggressive intervention[4, 5]. It is therefore crucial to evaluate the

clinical manifestations of patients in early stage however no agreed upon diagnostic criteria exists for HAND[6, 7]. Currently the diagnosis of HAND has rested on a comprehensive neurocognitive assessment which is expensive and time consuming and is not sutible for early screening of neurocognitive impairments[8, 9]. Scales such as the International HIV dementia scale (IHDS)[10], Minimum Mental State Examination (MMSE) or Montreal Cognitive Assessment (MoCA)[10, 11] are commonly used as the tools to detect the milder forms of HAND. However, screening for HAND continues to be difficult and imprecise in the clinical setting. With the cerebral dysfunction thought to appear before changes in white matter and presence of biochemical markers in the cerebrospinal fluid (CSF) therefore imaging data may provide more useful information[12-14].

Previous studies rarely evaluated for the relationship between the manifestations of neurocognitive impairments and the cerebral characteristics caused by HIV infected[15]. So this study is based on the hypothesis that HIV patients with and without neurocognitive impairment have independent brain imaging characteristics. The rest state functional magnetic resonance imaging (rs-fMRI) is a prominent technique which helps in the non-invasive analysis of cognitive impairment[16, 17]. In this study, we used fraction amplitude of low frequency fluctuation (fALFF)[18] and functional connectivity (FC)[19] to clarify the altered spontaneous activities and connectivity among different regions in the brain. Since fALFF is associated with the specific low-frequency oscillations, reflecting spontaneous brain activities it was used to assess the power of resting-state-specific low-frequency brain activation in a given voxel. Functional connectivity is defined as the time-series correlations and interaction between anatomically separated brain regions. Numerous studies have suggested the link between abnormal FC and neuropsychiatric disease given its high sensitivity to impaired brain function in a variety of clinical disorders[20]. Specifically, the value of FC was used in the examination of cognitive impairment in Alzheimer's disease[21], dementia[22], etc. One of the main focuses in previous studies has been on the analysis of cognitive performance in relation to specific seed or region of interest(ROI)[23]. The ROI can be selected based on fALFF's analysis results or accepted prior knowledge of different regions of the brain, such as the insula[24], cingulate cortex[25] or hippocampus[26]. The function of the hippocampus has been suggested to serve a critical role in the integration of cognition and processing with dysfunction of the hippocampus contributing to memory impairment[27]. In addition, the FC analysis based on fALFF comparison results can better reflect the influence of cerebral regional changes on brain networks. Therefore, fALFF and FC methods were used in this study to describe the brain functional activity state of patients from two different perspectives, local and network, respectively[18, 28]. In view of the fact that MMSE and IHDS are commonly used to evaluate neurocognitive impairment in HIV-infected patients, it is also necessary to explore the relationship between clinical scale features and changes in fALFF and FC in this study.

2. Materials and methods

2.1. Participants

This study was conducted in Pudong New Area of Shanghai, China from October 2021 to December 2022. It involved 66 subjects, aged between 40 and 80, were recuited from the Cohort of HIV-infected associated Chronic Diseases and Health Outcomes, Shanghai,China (CHCDO) which was established in 2018. HIV-infected individuals are registered with the Chinese National Information System for AIDS Prevention and Control (CNISAPC) and during routine follow-up, numerous patients within Pudong's health care system were consecutively enrolled in this cohort and were evaluated for NCI according to the results of Mini-Mental State Examination (MMSE), according which to divided the HIV-NCI and HIV-control groups. 33 individuals were recruited into the two groups respectively and these subjects were then frequency matched in sex, education, 5-year age categories and handedness. The fMRI scans in this study was performed at Shuguang Hospital affiliated to Shanghai University of Traditional Chinese Medicine. All participants included received a complete explanation of the study protocol and had normal structural-examination results. All participants read and signed an informed consent form prior the beginning of the study and all experiments were performed in accordance with relevant guidelines and regulations of the Declaration of Helsinki before beginning the study. Their personal data was kept confidential and they were allowed to withdraw at any time during the prospective study.All experimental protocols of this study were approved by the ethics committee of the Pudong New Area Center for Disease Control and Prevention(CDC).

2.2. Inclusion/Exclusion Criteria.

Inclusion criteria: 1) age between 40 and 80; 2)right-handed;

Exclusion criteria: 1)hearing problems; 2)history of drug abuse or alcohol dependence; 3)HCV-infection; 4)cerebral hemorrhage, stroke, multiple sclerosis or other central nervous system (CNS) conditions; 5)psychotic or psychological disorders such as schizophrenia, depression or bipolar mood disorder; 6) pregnant or breast feeding; 7)claustrophobia or had metal equipment that was surgically implanted (cardiac pacemaker, defibrillator, and stent) as these factors would affect fMRI scanning.

2.3. Clinical Evaluations Scale

All patients underwent cognitive and psychology assessment using Chinese version of MMSE questionnaires, IHDS, Self-rating Anxiety Scale (SAS), Pittsburgh sleep quality index (PSQI) after rs-fMRI scanning. The assessments were conducted by trained clinicians with strict adherence to guidelines and protocols.

2.5. Rs-fMRI scanning

Rs-MRI images were acquired using a 3.0-Tesla scanner (MAGNETOM Skyra, Siemens, Germany) with a 16-channel head coil. A foam head holder was used to prevent head movements. The parameters were set as follows: 3D-T1WI sequence structural imaging was performed with a magnetization-prepared rapid gradient echo(MP-RAGE). TR = 7.2ms, TE = 3.1ms, thickness = 1mm, flip angle = 10 °, FOV = 256mm × 256mm, 192 slices). BOLD-fMRI images were acquired with a single-shot gradient recalled echo planar

imaging (EPI) sequence. TR = 2000ms, TE = 30ms, thickness = 3.5mm, flip angle = 90 °, FOV = 224mm × 224mm, 33 slices, matrix = 64 × 64). Each scan lasted for 8 minutes, with a total of 240 time points. Participants were instructed to relax with their eyes closed during the scanning process.

2.6. Data processing of rs-fMRI

Image data were processed in MATLAB2019b program (mathworks.com) platform. The DPABI (http://rfmri.org/dpabi) was used to preprocess the data involving the following main steps: 1) The first 10 volumes were removed avoid instability due to T1-related relaxation effect. 2) Slice timing : corrects the time difference between data at each point in time and obtains the head motion parameters of the subject in the scanning time series. 3)Realigning : the data at all time points were spatially aligned with the data collected at the first time point to obtain the head motion parameters of the subject in the scanning time series. 4) Coregister and Normalization : all the collected data were resampled according to the Montreal Neurological Institute (MNI) standard template space with a 3 × 3 × 3 mm voxel size for spatial normalization. 5) Voxel-wise detrending: mean signals from white matter, CSF were regressed out , leaving the gray matter signal for denoising. 6) Filtering : the band-pass filtering range was set at 0.01 - 0.08 Hz to physiological and high frequency noise. 7) Smooth : a Gaussian kernel of 6 mm full width at half-maximum (FWHM) was used to smooth the images.

The fALFF was the ratio of the power spectrum in the low-frequency band (0.01−0.08 Hz) to the entire frequency range. The fALFF value of each voxel was divided by the global mean fALFF value for each participant to reduce the global effects. For FC analysis, we selected the regions of interest (ROI) based on the comparison results of fALFF values between HIV-NCI group and HIV-control group. The time series of all voxels in the ROI of each subject were averaged, and the Pearson correlation coefficient between the ROI time series of each subject and the time series of all voxels in the whole brain was calculated to obtain the z-score graph of FC. Additionally, the other brain regions also selected as ROIs for FC analysis. The seed point coordinates and radius of these ROIs are shown in Table 1:

Table 1. The seed points coordinates and radius.

Seed point	MNI coordinates			Radius
	X	Y	Z	(mm)
Left insula	-35	7	3	3mm
Right insula	39	6	2	3mm
Left anterior cingulate	-4	35	14	3mm
Right anterior cingulate	8	37	16	3mm
Left posterior cingulate	-5	-43	25	3mm
Right posterior cingulate	7	-42	22	3mm
Left hippocampus	-25	-21	-10	3mm
Right hippocampus	29	-20	-10	3mm

MNI: Montreal Neurological Institute.

2.7. Statistical analysis

Statistical analysis was performed using SPSS version 25.0 (http://www.spss.com). Continuous variable were expressed as mean ± standard deviation and categorical variables were described as frequency. The demographic data and clinical variable (except of gender) were compared using two independent-sample t-test, and gender was compared using chi-square test. P < 0.05 was used to indicate statistical significance. Statistical tests across the two groups were performed using a voxel-based, two independent sample T-test, with age, gender, and education level as covariates. The FDR correction for the results was set to $P < 0.01$, cluster size >50. Brain regions which exhibited difference between the two groups were further elected as ROIs. Mean fALFF and FC values were extracted within each of these ROIs for further analysis. Pearson correlation coefficients were then computed between the extracted mean fALFF and FC values within these ROIs and the clinical assessments of HIV patients, with significance level was set at $P < 0.05$ (two tailed).

3. Results

3.1. Demographic and clinical characteristics of participants

A total of 66 participants were recruited in the final data analysis. All participant completed the fMRI scanning without serious adverse events. No significant difference in age and years of education was identified between both groups (P > 0.05). Demographic data of all the subjects are shown in Table 2.

Table 2. Demographic data and clinical characteristics between two groups

	HIV-NCI (n=33)	HIV-control (n=33)	*P*-value
Average Age (year)	61.16±6.88	59.41±5.41	0.25[a]
Gender(male,%)	32(97.0)	30(90.9)	0.29[b]
Years of Education (n[%])			0.41[b]
Primary school and below	1(3.0)	3(9)	-
Junior school	20(60.6)	17(51.5)	-
Senior school	10(30.3)	8(24.2)	-
Undergraduate and above	2(6.0)	5(15.1)	-
MMSE score	22.26±2.98	26.55±1.30	0.002[a]
IHDS score	7.12±1.82	9.27±1.06	0.003[a]
PSQI score	8.03±3.68	7.40±3.03	0.44[a]
SAS score	41.88±7.26	40.15±8.06	0.36[a]

a: two independent-sample test; b: Chi-square test; NCI: neurocognitive impairment; wNCI: without neurocognitive impairment; MMSE: Minimum Mental State Examination; IHDS: International HIV Dementia Scale; PSQI: Pittsburgh Sleep Quality Index; SAS: Self-rating Anxiety Scale.

3.2. Comparison of fALFF and FC results between the two groups.

Compared with the HIV-control group, the fALFF values of bilateral calcarine gyrus, bilateral superior occipital gyrus, left middle occipital gyrus, left cuneus in the HIV-NCI group were increased, while no significant decrease was found elsewhere in the brain(Table 3, Figure 1). The FC values between right superior occipital gyrus and right olfactory cortex, bilateral gyrus rectus, right orbital part of middle frontal gyrus in the HIV-NCI group were increased, with no significant decrease was found elsewhere in the brain (Table 3, Figure 2). The FC values between left hippocampus and bilateral medial prefrontal cortex (mPFC), bilateral superior frontal gyrus were decreased, with no significant decrease was found elsewhere in the brain (Table 3, Figure 3). In addition, there were no significant difference in terms of FC values among other regions within the brain(bilateral calcarine gyrus, left superior occipital gyrus, left middle occipital gyrus, left cuneus) or ROIs (bilateral insula, bilateral anterior cingulate, bilateral posterior cingulate and right hippocampus) compared with the whole brain.

Table 3. Differences in fALFF and FC values between two groups.

Brain Areas	MNI Coordinates			Voxels	T*
	X	Y	Z		
fALFF					
Calcarine gyrus_L	-7	-79	6	133	3.46
Calcarine gyrus_R	16	-73	9	50	3.45
Superior occipital gyrus_L	-17	-84	28	110	3.42
Superior occipital gyrus_R	21	-93	21	82	3.56
Middle occipital gyrus_L	-36-	78	-8	78	3.43
Cuneus_L	3	-81	18	105	3.46
FC(seed as right superior occipital gyrus)					
Olfactory_R	3	24	-3	86	4.23
Rectus_R	8	36	18	78	4.12
Rectus_L	-5	37	-18	54	4.05
Middle frontal gyrus (orbital part)_R	33	53	-11	54	3.93
FC (seed as left hippocampus)					
Medial prefrontal cortex_L	-5	54	-7	237	-3.21
Medial prefrontal cortex_R	8	52	-7	225	-3.20
Superior frontal gyrus_L	-18	35	42	203	-3.73
Superior frontal gyrus_R	22	31	44	185	-3.13

*: voxel-based, independent-sample t-test with FDR corrections (P < 0.01, cluster size >50); R: right; L: Left; MNI: Montreal Neurological Institute;

3.3. Correlation between fMRI data and clinical characteristics (Figure 4).

The fALFF values of left cuneus in both two groups was negatively correlated with IHDS (R=-0.255, P=0.037) ; The fALFF values of left calcarine gyrus in both two groups was negatively correlated with MMSE (R=-0.316, P=0.009) ; The FC values between right superior occipital gyrus and right olfactory cortex (R=-0.396, P=0.001) in both two groups was negatively correlated with MMSE.

Discussion

The multiple and overlapping factors such as aging, cART neurotoxiciy and so on, resulted in adverse impacts on the neurocognitive function of people living with and affected by HIV[29]. The effects of the neurocognitive impairment of HIV infection remains an issue in clinical practice such as causing a decrease in cART adherence. Despite modern cART administration increasing life expectancy, it appears that HIV can still induce negative cognitive and psychological effects as evident by the prevalence of HAND not decreasing[30, 31]. It is worth noting that using the criteria of HAND, one must eliminate other potential etiologies of cognitive impairment, such as depression, vascular dementia(VD), diabetes or other diseases[1]. Although factors such as cART and aging have not been suggested to interact with fMRI data, to avoid confounding factors, all patients enrolled in this study were receiving cART and without other disease factors[32].

Current HIV-NCI diagnosis criteria has rested on the severity of cognitive impairment on clinical presentation of patients and neurological exam. Quantitative cognitive testing is the gold standard to evaluate for HIV-related cognitive impairment. Comprehensive testing is time consuming, including the speech, memory, executive, learning, information processing and motor functions. Whereas the short testing more frequently used, such as MMSE, IHDS or MoCA. According to previous study[8, 9, 11], the MMES and IHDS are well validated and have been applied to screening HAND while the sensitivity and specificity of MoCA are limited[33, 34]. Therefore, our study used the MMSE scores as the basis to divide the individuals to HIV-NCI and HIV-control group. Subsequently, we also recorded IHDS scores in both groups to eliminate the effects of education norms and age feature, which the factors are particularly considered in the MMSE[35].

Our study found that the brain regions with abnormal fALFF in HIV-NCI group were mainly concentrated in the visual cortex, including the calcarine gyrus, superior occipital gyrus, middle occipital gyrus and cuneus. The cuneus hub was functionally connected to the visual network while the calcarine cortex[36] functions as the secondary hub of this network[37], in combination these two hubs are activated by tasks that require visual processing (e.g. visual attention, target detection, and facial emotion recognition). The visual cortex is the initial area for the reception and processing of information, which is closely related to the further advanced processes such as emotional processing and reward feedback, etc.. Our results are concordant with several previous studies with other brain imaging research reporting the aberrations of visual processing and visual networks in HIV patients[36, 38]. A greater understanding of the visual cortex impairments has the potential to enhance diagnosis of HAND and inform prognosis and further delineation of HAND subtypes[39]. Another neuroimaging with magnetoencephalography (MEG) study also showed visuospatial dysfunction in HIV(+) patients[40]. These increased fALFF values in HIV-NCI patients may reflect increased recruitment of additional areas to meet cognitive demands[41].

Besides the brain regions that showed significant differences in the fALFF comparison between HIV-NCI and HIV-control group, we also selected the insula, cingulate cortex and hippocampus as the ROIs for FC analysis. Interestingly, the vast majority brain regions with significant differences in FC values were concentrated in the prefrontal cortex (PFC). Undoubtedly, the PFC is a crucial cortical region that

integrates information from numerous cortical subregion and plays essential roles in the higher cognitive processes[42], including semantic processing, memory control and visual perception[43]. Dysfunction of the PFC has been found in various disorders, such as addiction[44], depression[45], dementia or cognitive impairment[46]. Current evidence indicates that the PFC is critical for the generation dysregulation of emotion and motivation, through its interactions with the hippocampus and other cortical pathways[47]. It's worth noting that the PFC, cuneus and hippocampus were the important nodal region of Default Mode Network(DMN)[48]. The DMN is inhibited when focusing on external tasks, which is involved in self-awareness, episodic memory, and ongoing cognitive and emotional activities[49]. Decreased functional connectivity in the DMN of patients with Alzheimer's disease (AD) has been demonstrated[50]. The FC between hippocampus and the PFC decreased in HIV-NCI group indicates cognitive deficit of patients[49].

The significant difference in FC values of olfactory cortex was a new finding and has rarely been mentioned in previous HIV-related reports. Olfactory dysfunction usually has been seen as an early sign of neurodegenerative diseases such as Alzheimer's or Parkinson's disease(PD)[51, 52]. Further, olfactory information is processed in the secondary olfactory areas including the frontal cortex (OFC), insula, anterior cingulate cortex (ACC) and hippocampus. So we speculated the altered FC values of olfactory cortex might have a critical role in cognitive dysfunction in HAND, or along with longer duration of HIV infection or worse cognitive function according to the correlation with MMSE.

There are still some shortcoming that should be considered in this study. Firstly, this cross-sectional study hardly reflects the dynamic functional abnormalities present during the progression of HIV. Second, there were more male subjects than females in both groups which may bias our results with more male features. It should also be considered that recent evidence indicates that male and female may have different rates and patterns of neurocognitive impairment[53, 54]. Although many studies were under powered to reliably measure sex differences in cognitive impairment, a few have met this objective, showing evidence that women living with HIV may have greater neurocognitive impairment than men living with HIV[53]. Moreover, we only conducted whole brain FC for the brain regions with differences in fALFF and given ROIs which inevitably brought some subjective factors and further research is needed to understand these potential differences.

In conclusion, this study found differences in fMRI patterns between HIV-NCI and HIV-control group. These results suggest that the variation of fALFF and FC in given brain regions can be used to distinguish HIV(+) people with and without cognitive impairment. In particular, changes in fMRI patterns in specific brain regions of the occipital cortex were associated with HIV-related cognitive impairment. Our study showed that the abnormal spontaneous activity of HIV-NCI patients was mainly concentrated in the occipital cortex, while the defects in brain network mostly associated with prefrontal cortex. This study is helpful in extending our understanding of the neuropathophysiology of HIV.

Declarations

Data availability

The original contributions presented in the study are included in the article, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee of Pudong New Area Center for Disease Control and Prevention.

Author contributions

Pan-pan Chen and Xiang-yu Wei conceived the study and contributed equally to this study and should be considered co-first authors. Pan-pan Chen reviewed articles, and performed the recruitment of participants and data interpretation; Xiang-yu Wei was responsible for fMRI data processing, preparation of the tables and figures, and manuscript writing; The authors would like to thank Larissa Tao for her valuable support in polishing the manuscript language; Xin-Xin and Shao-tan Xiao aided recruitment of participants; Na He provided financial support for this study. All authors contributed to the discussion of the data and of the manuscript.

Conflicts of interest

The authors declare that they have no conflict of interest.

Acknowledgments

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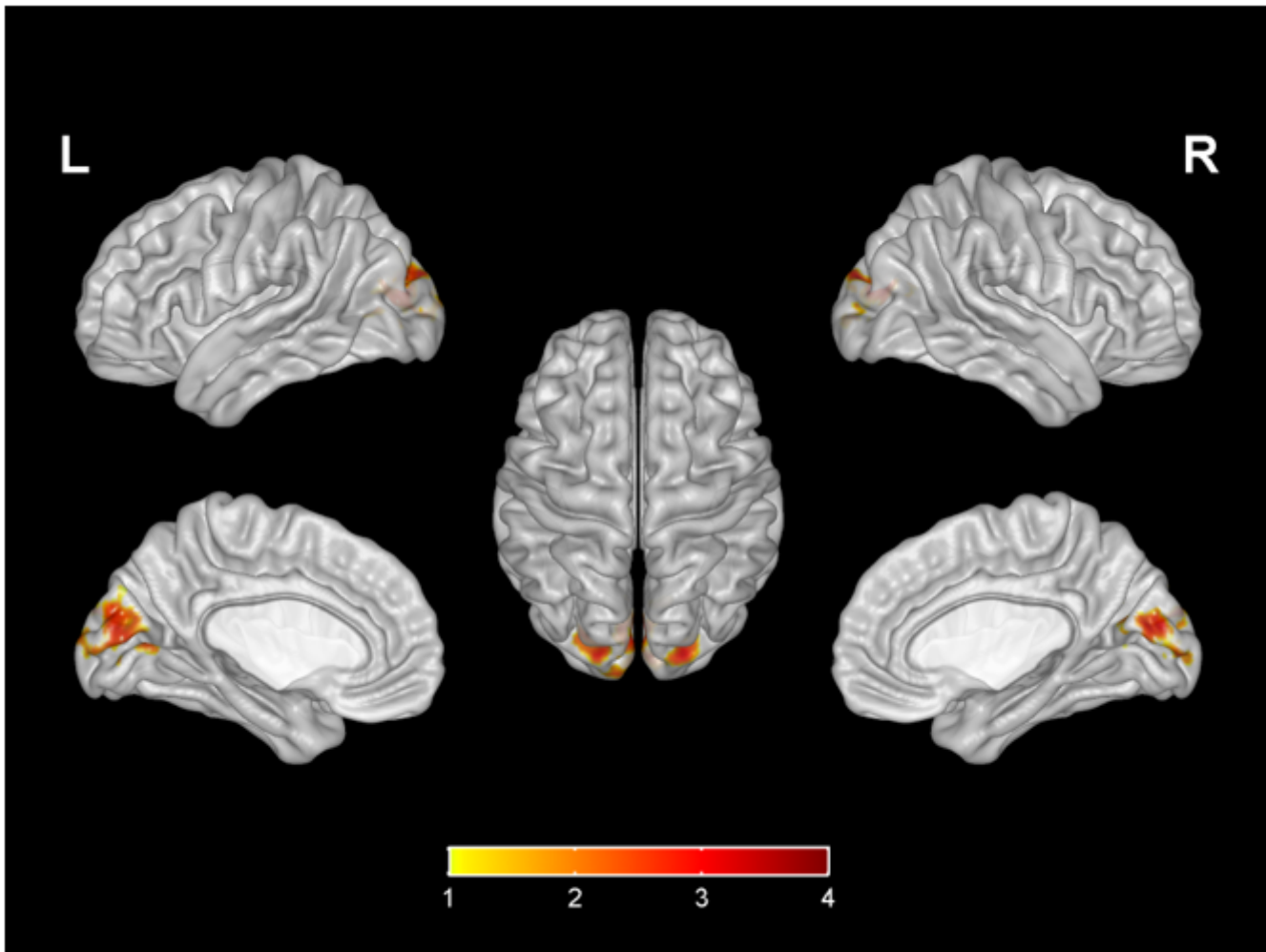
Figures

Figure 1

Compared with the HIV-control group, the fALFF values of bilateral calcarine gyrus, bilateral superior occipital gyrus, left middle occipital gyrus, left cuneus in the HIV-NCI group were increased, while no significantly decreased regions were found. voxel-based, independent-sample t-test with FDR corrections (P < 0.01, cluster size >50). The colored brain regions with red-yellow indicate a significantly increased fALFF value in HIV-NCI group compared with HIV-control group.
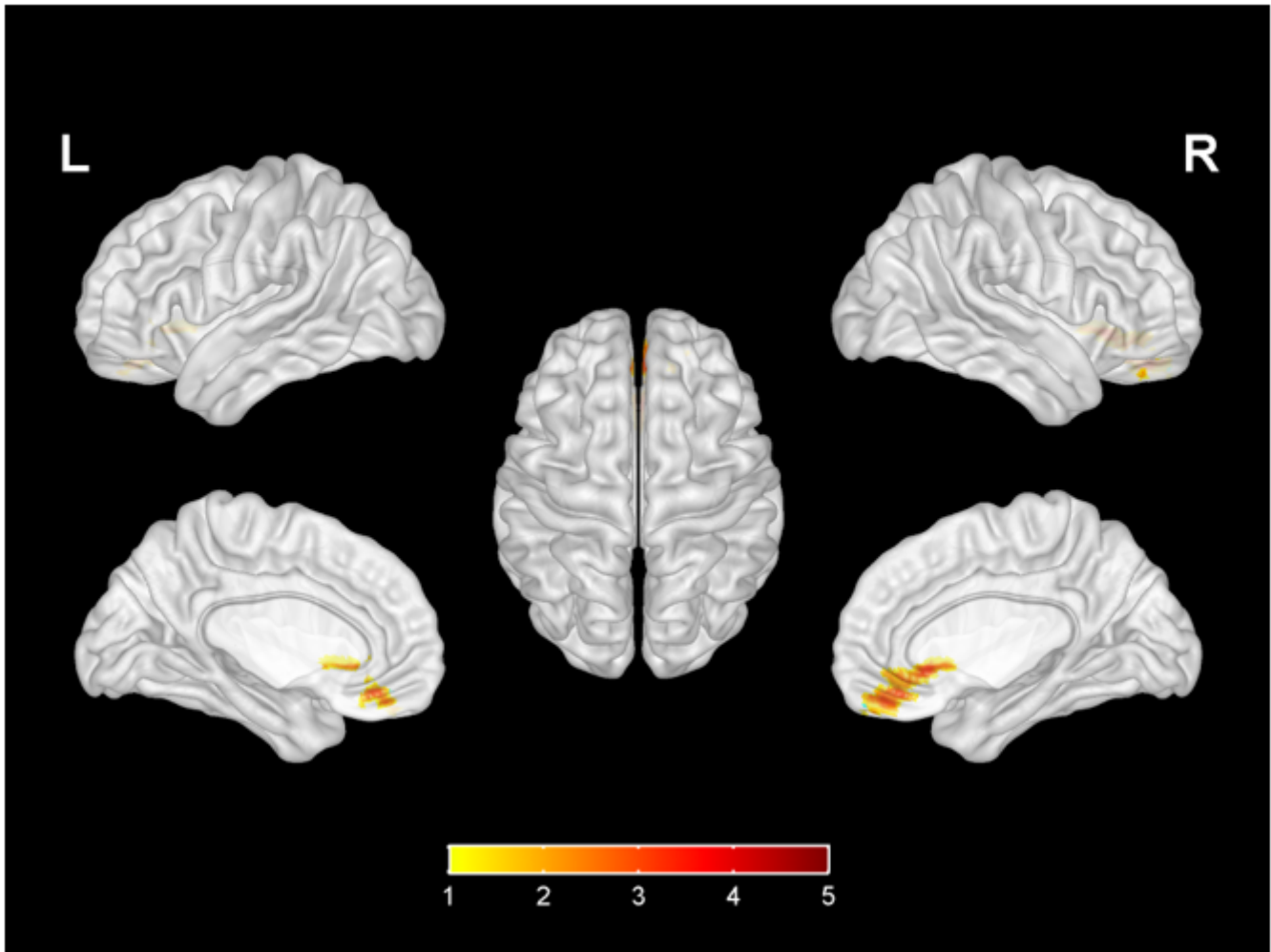
Figure 2

Compared with the HIV-control group, the FC values between right superior occipital gyrus and right olfactory cortex, bilateral gyrus rectus, right middle frontal gyrus in the HIV-NCI group were increased, while no significantly decreased brain regions were found. voxel-based, independent-sample t-test with FDR corrections (P < 0.01, cluster size >50). The colored brain regions with red-yellow indicate a significantly increased FC value in HIV-NCI group compared with HIV-control group.
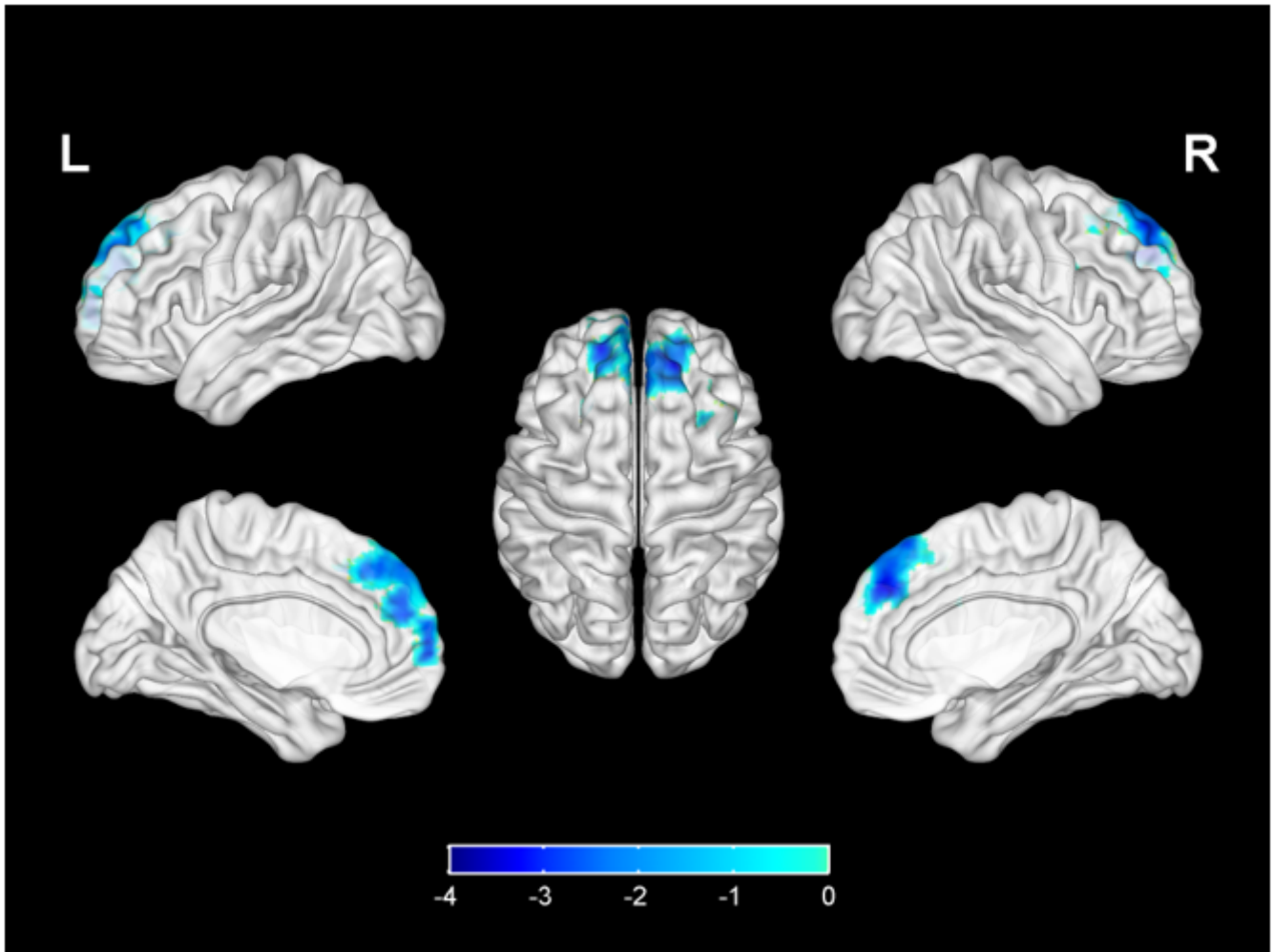
Figure 3

Compared with the HIV-control group, the FC values between left hippocampus and bilateral superior frontal gyrus(medial part), bilateral superior frontal gyrus in the HIV-NCI group were decreased, while no significantly increased regions were found. voxel-based, independent-sample t-test with FDR corrections (P < 0.01, cluster size >50). The colored brain regions with blue from light to dark indicate a significantly decreased FC value in HIV-NCI group compared with HIV-control group.
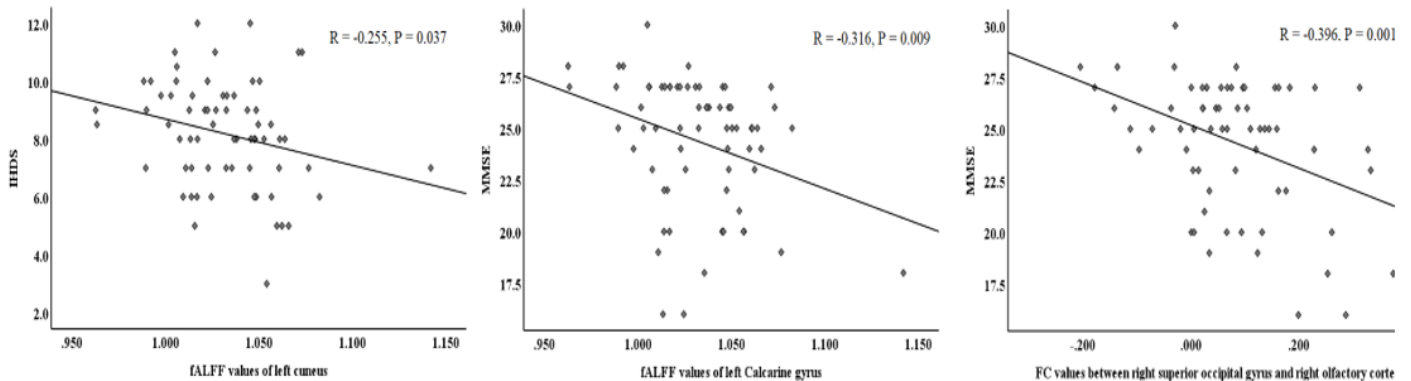
Figure 4

The fALFF values of left cuneus in both two groups was negatively correlated with IHDS (R=-0.255, P=0.037) ; The fALFF values of left calcarine gyrus in both two groups was negatively correlated with MMSE (R=-0.316, P=0.009) ; The FC values between right superior occipital gyrus and right olfactory cortex (R=-0.396, P=0.001) in both two groups was negatively correlated with MMSE.