Neurocognitive impairment and gray matter volume reduction in HIV-infected patients

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Abstract

Although neuropsychological studies of human immunodeficiency virus (HIV)-infected patients have demonstrated heterogeneity in neurocognitive impairment and neuroimaging studies have reported diverse brain regions affected by HIV, it remains unclear whether individual differences in neurocognitive impairment are underpinned by their neural bases. Here, we investigated spatial distribution patterns of correlation between neurocognitive function and regional gray matter (GM) volume across patients with HIV. Thirty-one combination antiretroviral therapy-treated HIV-infected Japanese male patients and 33 age- and sex-matched

healthy controls were included in the analysis after strict exclusion criteria, especially for substance use. Fifteen neurocognitive tests were used and volumetric magnetic resonance imaging was performed. We used voxel-based morphometry to compare GM volume between groups and identify regional GM volumes that correlated with neurocognitive tests across patients. Using the Frascati criteria, 10 patients were diagnosed with asymptomatic neurocognitive impairment, while the others were not diagnosed with HIV-associated neurocognitive disorders. Patients showed a significantly lower performance in five neurocognitive tests as well as significantly reduced GM volume relative to controls, with volume-reduced regions spread diffusely across the whole brain. Different aspects of neurocognitive impairment (i.e., figural copy, finger tapping, and Pegboard) were associated with different GM regions. Our findings suggest a biological background constituting heterogeneity of neurocognitive impairment in HIV infection, and supports the clinical importance of considering individual differences for tailor-made medicine for people living with HIV.

Keywords

HIV-associated neurocognitive disorders, individual differences, MRI, voxel-based morphometry

Introduction

The introduction of combination antiretroviral therapy (cART) has dramatically reduced human immunodeficiency virus (HIV)-associated mortality and morbidity and transformed this fatal disease into a manageable chronic disease. Despite these advances, up to half of HIV-infected patients have shown some degree of HIV-associated neurocognitive disorders (HAND) (Cysique et al. 2015; Heaton et al. 2010; Simioni et al. 2010; Wright et al. 2015). Currently, prevalence of HAND is predominantly driven by a milder severity, especially in medically asymptomatic patients (Saylor et al. 2016). Diagnosis of HAND must be determined by examining and observing at least five cognitive domains known to be affected by HIV infection (Antinori et al. 2007). The pattern of neurocognitive impairment has long been described as relatively diffuse or patchy, with variability across and within affected domains (Butters et al. 1990), especially among medically asymptomatic patients (Heaton et al. 1995; Heaton et al. 1994). The specificity and profile of impaired domains have been discussed. In some studies, primarily in the pre-cART era, attention, speed of information processing, learning, motor, and psychomotor skills were reported to be most affected (Heaton et al. 1995), forming a prototypical pattern consistent with primary subcortical brain involvement. Meanwhile, other studies, in both the pre- and post-cART era, have made negative suggestions about the existence of a prototypical pattern, and instead have shown heterogeneity of neuropsychological impairment in HIV infection (Dawes et al. 2008; Devlin and Giovannetti 2017).

Regarding the neural underpinnings, in the pre-cART era, significant volume loss was primarily reported in the basal ganglia and frontal white matter, while many studies suggested disruption of the fronto-striato-thalamo-cortical loops in HIV-infected patients (Woods et al. 2009). However, subsequent neuroimaging studies have been inconsistent, especially those conducted in the post-cART era. Accordingly, studies have reported atrophy in variable brain regions (Masters and Ances 2014; Thompson and Jahanshad 2015). While recent studies have also applied magnetic resonance imaging (MRI) with higher magnetic field strengths, enabling detection of mild and subtle volume changes in patients with HIV whose cognitive function were not significantly impaired (Towgood et al. 2012). Taken together, the findings of neuroimaging studies in HIV-infected patients have been less consistent regarding regions of brain atrophy.

Summarizing the above, neuropsychological studies have demonstrated heterogeneity of neurocognitive impairment in HIV-infected patients, while neuroimaging studies have reported non-specificity of brain regions affected by HIV. Nonetheless, the neural underpinnings of individual differences of HIV-associated

neurocognitive impairments that constitute the neurocognitive heterogeneity remain unclear. Thus, in this study, we aimed to investigate possible associations between neurocognitive task performance and regional gray matter (GM) volume changes in HIV-infected patients for each task in which patients demonstrated impairments.

Moreover, inconsistencies in previous studies might have resulted from variability among subjects regarding demographic variables and comorbidities (Devlin and Giovannetti 2017). We strictly excluded these confounders, particularly factors related to illegal substance use.

The first aim of this study was to examine neurocognitive function and GM volume of HIV-infected patients compared with healthy controls using whole brain voxel-based morphometry. All participants were Japanese and comorbid conditions were strictly excluded. The second aim was to examine possible correlation between neurocognitive function and regional GM volume across patients.

Methods

Subjects

Forty-four HIV-infected male outpatients from the National Hospital Organization Osaka National Hospital (Osaka, Japan) and 38 age- and sex-matched healthy controls were recruited between July 2014 and September 2016. The inclusion criteria were adults aged from 20 to 60 years of age who were native Japanese speakers for all subjects, and documented information on HIV infection for HIV-infected patients. The exclusion criteria were as follows: (1) Lack of capacity to provide informed consent; (2) Current acquired immunodeficiency syndrome (AIDS)-defining disease or history of opportunistic infection of the central nervous system (CNS); (3) Mental/developmental retardation; (4) A history of head trauma with loss of consciousness; (5) A history of vascular disease, including stroke, (6) Alzheimer's disease, frontotemporal lobar degeneration, Lewy body disease, prion disease, Parkinson's disease, or Huntington's disease; (7) Other non-HIV related CNS disease; (8) Former and current substance abuse or dependence of the following illegal drugs: cannabis, cocaine, methamphetamine, and heroin; (9) Other substance, medication, or alcohol abuse/dependence; (10) Schizophrenia and other psychotic disorders; (11) Mood disorders (bipolar disorders, depressive disorders, and other mood disorders); (12) Anxiety disorders (including obsessive-compulsive disorder and posttraumatic stress disorder); (13) Somatoform disorders; (14) Dissociative disorders; (15) Eating disorders; (16) Hepatitis C; (17) Current treatment for unstable systemic illness or other medical conditions causing neurocognitive impairment; and (18) MRI contraindications. If an MRI showed any incidental finding likely to represent non-HIV related

pathology, a brain anomaly, or large artifact not appropriate for brain morphometry, the subject was also excluded.

For all subjects, the following data were obtained from their medical records and by questionnaire and interviews: age, sex, sexuality, years of education, handedness, occupational history, living conditions, and medical history. Premorbid intelligence quotient (IQ) was measured using the Japanese Version of the National Adult Reading Test short form (Matsuoka and Kim 2006; Matsuoka et al. 2006), which is considered to reflect general premorbid ability. Medical history was carefully investigated for judgement of exclusion. For HIV-infected patients, nadir CD4 cell count, current CD4 cell count, highest viral load, current viral load, time since HIV diagnosis, time on antiretroviral therapy, history of AIDS defining illness, and CNS-involving opportunistic infection data were also obtained.

All subjects were evaluated for psychiatric disorders or a history of alcohol and substance usage using the Structural Clinical Interview for DSM-IV-TR Axis I Disorders-Patient Edition, which was administered by two trained psychiatrists to establish a diagnosis. In case of diagnostic discrepancy, the two psychiatrists carefully consulted to ensure their diagnoses corresponded.

Our study was approved by the Institutional Review Board of the National Hospital Organization Osaka National Hospital (approval number: 13042), and the Committee on Medical Ethics of Kyoto University (approval number: C1026). Following a complete description of the study, each subject provided written informed consent.

Neurocognitive assessment and diagnosis of HIV-associated neurocognitive disorders

The subjects completed a 15 neurocognitive test battery that assessed eight cognitive domains known to be commonly affected by HAND, based on the Frascati criteria (Antinori et al. 2007). The test battery consisted of: (1) Wechsler Adult Intelligence Scale, Third Edition (WAIS-III) Digit Symbol subtest and Trail Making Test (Part A) to assess speed of information processing, (2) WAIS-III Digit Span subtest to assess attention/working memory, (3) Trail Making Test (Part B) to assess executive function, (4) Rivermead Behavioural Memory Test (RBMT) (Immediate Story Recall) and Rey–Osterrieth Complex Figure Test (ROCFT) (Immediate Recall) to assess verbal and visual learning, (5) RBMT (Delayed Story Recall) and ROCFT (Delayed Recall) to assess verbal and visual memory, (6) Letter fluency and category fluency to assess verbal/language, (7) ROCFT (Copy) to assess visuospatial skills, and (8) Finger Tapping Test (FT) and Grooved Pegboard Test (GP) to assess motor

skills. Eight tests (WAIS-III Digit Symbol subtest, WAIS-III Digit Span subtest (Fujita et al. 2006), RBMT (Immediate Story Recall), RBMT (Delayed Story Recall) (Watamori et al. 2015), Letter fluency and category fluency, and GP (dominant and non-dominant) (Ruff and Parker 1993)) of six domains were used for HAND diagnosis due to lack of age-adjusted published norms based on large samples in the other tests. For Letter fluency and category fluency, unpublished data from Japanese healthy subjects were used, which was obtained from the Department of Neuropsychiatry, Keio University, School of Medicine (Tokyo, Japan) (n = 381, 20–59 years of age) (Konishi et al. 2014). Regarding GP, although the Japanese normative data were not available, because the task does not depend on language, we decided to use North American normative standards. Among six domains used for HAND diagnosis, a single test was available for four domains, and two tests were available for the other two domains. For the former, a cut-off of 1 standard deviation was applied to define impairment. Regarding the latter, raw scores were converted into z-scores whereby the mean for normative data was set to 0 and standard deviation was set to 1, the means of the two z-scores within the same domain were calculated, and a cut-off of 1 standard deviation was applied to define impairment.

Functional decline was classified as no significant decline, mild decline, or major decline by assessing three aspects, namely: (1) Reports of cognitive difficulties in everyday life were assessed using the Patient's Assessment of Own Functioning Inventory (PAOFI) (Chelune et al. 1986). Permission was obtained from the author to translate and use PAOFI in Japanese. Accordingly, the scale was translated into Japanese and then back-translated. (2) Increased dependence in performing instrumental activities of daily living (IADLs) was assessed with the Lawton and Brody Scale (Lawton and Brody 1969). (3) An employment questionnaire was administered that examined decreases in work productivity, accuracy and quality of work, increased effort to do usual job, and increased fatigue in usual workload.

The Frascati criteria were used for diagnosis of HAND, which was classified as asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorder, or HIV-associated dementia (Antinori et al. 2007).

Demographic, clinical, and neurocognitive task data

All data were analyzed using IBM SPSS Statistics for Windows 24.0 (SPSS 24.0, IBM Corp., Armonk, NY, USA). Two-sample t-test, Mann–Whitney U test, or Fisher's exact test were used for demographic and clinical data as appropriate. Group differences were considered significant at $p < 0.05$. Group differences of

neurocognitive tests were examined by two-sample *t*-test or Mann–Whitney *U* test, with correction for multiple comparisons using the Bonferroni test. An initial alpha level of 0.05 was set, with a corrected alpha level (0.05/15 = 0.0033) for the 15 neurocognitive tests.

MRI data acquisition

Subjects except those with MRI contraindications underwent MRI scans. Scans were acquired on 1.5 Tesla Philips Achieva (Philips, Healthcare, Eindhoven, the Netherlands) equipped with an 8-channel phased array head coil in the National Hospital Organization Osaka National Hospital. Scanning parameters for the T1-weighted three-dimensional turbo field echo (3D–TFE) sequence were: repetition time (TR) = 8.3 ms, echo time (TE) = 3.8 ms, flip angle = 30, field-of-view (FOV) = 256 × 256 mm, slice thickness = 1 mm, voxel size = 1.0 × 1.0 × 1.0 mm^3, frequency = 256, phase = 256, number of excitations (NEX) = 1, shimming = auto, frequency direction = R/L, sensitivity encoding (SENSE) = none, and total scan time = 4 min 46 s. For inspection of non-HIV related pathology, multislice, whole brain, T2-weighted fast spin echo and fluid attenuated inversion recovery scans were also collected.

MRI data processing

MRI data were processed using Statistical Parametric Mapping software (SPM12; Wellcome Trust Center for Neuroimaging, London, UK; http://www.fil.ion.ucl.ac.uk/spm) and the Computational Anatomy Toolbox (CAT12, http://dbm.neuro.uni-jena.de/vbm/) running on Matlab R2016b (MathWorks, Natick, MA, USA). In brief, all 3D T1-weighted images were tissue classified and spatially normalized to the same stereotaxic space using the diffeomorphic anatomical registration through exponentiated lie algebra (DARTEL) algorithm (Ashburner, 2007). Three tissue components, GM, white matter, and cerebrospinal fluid, were obtained to calculate total intracranial volume (TIV) in the native space. Voxel values of segmented and normalized GM images were modulated by Jacobian determinants obtained from nonlinear normalization steps. The preprocessing steps were performed using the CAT12 toolbox with the default setting, except for selecting the International Consortium for Brain Mapping (ICBM) space template (East Asian brains) in affine registration. After completion of the preprocessing pipeline, a quality check was performed using the CAT12 toolbox to assess homogeneity of the GM tissue. Finally, the resultant GM images were smoothed with a Gaussian kernel of 8 mm full-width at half-maximum, on which all analyses were performed.

Voxel-based morphometry analysis

Comparison of calculated brain tissue components between HIV-infected patients and healthy controls was performed using two-sample *t*-tests within SPSS 24.0. Components of three tissue volumes were divided by TIV to correct for head size. The statistical significance level was defined as $p < 0.05$. Regional GM volume differences between HIV-infected patients and healthy controls were examined by two-sample *t*-test in CAT12. A statistical threshold of $p < 0.001$ (uncorrected) with an extent threshold of 100 voxels was applied to examine distribution of brain atrophy. To identify correlated brain regions between neurocognitive tasks and regional GM volumes in the whole brain of HIV-infected patients, multiple regression analyses were performed on tests with Bonferroni-corrected significantly lower scores relative to controls, using the CAT12 model design tool. The statistical significance level was defined as $p < 0.001$ (uncorrected) with an extent threshold of 100 voxels for these correlational analyses. As for the above-mentioned imaging analyses, the effect of age and TIV were treated as nuisance covariates.

Results

Demographic and clinical data

Eighty-two subjects (44 HIV-infected patients, 38 healthy controls) were recruited. Of these, 18 subjects (13 HIV-infected patients, 5 healthy controls) were excluded from the study: seven because of former illegal drug abuse or other substance abuse, four because of large MRI artifacts, two because of non-HIV related CNS disease, two because of a brain anomaly not appropriate for brain morphometry, one because of a history of loss of consciousness, one because of major depressive disorder, and one because of MRI contraindication. Subsequently, 64 subjects (31 HIV-infected patients, 33 healthy controls) were included in the final analysis. Table 1 shows the demographic and clinical information. There were no significant differences in age, years of education, handedness and premorbid IQ between HIV-infected patients and healthy controls. All HIV-infected patients were on cART and had achieved viral suppression.

Characteristics of neurocognitive tests and prevalence of HIV-associated neurocognitive disorders

Table 2 shows the neurocognitive test results. On average, HIV-infected patients performed worse than healthy controls in all 15 tests. Significant group differences following Bonferroni correction for multiple comparisons

were detected with WAIS-III Digit Symbol subtest, ROCFT (Copy), FT (dominant), FT (non-dominant), and GP (dominant).

Of 31 patients, 10 (32.2%) patients were diagnosed with HAND based on the Frascati criteria. All of these 10 patients were diagnosed with ANI. The other 21 patients were not diagnosed with HAND. In addition, between 10 patients diagnosed with ANI and 21 patients not diagnosed with HAND (non-HAND), there were no significant differences (statistical significance: $p < 0.05$) in age (ANI: 41.7 ± 10.3, non-HAND: 43.1± 6.0; $p = 0.637$), years of education (ANI: 12.9 ± 2.3, non-HAND: 13.2 ± 2.3; $p = 0.704$), handedness (R/L) (ANI: 9/1, non-HAND 19/2; $p = 0.704$) or sexuality (homosexual/bisexual/heterosexual) (ANI: 5/3/2, non-HAND: 16/2/3; $p = 0.378$).

Voxel-based morphometry

HIV-infected patients showed significant (TIV-corrected) GM volume reductions (2.8%) and (TIV-corrected) cerebrospinal fluid volume increases relative to healthy controls (Table 3). Significant GM volume reductions were spread diffusely across the whole brain (Fig. 1a, Table 4). To visualize global trend patterns of brain atrophy, including putative mild and subtle volume differences, we displayed regions of GM volume reductions whose statistical significance level was leniently defined as $p < 0.05$ (uncorrected) with an extent threshold of 1000 voxels (Fig. 1b). There were no regions in which GM volumes significantly increased in patients relative to controls using the same statistical thresholds. In addition, we compared (TIV-corrected) GM volumes between 10 patients diagnosed with ANI, 21 non-HAND and 33 healthy controls (HC). (TIV-corrected) GM volumes and standard deviation were 0.4205 ± 0.019 (ANI), 0.4246 ± 0.016 (non-HAND), 0.4358 ± 0.014 (HC), respectively. One-way analysis of variance (ANOVA) followed by Tukey's honestly significant difference (HSD) test for post hoc comparison was performed (statistical significance: $p < 0.05$). The result of one-way ANOVA showed significant difference between the three groups ($F(2, 61) = 5.080$, $p = 0.009$). Tukey's HSD test showed no significant difference between ANI and non-HAND ($p = 0.784$, Cohen's $d = -0.235$), and showed significant differences between non-HAND and HC ($p = 0.040$, Cohen's $d = -0.725$), and between ANI and HC ($p = 0.028$, Cohen's $d = -0.969$).

We identified clusters in which regional GM volumes significantly correlated with neurocognitive test scores in the whole brain of patients in four out of five tests that survived Bonferroni correction, namely, ROCFT (Copy), FT (dominant), FT (non-dominant) and GP (dominant). For ROCFT (Copy), test scores positively

correlated with GM volume in bilateral angular gyrus, left middle occipital gyrus, lingual gyrus, middle temporal gyrus, posterior cingulate gyrus, and cuneus. For FT, test scores positively correlated with GM volume in the anterior cingulate gyrus (both for FT-dominant and FT-non-dominant) and posterior cingulate gyrus (for FT-non-dominant). For GP, test scores negatively correlated with GM volume in the left calcarine sulcus and cuneus (Fig. 2, Table 5). Finally, for WAIS-III Digit Symbol subtest, test scores were not significantly correlated with any regional gray matter volume. In addition, to confirm whether these correlations were present even after controlling for the effects of overall measures of GM volume, we performed the multiple regression analyses, now including (TIV-corrected) GM volume as a nuisance covariate. The results were essentially the same as those of the main analyses, except for ROCFT (Copy) in which significant correlations disappeared in some regions (Supplementary Fig. 1, Table 1).

Furthermore, as exploratory analyses, we also investigated possible correlations between task performance and regional (as well as total) GM volume for tests in which group differences in neurocognitive test results were detected with a more lenient statistical threshold (uncorrected $p < 0.05$), namely, Trail Making Test (Part A and B), WAIS-III Digit Span subtest, ROCFT (Immediate and Delayed Recall), Letter fluency and category fluency, and GP (non-dominant). For the eight tests additionally analyzed, we did not find any correlations between the task performance and regional (as well as total) GM volume.

Discussion

In our study, the patient subjects were cART-treated HIV-infected patients who were diagnosed as either ANI or not diagnosed as HAND. Although the severity of each patient's neurocognitive impairment was mild or minimal, their neurocognitive performance was lower than controls in all tests, with total GM volume (TIV-adjusted) significantly lower relative to controls. Regions of GM volume reductions were widespread across the whole brain. Furthermore, it was notable that performances of multiple neurocognitive tasks, namely, ROCFT (Copy), FT, and GP, were correlated with GM volume of different cortical regions.

Our finding of global cognitive impairment of HIV-infected patients was generally consistent with the literature. In the pre-cART era, neurocognitive impairment in HIV infection was regarded as subcortical dementia (Navia et al. 1986; Tross et al. 1988; Woods et al. 2009). Meanwhile, findings of studies published in the post-cART era have been more variable, and heterogeneity of neuropsychological performance in HIV infection has continued to be described (Devlin and Giovannetti 2017; Heaton et al. 2011; Reger et al. 2002).

Dawes et al. concluded that there does not appear to be a single, prototypical pattern of neuropsychological impairment associated with HIV infection (Dawes et al. 2008). Indeed, in clinical settings, heterogeneity of HIV-associated neurocognitive impairment is quite commonly observed. For example, memory function declines in some patients, while motor function declines in others.

Our finding of diffuse brain atrophy in HIV-positive patients was also consistent with the literature. In the pre-cART era, brain atrophy was most often reported in the basal ganglia and frontal white matter (Schouten et al. 2011; Woods et al. 2009). However, in the post-cART era, brain atrophy was reported non-specifically in all lobes (frontal (Towgood et al. 2012; Chiang et al. 2007), parietal (Becker et al. 2012; Lewis-de Los Angeles et al. 2017), temporal (Becker et al. 2012), and occipital lobes (Underwood et al. 2017; Li et al. 2018)) as well as the basal ganglia (Chiang et al. 2007) and cerebellum (Klunder et al. 2008).

Variability and inconsistency of neuropsychological and neuroimaging findings in the post-cART era might be attributed to potential modification of affected brain regions by cART, for instance, by effective HIV suppression in regions where otherwise the virus tends to preferentially accumulate. Alternatively, non-domain-specificity of neuropsychological findings as well as non-region-specificity of brain damage might be attributed to higher sensitivity and comprehensiveness of neuropsychological assessments as well as methodological progress of brain imaging in the post-cART era.

Neuropsychological impairment as well as brain damage is likely to be milder in the post-cART era, as observed in our subjects (effect size < 1 in most neurocognitive tests, and adjusted cortical volume reduction of 2.8%), and the impact of neuronal damage by HIV would be variable across patients. However, the neural underpinning of individual differences of HIV-associated neurocognitive impairments remains unclear. Consequently, it is essential to focus on detailed neuropsychological impairments, distribution of brain injuries, as well as their interrelationship. More specifically, for each cognitive task with an impairment detected, namely, ROCFT (Copy), FT, and GP, we analyzed its association with regional GM changes.

ROCFT (Copy) assesses visuospatial perception and construction (Osterrieth, 1944). Task performance correlated with volume in multiple cortical regions in our results. It is notable that all of these correlated clusters, namely, bilateral angular gyrus, left middle occipital gyrus, lingual gyrus, middle temporal gyrus, posterior cingulate cortex (PCC), and cuneus, were located in posterior regions of the cerebral cortex (i.e., occipital, parietal, and temporal lobes). These regions belong to either primary/secondary visual cortices or to parietal/temporal/multimodal association cortices, all of which are important for visual processing (Amaral,

2013; Goldberg and Wurtz, 2013). More specifically, a recent lesion study revealed that integrity of the right angular gyrus is crucial for the visuoconstructive component of ROCFT (Copy) (Biesbroek et al. 2014). Overall, the pattern of correlation in our results is reasonably interpreted as visuospatial impairment primarily attributed to brain damage of posterior cortical areas.

In contrast, impaired performance of FT, which is a basic motor speed task, was associated with reduced volume in the anterior cingulate cortex and PCC. These clusters covered both the cortex on the interhemispheric surface and the cortex on the cingulate sulcus. Although the cingulate cortex is mainly involved in the emotion, motivation, and autonomic functions, the cortex on the banks of the cingulate sulcus appear to be involved in the motor function (Dum et al. 1993), which some functional neuroimaging studies have examined in human brain (Picard et al. 2001; Amiez and Petrides 2014). The anterior cingulate cortex has been shown to be involved in a variety of cognitive processes, including motor speed (Bush et al. 2000), which was demonstrated using the finger tapping task (Lench et al. 2017). Meanwhile, the PCC has been shown to be one of three premotor areas of the cingulate cortex (i.e., the cingulate motor area (Amiez and Petrides 2014; Loh et al. 2018)), with a functional MRI study reporting activation of the cingulate motor area during FT (Ullen et al. 2003). Overall, correlation of impaired motor speed with cingulate cortex damage in our study would again be reasonably interpreted.

Another motor task, namely GP, was also found to be associated with regional volume changes. Spatial distribution of the correlated regions was different from that of FT. For GP, clusters correlated with this task were found in the calcarine sulcus and cuneus. Further, these clusters extended to cover the occipital pole. Although HAND diagnostic criteria classifies GP as a motor domain, this task is a timed task of complex visual–motor coordination (Lafayette Instrument, 2014). Thus, here again, correlation between task performance and correlated brain regions is interpreted without difficulty. Our result is also consistent with another functional MRI study, which reported negative correlation between GP impairment and impaired functional connectivity in the lateral occipital cortex network, including the occipital pole, in patients of early HIV infection (Wang et al. 2011).

Finally, we found no correlation between Digit Symbol and patient GM volume. This may result from the small number of subjects or low power of MRI for detection of small volume changes.

In summary, multiple associations between performance of impaired neurocognitive tasks and regional GM volumes were detected, and these correlations were anatomically and functionally plausible. Pathology of

different brain regions appears to have a differential impact on neurocognitive impairment in HIV-infected patients.

Considering that HIV infection is a viral disease, the regions of infiltration and proliferation of HIV within the CNS are likely to be diverse, and the host response is also likely to be diverse, especially in the post-cART era when systemic viral suppression has been achieved. Therefore, each individual patient may have a different pattern of injury distribution as well as subsequent neurocognitive impairment. Molecular diversity of the HIV genome (Dahiya et al. 2013), intra-individual HIV genetic diversity (Hightower et al. 2012), and differences in host genetics (Olivier et al. 2018) may also prompt variability of neurocognitive impairment.

Although we discussed the association between neurocognitive impairment and GM volume reduction, it should be stressed that the current study was exploratory in nature, with no a priori hypotheses about which regions would relate to which test performances. We interpreted these associations as being anatomically and functionally plausible. However, these specific findings should be considered exploratory, requiring replication in a future confirmatory study with an independent sample.

We used strict exclusion criteria to reduce confounders and to investigate the impact of HIV as specifically as possible. However, our inclusion/exclusion criteria may have limited the generalizability of the current findings to people living with HIV.

Several other limitations of this study should be acknowledged. First, we were not able to certify seronegativity of the control group. In Japan, the percentage of total reported cumulative number of HIV- and AIDS-reported cases (excluding coagulating agent-related cases) from 1985 to 2017 within the population (at January 1, 2018) was 0.022%, that is relatively low (National Institute of Infectious Diseases, Japan 2018; Ministry of Internal Affairs and Communications, Japan 2018). Moreover, in Japan, the rate of men who had sexual contact with men, including bisexual contacts in HIV-reported cases, is high. For instance, in 2017, 82% of total “HIV” cases were Japanese males and 78% of Japanese male “HIV” cases were men who had sexual contact with men, while 13% of Japanese male “HIV” cases were infected through heterosexual contact. Our healthy control subjects were all Japanese and heterosexual men, therefore seropositivity of the control group was assumed to be relatively low. To reduce potential seropositivity, subjects were asked about their chances of infection (including blood transfusion, acupuncture, as well as risky sexual intercourse) through medical interview. Second, although we matched demographic variables as much as possible, we were not able to match all of the HIV risk factors. Specifically, sexuality was not matched in the current study. Third, the HAND

diagnostic procedure of this study is a potential limitaion. Due to the lack of age-adjusted published norms based on large samples in Japan, only eight tests out of 15 neuropsychological tests were available for diagnosing HAND. We estimated the prevalence of HAND as 32.2% (10 patients). However, due to our abbreviated diagnostic procedure, the prevalence of HAND in the current study might have been underestimated. Fourth, the magnetic field used for MRI was 1.5 Tesla, with a lower signal/noise ratio compared with 3 Tesla MRI applied in recent studies. The final limitation of this study is a lack of power due to a small sample size.

Despite these limitations, the strength of our study is a higher level of subject uniformity, avoiding major confounders to limit the interpretation of our results. Further, not only current but also former illegal substance use (e.g., cocaine (Bell et al. 2011; Hanlon et al. 2011; He et al. 2018), methamphetamine (Wang et al. 2004; Zhang et al. 2018), cannabis (Korponay et al. 2017), and heroin (Wang et al. 2016)) affects cognitive function and brain structure. However, considerable studies have excluded former substance usage only leniently. In Japan, the rate of illegal substance use is extremely low compared with other countries (Ministry of Health, Labour and Welfare, Japan 2017; United Nations Office on Drugs and Crime 2017), which enabled us to exclude illegal substance users more strictly. In addition, our subjects were all Japanese, which reduced the ethnic variability.

In conclusion, our study showed mild neurocognitive impairment and mild GM atrophy in HIV-infected patients, with damaged brain regions spread diffusely across the whole brain. Further, patients' performances in multiple neurocognitive tasks correlated with regional GM volumes. Different aspects of neurocognitive impairment were associated with pathology in different GM regions, suggesting a biological background for heterogeneity of neurocognitive impairment in HIV infection. Our study supports the reasoning that it is essential to pay attention to individual differences for care and social support of people living with HIV.

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Conflict of interest

The authors declare no conflict of interest.

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Table 1 Demographic and clinical characteristics of subjects

	HIV (n = 31)	HC (n = 33)	Statistics
	Mean (SD)	Mean (SD)	p-value
Age (years)	42.6 (7.5)	41.1 (8.9)	0.465[a]
Sexuality (homosexual/bisexual/heterosexual), n	21/5/5	0/0/33	0.000[b*]
Years of education	13.1 (2.3)	14.0 (2.0)	0.107[c]
Handedness (R/L), n	28/3	30/3	0.633[b]
Premorbid IQ (JART)	107.5 (8.0)	110.4 (7.0)	0.096[c]
HIV variables			
Years since diagnosis	7.6 (3.7)		
Years since cART	6.5 (3.7)		
Nadir CD4 cells/mm^3	128.4 (103.2)		
Current CD4 cells/mm^3	574.4 (209.3)		
Highest HIV RNA, $\log_{10}$ copies/mL	5.9 (6.2)		
Current HIV RNA < 20 copies/mL, n (%)	31 (100.0)		

Abbreviations: HIV, HIV-infected patients; HC, healthy controls; SD, standard deviation; R, right; L, left; JART, Japanese Version of the National Adult Reading Test short form; cART; combination antiretroviral therapy.

[a]Two-sample t-test; [b]Fisher's exact test; and [c]Mann–Whitney U test. [*]Significant difference: $p < 0.05$

Table 2 Neurocognitive test scores

	HIV (n = 31)	HC (n = 33)	Statistics	
	Mean (SD)	Mean (SD)	p-value	Cohen's d
Speed of information processing				
WAIS-III Digit Symbol subtest	81.8 (15.5)	93.4 (11.2)	0.0011[a] *	-0.862
Trail Making Test (Part A)	85.0 (27.0)	68.7 (19.1)	0.0081[b]	0.700
Attention/working memory				
WAIS-III Digit Span subtest	16.9 (3.3)	19.4 (4.1)	0.0093[a]	-0.669
Executive function				
Trail Making Test (Part B)	106.8 (40.2)	82.5 (21.6)	0.0197[b]	0.759
Verbal and visual learning				
RBMT (Immediate Story Recall)	11.0 (4.2)	12.6 (3.0)	0.0848[a]	-0.440
ROCFT (Immediate Recall)	18.4 (6.9)	22.3 (5.8)	0.0199[a]	-0.613
Verbal and visual memory				
RBMT (Delayed Story Recall)	10.5 (3.5)	11.4 (3.1)	0.2574[a]	-0.272
ROCFT (Delayed Recall)	18.2 (6.4)	21.7 (5.8)	0.0242[a]	-0.573
Verbal/language				
Letter fluency	26.0 (10.3)	32.9 (9.7)	0.0078[a]	-0.690

Category fluency	43.9 (9.9)	50.9 (10.6)	0.0084[a]	-0.681
Visuospatial skills				
ROCFT (Copy)	30.2 (3.6)	32.8 (2.4)	0.0031[b] *	-0.855
Motor skills				
Finger Tapping Test (dominant)	56.9 (6.3)	61.6 (5.1)	0.0018[a] *	-0.822
Finger Tapping Test (non-dominant)	52.6 (5.6)	56.8 (5.3)	0.0029[a] *	-0.771
Grooved Pegboard Test (dominant)	66.7 (8.2)	58.9 (7.0)	0.0001[a] *	1.025
Grooved Pegboard Test (non-dominant)	70.1 (12.9)	63.3 (8.8)	0.0247[b]	0.619

Abbreviations: HIV, HIV-infected patients; HC, healthy controls; SD, standard deviation; WAIS-III, Wechsler Adult Intelligence Scale, Third Edition; RBMT, Rivermead Behavioural Memory Test; ROCFT, Rey–Osterrieth Complex Figure Test. [a]Two-sample *t*-test; and [b]Mann–Whitney *U* test. [*]Significant difference after Bonferroni correction: $p < 0.0033$

Table 3 Segmented brain volume

	HIV (n = 31)	HC (n = 33)	Statistics
	Mean (SD)	Mean (SD)	p-value
GMV (ml)	662.6 (45.2)	676.7 (49.1)	0.238
WMV (ml)	529.7 (51.9)	528.8 (58.9)	0.949
CSFV (ml)	374.7 (49.5)	348.5 (34.5)	0.018
TIV (ml)	1567.0 (113.0)	1554.0 (122.1)	0.661
GMV/TIV	0.4233 (0.017)	0.4358 (0.014)	0.003*
WMV/TIV	0.3377 (0.017)	0.3396 (0.016)	0.651
CSFV/TIV	0.2389 (0.024)	0.2244 (0.016)	0.007*

Abbreviations: HIV, HIV-infected patients; HC, healthy controls; SD, standard deviation; GMV, GM volume; WMV, white matter volume; CSFV, cerebrospinal fluid volume; TIV, total intracranial volume. *Significant difference: $p < 0.05$

Table 4 Regions of gray matter volume reductions in HIV-infected patients compared with healthy controls

Region	Peak-level MNI coordinates			T value	Cluster size
	x	y	z		
Right inferior frontal gyrus	50	21	-10	5.54	450
Right middle temporal gyrus	64	-36	4	5.19	1085
Right inferior frontal gyrus	50	12	14	4.47	458
Right uncus of hippocampus	20	6	-24	4.44	218
Right posterior cingulate gyrus	9	-32	42	4.12	313
Right angular gyrus	52	-68	34	4.05	505
Right superior frontal gyrus	27	60	3	4.03	205
Left cuneus	-9	-75	30	4.02	436
Left insula	-28	12	12	3.92	236
Left lingual gyrus	-22	-80	-15	3.66	123

Abbreviation: MNI, Montreal Neurological Institute

Table 5 Gray matter regions correlated with neuropsychological tests in the whole brain of HIV-infected patients

Region	Peak-level MNI coordinates			T value	Cluster size
	x	y	z		
Rey Complex Figure Test (Copy)					
Left middle occipital gyrus	-54	-74	10	5.99	807
Left middle occipital gyrus	-28	-88	32	4.77	107
Left lingual gyrus	-20	-70	-9	4.67	135
Left angular gyrus	-44	-72	45	4.6	198
Left middle temporal gyrus	-68	-45	3	4.52	116
Right angular gyrus	54	-66	30	4.4	178
Left posterior cingulate gyrus	0	-64	15	4.2	117
Left cuneus	-6	-92	18	4.11	139
Finger Tapping (dominant)					
Right anterior cingulate gyrus	12	40	0	4.24	179
Finger Tapping (non-dominant)					
Left posterior cingulate gyrus	-4	-34	39	4.52	226
Right anterior cingulate gyrus	8	45	0	3.94	187

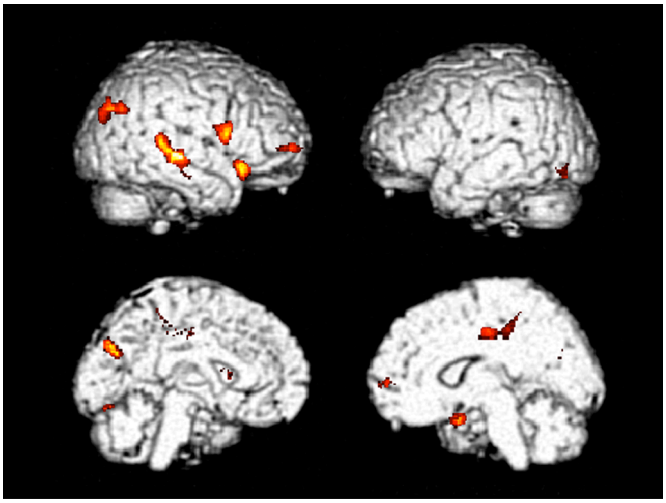
Grooved Pegboard (dominant)					
Left calcarine sulcus	-9	-88	6	4.85	383
Left cuneus	-6	-93	20	4.35	230

Abbreviation: MNI, Montreal Neurological Institute

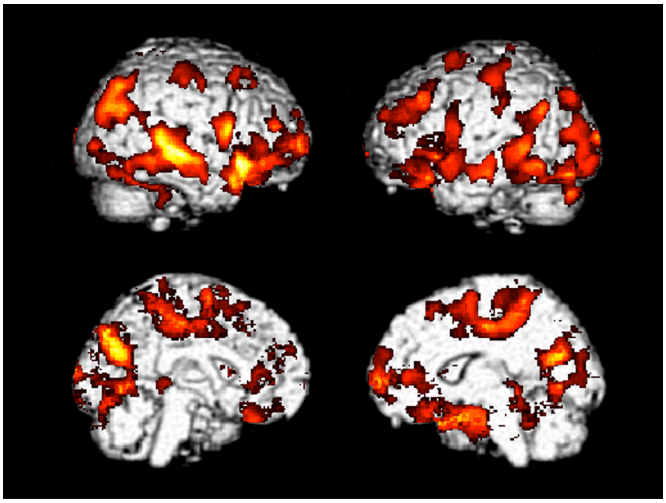
Figure Captions

Fig. 1 Areas of gray matter volume reductions in HIV-infected patients compared with healthy controls. **(a)** Uncorrected $p < 0.001$, extent threshold = 100 voxels. **(b)** Uncorrected $p < 0.05$, extent threshold = 1000 voxels. The results are displayed on the brain surface

Fig. 2 Gray matter regions correlated with neuropsychological tests in the whole brain of HIV-infected patients. Uncorrected $p < 0.001$, extent threshold = 100 voxels. The results are displayed on the brain surface. **(a)** Rey–Osterrieth Complex Figure Test (Copy); **(b)** Finger Tapping Test (dominant); **(c)** Finger Tapping Test (non-dominant); **(d)** Grooved Pegboard Test (dominant)



(a)



(b)

Fig. 1

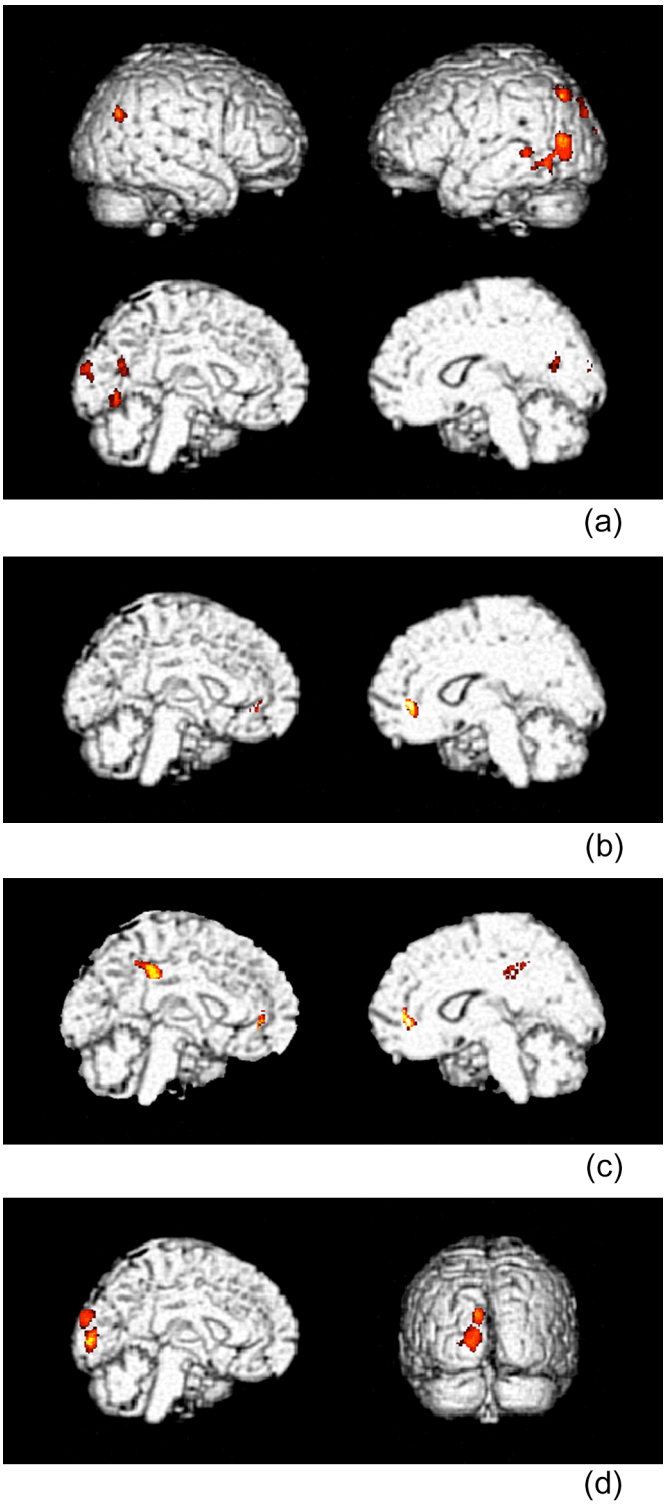
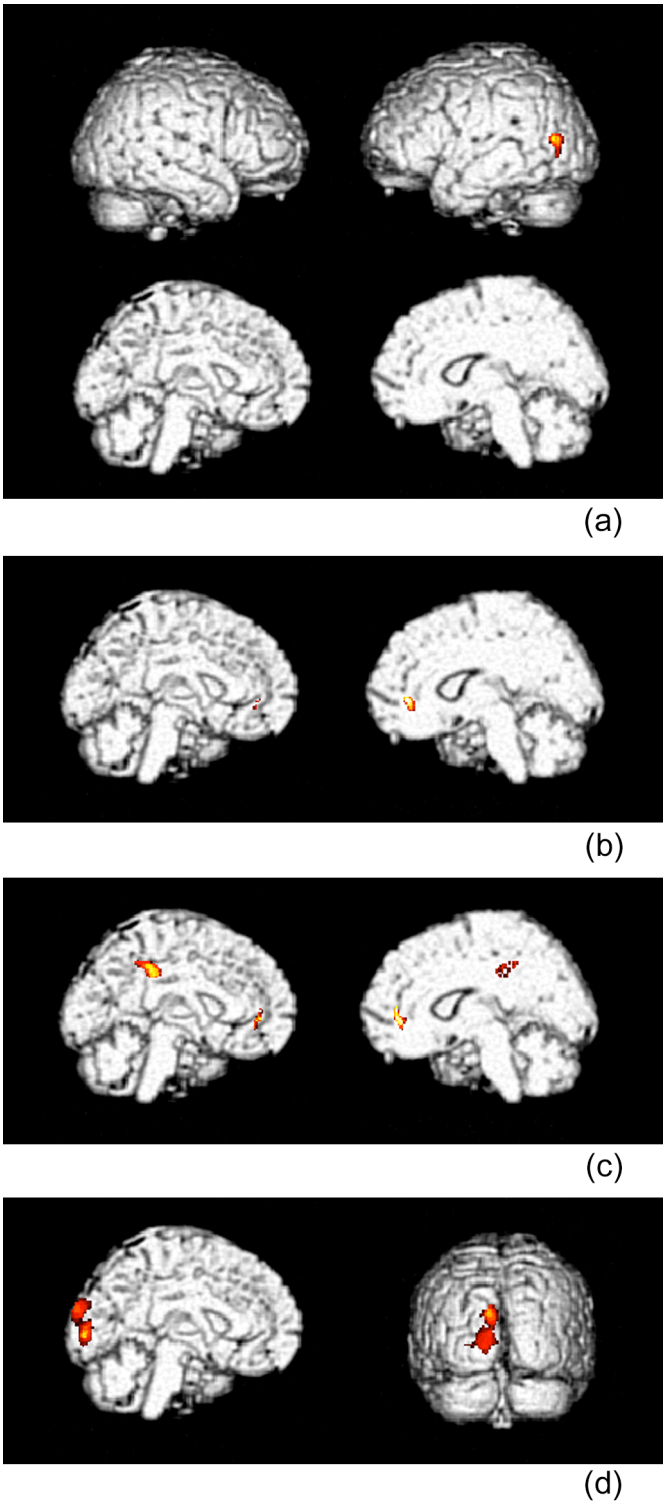


Fig. 2



Spplementary Fig. 1 Gray matter regions correlated with neuropsychological tests in the whole brain of HIV-infected patients, including gray matter volume (total intracranial volume corrected) as nuisance covariate.

Uncorrected $p < 0.001$, extent threshold = 100 voxels. The results are displayed on the brain surface. **(a)** Rey–Osterrieth Complex Figure Test (Copy); **(b)** Finger Tapping Test (dominant); **(c)** Finger Tapping Test (non-dominant); **(d)** Grooved Pegboard Test (dominant)

Supplementary Table 1 Gray matter regions correlated with neuropsychological tests in the whole brain of HIV-infected patients, including gray matter volume (total intracranial volume corrected) as a nuisance covariate

Region	Peak-level MNI coordinates			T value	Cluster size
	x	y	z		
Rey–Osterrieth Complex Figure Test (Copy)					
Left middle occipital gyrus	-54	-74	10	5.17	186
Finger Tapping (dominant)					
Right anterior cingulate gyrus	12	40	0	4.07	121
Finger Tapping (non-dominant)					
Left posterior cingulate gyrus	-4	-36	40	4.82	246
Right anterior cingulate gyrus	8	46	2	4.36	196
Grooved Pegboard (dominant)					
Left calcarine sulcus	-8	-88	6	5.10	823

Abbreviation: MNI, Montreal Neurological Institute