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Structural connectome differences in HIV infection: brain network segregation associated with nadir CD4 cell count

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Abstract

This study investigated structural brain organization using diffusion tensor imaging (DTI) in 35 HIV-positive and 35 HIV-negative individuals. We used global and nodal graph theory metrics to investigate whether HIV was associated with differences in brain network organization based on fractional anisotropy (FA) and mean diffusivity (MD). Participants also completed a comprehensive neuropsychological testing battery. For global network metrics, HIV-positive individuals displayed lower FA clustering coefficient relative to HIV-negative individuals. For nodal network metrics, HIV-positive individuals had less MD nodal degree in the left thalamus. Within HIV-positive individuals, FA global clustering coefficient was positively correlated with nadir CD4 cell count. Across the sample, cognitive performance was negatively correlated with characteristic path length and positively correlated with global efficiency for FA. These results suggest that, despite management with cART, HIV infection is associated with altered structural brain network segregation and thalamic centrality, and that low nadir CD4 cell count may be a risk factor. These graph theory metrics may serve as neural biomarkers to identify individuals at risk for HIV-related neurological complications.

Keywords

Graph theory; HIV; Connectome; Structural connectivity

INTRODUCTION

HIV infection is known to impair neurocognitive function in up to 50% of infected individuals (Cysique et al., 2006; Heaton et al., 2010; Navia et al., 1986; Woods et al., 2009). HIV-associated neurocognitive impairment (NCI) persists, albeit to a lesser degree, even when HIV-positive individuals are treated with combination antiretroviral therapy (cART) (Heaton et al., 2011; Heaton et al., 2015). HIV-associated NCI impacts daily

functioning (e.g., driving ability, employment, medication adherence) and is predictive of increased morbidity and mortality (Doyle et al., 2013; Heaton et al., 2004a; Lovejoy and Suhr, 2009; Marcotte et al., 2004; Rabkin et al., 2004; Vivithanaporn et al., 2010). Given the high prevalence of NCI, there is a need for neural biomarkers to facilitate diagnosis in clinical settings (Gates and Cysique, 2016).

Diffusion tensor imaging (DTI) metrics fractional anisotropy (FA) and mean diffusivity (MD) have been extensively used in neuroHIV research to assess white matter (WM) integrity in the brain (Masters and Ances, 2014). FA and MD provide complementary information on WM structure, with FA being more indicative of axonal structural integrity (Winston, 2012), while MD is more sensitive to WM microstructural density including cellular and axonal loss resulting from neuroinflammation (Alexander et al., 2007; Lentz et al., 2014). Typically, reduced FA and increased MD indicate compromised WM integrity (Chanraud et al., 2010).

Whole-brain analyses have shown overall decreased FA and increased MD in HIV-positive individuals when compared to HIV-negative controls; these deficits are associated with severity of HIV disease and neurologic dysfunction (Heaps et al., 2011; Ragin et al., 2005; Stubbe-Drager et al., 2012; Su et al., 2016). More specifically, HIV has been associated with diffuse decreases in FA across projection, association, and commissural WM tracts (Chen et al., 2009; Stubbe-Drager et al., 2012; Su et al., 2016; Wakim et al., 2017). Increased MD has been reported in internal and external capsule fibers and superior cingulate bundles (Pfefferbaum et al., 2009). Together, these studies suggest that WM deficits secondary to HIV infection occur diffusely, are associated with worse HIV disease characteristics, and are correlated with deficits in cognitive ability. As such, they may represent important biological markers for neurological HIV disease progression.

Neurobiological insults are hypothesized to lead to aberrant brain networks, which can be measured using graph theory methodology (Fornito et al., 2015). DTI metrics can be used to explore relationships between whole-brain structural connectivity through identification of WM microstructure integrity between cortical regions (Hagmann et al., 2007). This whole-brain structural connectivity data is referred to as a connectome and describes the topological organization of brain networks (Sporns et al., 2005). These measures allow for quantification of the degree to which regional segregation and separation of function is balanced with interconnectivity across the brain (Fornito and Bullmore, 2015; Watts and Strogatz, 1998). While segregation refers to clusters of regions that interact to efficiently perform specific cognitive tasks, integration refers to interactions between segregated clusters to enable complex, integrative tasks (Bullmore and Sporns, 2012). An important component of integration involves the concept of centrality, which refers to how focal a specific region is to network organization within structurally related clusters of regions (Bullmore and Sporns, 2012).

This study applies connectomic methodology to evaluate the association between HIV infection and structural brain network connectivity. A recent investigation of structural connectivity using DTI in HIV-positive young adults in South Africa ($n=29$) showed lower characteristic path length, global efficiency, connection strength, and clustering coefficient

relative to HIV-negative controls ($n=16$) (Baker et al., 2017). In addition, HIV-associated NCI was negatively correlated with clustering coefficient. One limitation of this study is that the sample had limited or no treatment history. The present study builds upon these initial findings in structural connectivity by investigating neural network organization in HIV-positive adults who are receiving cART. In addition, we also investigated individual cortical and subcortical regions for their contribution to structural brain network connectivity. For this, we mapped FA and MD connectivity data between atlas-defined regions and used graph theory to derive global and nodal metrics of network organization between HIV-positive and HIV-negative individuals. We hypothesized that HIV infection would be associated with lower global and nodal structural connectivity relative to HIV-negative individuals, and that differences between groups would be related to HIV disease characteristics and neurocognitive function.

METHODS

Participants and procedures

The sample included 70 adults recruited from the Raleigh-Durham area in North Carolina, USA. Eligibility criteria were between 18–55 years old, English fluency and literacy, confirmed HIV status (positive or negative), and no MR contraindications. All HIV-positive participants were currently engaged in HIV care and prescribed cART. Their HIV status was confirmed via medical record review. For HIV-negative individuals, an OraQuick© rapid test confirmed their HIV status. Exclusion criteria were: <8th grade education; severe learning disability with functional impairment; serious neurological disorders; acute opportunistic brain infections or a history of such infections without return to normal cognition; severe head trauma with loss of consciousness >30 minutes and persistent functional decline; indicators of severe mental illness; and impaired mental status. These exclusions are consistent with current guidelines for classifying contributing or confounding conditions to HAND (Antinori et al., 2007). Current alcohol, marijuana, and nicotine use were permitted, but participants could not have a current alcohol or marijuana use disorder. For all other illicit drugs, individuals were excluded for lifetime abuse or dependence, any history of regular use, and/or a positive drug screen.

Both HIV-positive and HIV-negative participants were recruited between October 2011 and May 2015 via advertisements in local newspapers and websites, flyers and brochures at community-based organizations and infectious diseases clinics, and participant referrals. Interested participants contacted the study and completed a brief telephone pre-screening. Potentially eligible participants were invited for a comprehensive in-person screening. After providing written informed consent, participants completed clinical interviews and questionnaires, and provided urine samples for pregnancy (if applicable) and drug screening. Eligible participants returned to complete a neurobehavioral assessment and an MRI brain scan. Participants were drawn from two protocols with shared procedures that were approved by the institutional review board at Duke University Health System.

Screening measures

The Mini International Neuropsychiatric Interview was used to confirm the absence of disqualifying psychiatric disorders and conditions (Sheehan et al., 1998). The Addiction Severity Index-Lite (McLellan et al., 1992) and the Structured Clinical Interview for DSM-IV-TR (First et al., 1996) were used to assess substance use and substance use disorders, respectively. At all visits, urine toxicology screens were used to corroborate self-report of recent drug use. Participants also completed an audio computer-assisted self-interview that included a demographics survey.

Neurobehavioral and clinical assessment

Medical records were reviewed to obtain HIV-related clinical variables (i.e., date of diagnosis, current and nadir CD4 count, and current viral load). HIV viral suppression was dichotomized at 50 copies/mL. Self-report was used when medical records were incomplete ($n=7$).

Neurocognitive functioning was measured using a comprehensive battery that assessed seven domains: processing speed [Trail Making Test Part A (Reitan and Wolfson, 1993)], attention [Paced Auditory Serial Addition Task-50 or 100 (Diehr et al., 2003); NAB Digits Forward/Digits Backward Test (Stern and White, 2009)], learning [Hopkins Verbal Learning Test – Revised (HVLTR), immediate trials (Brandt and Benedict, 2001)], memory [HVLTR, delayed trial (Brandt and Benedict, 2001)], executive functioning [Stroop Color and Word Test, interference score (Golden, 1978); Trail Making Test Part B (Reitan and Wolfson, 1993)], verbal fluency [FAS letter fluency and category fluency (Benton et al., 1983)], and motor functioning [Grooved Pegboard Test, dominant and non-dominant hands (Klove, 1963)]. Raw scores were converted to standardized T-scores ($M=50$, $SD=10$) using up-to-date published norms (Diehr et al., 2003; Heaton et al., 2004b; Norman et al., 2011; Stern and White, 2009; Wechsler, 1997). T-scores for each test within a domain were averaged to create a domain T-score, and a global T-score was calculated by taking the mean of all domain T-scores.

Imaging protocol

All scans were performed on the same 3T GE Discovery MR750 imaging system with an 8-channel head coil at Duke University Hospital. DTI images were acquired in the axial plane using a single shot spin-echo diffusion sensitized EPI sequence in 30 directions (FOV = 25.6 cm, matrix = 128×128 , flip angle 90° , interleaved slices of 2.0 mm thickness). Additional parameters differed slightly between protocol 1 (b-factor = 900 s/mm^2 , TR/TE = 10,000/83.2ms, 73 slices) and protocol 2 (b-factor = 800 s/mm^2 , TR/TE = 8,000/77.9ms, 67 slices). Thirty three participants were from protocol 1 (53.1% HIV-positive) and 37 were from protocol 2 (47.1% HIV-positive), with no differences in HIV status by protocol ($\chi^2(1) = 0.057$, $p = .811$).

Pre-processing and quality control

The DTI data was visually checked, and then preprocessed using DTIPrep, a quality control pipeline that includes image dimension, slice-wise, interlace-wise, and gradient-wise checking along with baseline averaging, head motion correction, and eddy current correction

(Oguz et al., 2014). From an initial sample of 72, two participants were excluded due to too many bad gradient directions after DTIPrep, leaving a final sample of 70.

Data analysis

Connectome build—Deterministic tractography was run via a module of the Connectome Mapper Toolkit (CMTK) (Gerhard et al., 2011) that utilizes a classical streamline fiber-tracking algorithm (Hagmann et al., 2003). Fibers were spline-filtered with the Diffusion Toolkit before the connection matrix was created. Inter-regional fibers are defined as those that begin and end in pairs of gray matter (GM) nodes and pass through the WM mask. Length thresholds were applied to whole brain tractography, excluding fibers <2 mm and >40 mm in length as artifacts.

CMTK was then used to create a weighted connectivity matrix for subsequent graph theory analyses based on FA and MD values. Whole-brain tractography and cortical and sub-cortical segmentation were combined using Freesurfer (Daducci et al., 2012). Registration transformations were applied to the WM mask and the GM parcellation in order to map both to diffusion space. Edges were defined between nodes using random seed points chosen within each voxel of a node and streamlines were propagated in two opposite directions of the local diffusion directions (FA or MD) with a fixed step size of 1 mm (Hagmann et al., 2007). Final edge definition consisted of the averaged pattern of diffusion for MD and FA separately. The propagation was constrained within the WM mask, and this propagation was stopped when it reached the defined boundary between the WM and GM masks and/or there was inconsistency between diffusion directions in adjacent voxels (Daducci et al., 2012).

Graph theory metrics: Nodes were defined from cortical and subcortical regions using Freesurfer and utilizing the Desikan-Killiany Atlas for automatic subcortical segmentation and cortical parcellation of native-space T1 anatomical scans (Desikan et al., 2006). Each participant's parcellation result was visually verified for anatomical accuracy. Nodes were restricted to GM voxels by subtracting from WM masks. A total of 83 nodes were defined for each participant (41 GM nodes per hemisphere plus brainstem).

Network analysis was completed using GREYNET Version 1.2 (Wang et al., 2015). We examined four common global metrics that describe the characteristics for the network as a whole: connection strength (the sum of all nodal connections), characteristic path length (a measure of integration defined as the average shortest path between all nodes), global efficiency (a measure of integration defined as the inverse of the characteristic path length), and global clustering coefficient (a measure of segregation defined as the degree of interconnected neighborhoods of nodes). We also examined three nodal network metrics describing integration and centrality of specific nodes (Fornito and Bullmore, 2015; Sporns, 2014): nodal degree (the number of edges emanating from a node), nodal efficiency (the inverse of the average shortest path length of a node to every other node), and nodal betweenness centrality (the fraction of shortest paths that pass through a node). To avoid biases associated with a single threshold, we used a sparsity threshold range of 5% to 40% in steps of 1%. For all variables, the area under the curve (AUC) was computed for the full range of sparsity values.

For each network metric, between-group comparisons were performed using nonparametric permutation analyses. With age included as a covariate, permutation testing was carried out by randomly reassigning the network metrics to different individuals 5000 times. This created a non-parametric distribution from which a p -value for the group difference was estimated by measuring the proportion of permutations for significant global and nodal network differences between HIV-positive and HIV-negative persons. For nodal analyses, this procedure was carried out for each of the 83 nodes separately and Bonferroni corrected ($p = 0.0006$).

Association between graph theory metrics and clinical variables: Among HIV-positive participants, we investigated the relationship between network metrics and markers of HIV disease severity using non-parametric permutation testing. With age included as a covariate, partial correlation (for continuous variables) and between-group (for dichotomous variables) permutation testing was carried out by randomly reassigning the network metrics to different individuals 5000 times on global and nodal network metrics. We examined nadir CD4 cell count, current CD4 cell count, years since HIV diagnosis, and current HIV viral load suppression.

In the full sample, we investigated the relationship of global network metrics to global T-score using non-parametric permutation testing as described above. We also examined the relationship between nodal network metrics that differed between groups and global T-score.

RESULTS

Participant characteristics

Table 1 summarizes the sample characteristics overall and by study groups. The majority of participants identified as male (67%) and African-American (74%). They ranged in age from 24 to 55 years ($M = 41.66$, $SD = 8.83$), and most (86%) had completed at least a high school diploma. There were no significant group differences on any characteristics. The mean standardized T-score for global neurocognitive functioning was 48.37 ($SD = 6.10$), with no group differences.

HIV-positive participants had been diagnosed with HIV for 9.9 years on average ($SD = 7.7$). The median nadir CD4 cell count was 204 ($Q1 = 108$, $Q3 = 439$), and the median most recent CD4 cell count was 574 ($Q1 = 290$, $Q3 = 776$). Despite cART, 26% ($n = 9$) had a detectable HIV viral load at >50 copies/mL, 74% were virally suppressed ($n = 26$).

Graph theory metrics

HIV-positive individuals had significantly lower clustering coefficient for FA compared to the HIV-negative individuals ($p = 0.05$) (see Figure 1 and Table 2). HIV-positive participants also had lower MD clustering coefficient, although this difference did not reach statistical significance ($p = 0.07$). There were no differences between groups for characteristic path length, global efficiency, or connection strength.

When examining the nodal metrics, HIV-positive individuals had less MD nodal degree in the left thalamus relative to HIV-negative individuals ($p = 0.0006$; Bonferroni corrected) (see

Table 2). They also had lower nodal degree for FA in the left thalamus ($p=0.04$), although this difference did not survive Bonferroni correction. No group differences were found for right thalamic nodal degree. While there were other group differences for multiple regions ($p<0.05$), they did not survive Bonferroni correction (see Appendix).

Examination between graph theory metrics and clinical variables

Among HIV-positive participants, nadir CD4 count was positively correlated with FA clustering coefficient ($r=0.39$; $p=0.03$). HIV-positive participants with suppressed HIV viral load had higher FA connection strength relative to patients without suppressed HIV viral load ($t(32) = 2.00$; $p=0.04$). Network metrics were unrelated to most recent CD4 count and years since HIV diagnosis.

In the full sample, global T-score was negatively correlated with FA characteristic path length ($r=-0.26$; $p=0.03$) and positively correlated with FA global efficiency ($r=0.24$; $p=0.03$), but FA clustering coefficient and connection strength were unrelated ($r=-0.14$; $p=0.29$ and $r=-0.17$; $p=0.13$). There were no significant correlations for MD global network metrics.

DISCUSSION

The results of this study suggest that HIV infection is associated with altered global and nodal connectivity in the structural connectome. HIV-positive participants showed lower global clustering coefficient indicative of reduced segregation compared to the HIV-negative participants, as well as lower nodal degree in the left thalamus. Reduced network segregation was associated with lower nadir CD4 count in HIV-positive participants, suggesting that brain network organization may be adversely affected by a history of greater immune suppression. Neurocognitive functioning across groups was associated with lower FA characteristic path length and higher FA global efficiency, although this effect was not specific to HIV. These results point to global brain network segregation and thalamic centrality being altered in HIV infection despite cART prescription and minimal NCI.

Our finding of lower global clustering coefficient suggests HIV infection is associated with less structural connectivity within clusters of functionally related cortical and subcortical regions. Global clustering coefficient is a measure of network segregation that reflects specialization of discrete brain regions or systems in performing specific mental operations (Fornito and Bullmore, 2015). Lower global clustering coefficient could reflect dedifferentiation, a concept of deficient structural connectivity producing a break-down of network segregation that then results in decreased cognitive specialization. The hypothesized result of this breakdown in network segregation is increased neural activity in less efficient neural clusters (Fornito and Bullmore, 2015). Indeed, multiple neuroimaging studies of cognitive function in HIV have found increased neural activation during executive function tasks despite comparable behavioral performance relative to HIV-negative individuals (Meade et al., 2016; Plessis et al., 2015). Lower clustering coefficient was also associated with lower nadir CD4 cell count. This relationship suggests a role of historical immune suppression in structural brain network connectivity related to network segregation. This finding is consistent with other studies that have reported an association between lower nadir

CD4 count and lower total WM and GM volumes and higher ventricular and sulcal cerebrospinal fluid (Cohen et al., 2010; Jernigan et al., 2011). It has been suggested that a history of severe immune suppression may reflect greater viral replication (Cohen et al., 2010; Jernigan et al., 2011), which could result in greater neural damage that affects brain network segregation. Our results add to research showing historical immune suppression being detrimentally related to altered brain morphology, with this study extending those findings to higher-level structural brain organization.

At the regional level, HIV-positive individuals showed less MD nodal degree in the left thalamus relative to HIV-negative individuals, suggestive of less structural connectivity between this region and other areas of the brain. A DTI investigation of HIV found decreased WM integrity using MD in the internal capsule of HIV-positive individuals (Pfefferbaum et al., 2009), a WM tract that projects from the thalamus to multiple cortical and subcortical regions. HIV infection has consistently been associated with decreased volume of the thalamus (Chiang et al., 2007; Janssen et al., 2015; Kallianpur et al., 2013; Sanford et al., 2017), and thalamic volume has been linked to deficits in motor (Janssen et al., 2015) and memory function (Fama and Sullivan, 2015) in HIV-positive individuals. Thalamic insult is observed in multiple neurodegenerative disorders and conditions including traumatic brain injury, dementia, multiple sclerosis, alcohol exposure in utero, global hypoxia, and thiamine deficiency (Brandel et al., 1991; Kipp et al., 2015; Livy et al., 2001; Meng and Okeda, 2003; Mrozek et al., 2016; Muthuswamy et al., 2002; Pasternak et al., 1991). The thalamus functions as a relay center for signals across the brain (Sherman, 2005), and it has been proposed that thalamic connectivity may serve as a biomarker of neurodegenerative disease (Power and Looi, 2015). As our results showed a lower number of connections between the left thalamus and all other nodes, it may be that HIV infection is linked with a reduced ability for the thalamus to serve as a relay center. Hypothesized mechanisms of thalamic compromise in neurodegenerative disease processes include trans-synaptic neurodegeneration and propagation of proteopathies (Power and Looi, 2015). These mechanisms are in line with our findings of group differences in MD, but not FA, as MD is theorized to best reflect WM microstructural density (Alexander et al., 2007; Lentz et al., 2014). The effects on nodal degree were specific to the left thalamus. Left thalamic atrophy is associated with Parkinson Disease with dementia (Summerfield et al., 2005) and alcohol-use disorders (Yang et al., 2016). In addition, the effects resulting from thalamic insult are lateralized, with deficits in the left thalamus specifically associated with amnesic problems, executive dysfunction, and behavioral and/or mood alterations (De Witte et al., 2011), cognitive deficits that are also evident in HIV-associated neurocognitive disorders (Heaton et al., 2015). Less MD nodal degree in the left thalamus may therefore serve as a marker of HIV-related neural damage, but more research is necessary to determine how thalamic structural connectivity is related to HIV infection.

We also observed that lower FA characteristic path length and higher FA global efficiency, both measures of integration, were associated with higher neurocognitive function across all participants. Lower FA characteristic path length and higher FA global efficiency are network metrics that describe greater network integration (Bullmore and Sporns, 2012). Previous studies have also shown a relationship between these global network metrics and neurocognitive function in persons with neurodegenerative disorders (Chang et al., 2016; Ma

et al., 2017). It may be that higher neurocognitive function reflects increased integration within the structural brain network. However, we did not detect a relationship between global neurocognitive function and FA clustering coefficient. We also did not detect a relationship between global neurocognitive function and MD nodal degree in the left thalamus. Our ability to detect the relationship between neurocognitive function and network metrics may have been limited by the minimal amount of global impairment within our sample. Overall, neurocognitive performance in the sample was well within one standard deviation of the mean for standardized T scores, and there was not a significant difference in performance by HIV status. We utilized a battery of well-validated measures to assess HIV-associated NCI, but it is possible that testing batteries more focused on particular domains of function may be more sensitive in detecting the links between cognitive function and brain organization deficits.

It is noteworthy that the HIV-positive group did not display differences in connection strength or network integration as observed in a previous investigation of HIV (Baker et al., 2017). Our study may have been underpowered to detect small differences between groups. It is also possible that treatment with cART may prevent or reverse damage due to HIV. This could occur through higher nadir CD4 levels that would help prevent viral replication resulting in neural insult. Future examinations could examine additional metrics of global network integration, such as gamma, lambda, and sigma of efficiency, to further explore global network integration. Additionally, we performed correlational analyses using years since HIV diagnosis as a dependent variable. These analyses may be constrained by the inability to know for certain infection duration prior to diagnosis. Strengths of this study include a representative cART-receiving sample with good generalizability to HIV-positive populations in the United States.

In conclusion, these results suggest that global structural connectomic differences in HIV-positive individuals may reflect the detrimental effects of historical immune suppression on brain network organization. With more effective cART, HIV-positive individuals are experiencing increased longevity, making the management of HIV-associated NCI increasingly important (Gates and Cysique, 2016). Since most cases of HIV-related NCI are mild to moderate, neural biomarkers that are sensitive to early changes in network organization are critical for optimizing treatments. Future research should further explore the role of these structural connectivity differences in brain organization and its relationship to HIV-associated NCI to help in the identification and management of neurological comorbidities.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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study; CSM, LLB, RPB, and SLT conducted the analyses; RPB, SLT, and CSM drafted the manuscript; and all authors contributed to and have approved the final manuscript.

References

- Alexander AL, Lee JE, Lazar M, Field AS. Diffusion tensor imaging of the brain. *Neurotherapeutics*. 2007; 4:316–329. [PubMed: 17599699]
- Antinori A, Arendt G, Becker JT, Brew BJ, Byrd DA, Cherner M, Clifford DB, Cinque P, Epstein LG, Goodkin K, Gisslen M, Grant I, Heaton RK, Joseph J, Marder K, Marra CM, McArthur JC, Nunn M, Price RW, Pulliam L, Robertson KR, Sacktor N, Valcour V, Wojna VE. Updated research nosology for HIV-associated neurocognitive disorders. *Neurology*. 2007; 69:1789–1799. [PubMed: 17914061]
- Baker LM, Cooley SA, Cabeen RP, Laidlaw DH, Joska JA, Hoare J, Stein DJ, Heaps-Woodruff JM, Salminen LE, Paul RH. Topological organization of whole-brain white matter in HIV infection. *Brain Connectivity*. 2017; 7:115–122. [PubMed: 28076974]
- Becker JT, Sanders J, Madsen SK, Ragin A, Kingsley L, Maruca V, Cohen B, Goodkin K, Martin E, Miller EN, Sacktor N, Alger JR, Barker PB, Saharan P, Carmichael OT, Thompson PM. Subcortical brain atrophy persists even in HAART-regulated HIV disease. *Brain Imaging and Behavior*. 2011; 5:77–85. [PubMed: 21264551]
- Benton A, Hamsher K, Sivan A. Multilingual Aphasia Examination. 3rd. AJA Associates; Iowa City, IA: 1983.
- Brandel JP, Hirsch EC, Malessa S, Duyckaerts C, Cervera P, Agid Y. Differential vulnerability of cholinergic projections to the mediodorsal nucleus of the thalamus in senile dementia of Alzheimer type and progressive supranuclear palsy. *Neuroscience*. 1991; 41:25–31. [PubMed: 2057062]
- Brandt J, Benedict RHB. Hopkins Verbal Learning Test – Revised professional manual. Psychological Assessment Resources, Inc; Lutz, FL: 2001.
- Bullmore E, Sporns O. The economy of brain network organization. *Nat Rev Neurosci*. 2012; 13:336–349. [PubMed: 22498897]
- Chang TY, Huang KL, Ho MY, Ho PS, Chang CH, Liu CH, Chang YJ, Wong HF, Hsieh IC, Lee TH, Liu HL. Graph theoretical analysis of functional networks and its relationship to cognitive decline in patients with carotid stenosis. *J Cereb Blood Flow Metab*. 2016; 36:808–818. [PubMed: 26661184]
- Chanraud S, Zahr N, Sullivan E, Pfefferbaum A. MR diffusion tensor imaging: a window into white matter integrity of the working brain. *Neuropsychol Rev*. 2010; 20:209–225. [PubMed: 20422451]
- Chen Y, An H, Zhu H, Stone T, Smith JK, Hall C, Bullitt E, Shen D, Lin W. White matter abnormalities revealed by diffusion tensor imaging in non-demented and demented HIV+ patients. *NeuroImage*. 2009; 47:1154–1162. [PubMed: 19376246]
- Chiang MC, Dutton RA, Hayashi KM, Lopez OL, Aizenstein HJ, Toga AW, Becker JT, Thompson PM. 3D pattern of brain atrophy in HIV/AIDS visualized using tensor-based morphometry. *NeuroImage*. 2007; 34:44–60. [PubMed: 17035049]
- Cohen RA, Harezlak J, Schifitto G, Hana G, Clark U, Gongvatana A, Paul R, Taylor M, Thompson P, Alger J, Brown M, Zhong J, Campbell T, Singer E, Daar E, McMahon D, Tso Y, Yiannoutsos CT, Navia B. Effects of nadir CD4 count and duration of human immunodeficiency virus infection on brain volumes in the highly active antiretroviral therapy era. *J Neurovirol*. 2010; 16:25–32. [PubMed: 20113183]
- Cysique LA, Maruff P, Brew BJ. The neuropsychological profile of symptomatic AIDS and ADC patients in the pre-HAART era: a meta-analysis. *J Int Neuropsychol Soc*. 2006; 12:368–382. [PubMed: 16903129]
- Daducci A, Gerhard S, Griffa A, Lemkaddem A, Cammoun L, Gigandet X, Meuli R, Hagmann P, Thiran JP. The connectome mapper: an open-source processing pipeline to map connectomes with MRI. *PLoS ONE*. 2012; 7:e48121. [PubMed: 23272041]
- De Witte L, Brouns R, Kavadias D, Engelborghs S, De Deyn PP, Marien P. Cognitive, affective and behavioural disturbances following vascular thalamic lesions: a review. *Cortex*. 2011; 47:273–319. [PubMed: 21111408]

- Desikan RS, Ségonne F, Fischl B, Quinn BT, Dickerson BC, Blacker D, Buckner RL, Dale AM, Maguire RP, Hyman BT, Albert MS, Killiany RJ. An automated labeling system for subdividing the human cerebral cortex on MRI scans into gyral based regions of interest. *NeuroImage*. 2006; 31:968–980. [PubMed: 16530430]
- Diehr MC, Cherner M, Wolfson TJ, Miller SW, Grant I, Heaton RK. The 50 and 100-item short forms of the Paced Auditory Serial Addition Task (PASAT): Demographically corrected norms and comparisons with the full PASAT in normal and clinical samples. *J Clin Exp Neuropsychol*. 2003; 25:571–585. [PubMed: 12911108]
- Doyle KL, Morgan EE, Morris S, Smith DM, Little S, Iudicello JE, Blackstone K, Moore DJ, Grant I, Letendre SL, Woods SP. Real-world impact of neurocognitive deficits in acute and early HIV infection. *J Neurovirol*. 2013; 19:565–573. [PubMed: 24277439]
- Fama R, Sullivan EV. Thalamic structures and associated cognitive functions: Relations with age and aging. *Neurosci Biobehav Rev*. 2015; 54:29–37. [PubMed: 25862940]
- First MB, Spitzer RL, Gibbon M, Williams JBW. Structured Clinical Interview for DSM-IV Axis I Disorders, Research Version, Patient/Non-patient Edition. Biometrics Research, New York State Psychiatric Institute; New York: 1996.
- Fornito A, Bullmore ET. Connectomics: a new paradigm for understanding brain disease. *Eur Neuropsychopharmacol*. 2015; 25:733–748. [PubMed: 24726580]
- Fornito A, Zalesky A, Breakspear M. The connectomics of brain disorders. *Natural Reviews Neuroscience*. 2015; 16:159–172.
- Gates TM, Cysique LA. The chronicity of HIV infection should drive the research strategy of neuroHIV treatment studies: a critical review. *Central Nervous System Drugs*. 2016; 30:53–69.
- Gerhard S, Daducci A, Lemkaddem A, Meuli R, Thiran JP, Hagmann P. The connectome viewer toolkit: an open source framework to manage, analyze, and visualize connectomes. *Frontiers in Neuroinformatics*. 2011; 5:3. [PubMed: 21713110]
- Golden CJ. Stroop Color and Word Test. Stoelting; Chicago, IL: 1978.
- Hagmann P, Kuran M, Gigandet X, Thiran P, Wedeen VJ, Meuli R, Thiran J-P. Mapping human whole-brain structural networks with diffusion MRI. *PLoS ONE*. 2007; 2:e597. [PubMed: 17611629]
- Hagmann P, Thiran JP, Jonasson L, Vandergheynst P, Clarke S, Maeder P, Meuli R. DTI mapping of human brain connectivity: statistical fibre tracking and virtual dissection. *NeuroImage*. 2003; 19:545–554. [PubMed: 12880786]
- Heaps J, Niehoff J, Lane E, Kroutil K, Boggiano J, Paul R. Application of neuroimaging methods to define cognitive and brain abnormalities associated with HIV. In: Cohen RA, Sweet LH, editors *Brain Imaging in Behavioral Medicine and Clinical Neuroscience*. Springer; New York: 2011. 341–353.
- Heaton RK, Clifford DB, Franklin DR Jr, Woods SP, Ake C, Vaida F, Ellis RJ, Letendre SL, Marcotte TD, Atkinson JH, Rivera-Mindt M, Vigil OR, Taylor MJ, Collier AC, Marra CM, Gelman BB, McArthur JC, Morgello S, Simpson DM, McCutchan JA, Abramson I, Gamst A, Fennema-Notestine C, Jernigan TL, Wong J, Grant I. HIV-associated neurocognitive disorders persist in the era of potent antiretroviral therapy: CHARTER Study. *Neurology*. 2010; 75:2087–2096. [PubMed: 21135382]
- Heaton RK, Franklin D, Ellis R, McCutchan J, Letendre S, LeBlanc S, Corkran S, Duarte N, Clifford D, Woods S, Collier A, Marra C, Morgello S, Mindt M, Taylor M, Marcotte T, Atkinson J, Wolfson T, Gelman B, McArthur J, Simpson D, Abramson I, Gamst A, Fennema-Notestine C, Jernigan T, Wong J, Grant I. HIV-associated neurocognitive disorders before and during the era of combination antiretroviral therapy: differences in rates, nature, and predictors. *J Neurovirol*. 2011; 17:3–16. [PubMed: 21174240]
- Heaton RK, Franklin DR Jr, Deutsch R, Letendre S, Ellis RJ, Casaletto K, Marquie MJ, Woods SP, Vaida F, Atkinson JH, Marcotte TD, McCutchan JA, Collier AC, Marra CM, Clifford DB, Gelman BB, Sacktor N, Morgello S, Simpson DM, Abramson I, Gamst AC, Fennema-Notestine C, Smith DM, Grant I. Neurocognitive change in the era of HIV combination antiretroviral therapy: the longitudinal CHARTER study. *Clin Infect Dis*. 2015; 60:473–480. [PubMed: 25362201]

- Heaton RK, Marcotte TD, Mindt MR, Sadek J, Moore DJ, Bentley H, McCutchan JA, Reicks C, Grant I. The impact of HIV-associated neuropsychological impairment on everyday functioning. *J Int Neuropsychol Soc.* 2004a; 10:317–331. [PubMed: 15147590]
- Heaton RK, Miller SW, Taylor MJ, Grant I. Revised Comprehensive Norms for an Expanded Halstead-Reitan Battery: Demographically Adjusted Neuropsychological Norms for African American and Caucasian Adults. Psychological Assessment Resources, Inc; Lutz, FL: 2004b.
- Janssen MA, Meulenbroek O, Steens SC, Goraj B, Bosch M, Koopmans PP, Kessels RP. Cognitive functioning, wellbeing and brain correlates in HIV-1 infected patients on long-term combination antiretroviral therapy. *AIDS.* 2015; 29:2139–2148. [PubMed: 26544578]
- Jernigan TL, Archibald SL, Fennema-Notestine C, Taylor MJ, Theilmann RJ, Julaton MD, Notestine RJ, Wolfson T, Letendre SL, Ellis RJ, Heaton RK, Gamst AC, Franklin DR Jr, Clifford DB, Collier AC, Gelman BB, Marra C, McArthur JC, McCutchan JA, Morgello S, Simpson DM, Grant I. Clinical factors related to brain structure in HIV: the CHARTER study. *J Neurovirol.* 2011; 17:248–257. [PubMed: 21544705]
- Kallianpur KJ, Shikuma C, Kirk GR, Shiramizu B, Valcour V, Chow D, Souza S, Nakamoto B, Sailasuta N. Peripheral blood HIV DNA is associated with atrophy of cerebellar and subcortical gray matter. *Neurology.* 2013; 80:1792–1799. [PubMed: 23596064]
- Kipp M, Wagenknecht N, Beyer C, Samer S, Wuerfel J, Nikoubashman O. Thalamus pathology in multiple sclerosis: from biology to clinical application. *Cellular and Molecular Life Science.* 2015; 72:1127–1147.
- Klove H. Grooved Pegboard. Lafayette Instruments; Lafayette, IN: 1963.
- Lentz MR, Peterson KL, Ibrahim WG, Lee DE, Sarlls J, Lizak MJ, Maric D, Reid WC, Hammoud DA. Diffusion tensor and volumetric magnetic resonance measures as biomarkers of brain damage in a small animal model of HIV. *PLoS ONE.* 2014; 9:e105752. [PubMed: 25144656]
- Livy DJ, Maier Se, West JR. Fetal alcohol exposure and temporal vulnerability: effects of binge-like alcohol exposure on the ventrolateral nucleus of the thalamus. *Alcoholism: Clinical and Experimental Research.* 2001; 25:774–780.
- Lovejoy TI, Suhr JA. The relationship between neuropsychological functioning and HAART adherence in HIV-positive adults: A systematic review. *J Behav Med.* 2009; 32:389–405. [PubMed: 19291386]
- Ma Q, Huang B, Wang J, Seger C, Yang W, Li C, Wang J, Feng J, Weng L, Jiang W, Huang R. Altered modular organization of intrinsic brain functional networks in patients with Parkinson's disease. *Brain Imaging and Behavior.* 2017; 11:430–443. [PubMed: 26860909]
- Marcotte TD, Wolfson T, Rosenthal TJ, Heaton RK, Gonzalez R, Ellis RJ, Grant I. A multimodal assessment of driving performance in HIV infection. *Neurology.* 2004; 63:1417–1422. [PubMed: 15505158]
- Masters M, Ances BM. Role of neuroimaging in HIV-associated neurocognitive disorders. *Semin Neurol.* 2014; 34:89–102.
- McLellan AT, Kushner H, Metzger D, Peters R, Smith I, Grissom G, Pettinati H, Argeriou M. The fifth edition of the Addiction Severity Index. *J Subst Abuse Treat.* 1992; 9:199–213. [PubMed: 1334156]
- Meade CS, Cordero DM, Hobkirk AL, Metra BM, Chen N-K, Huettel SA. Compensatory activation in fronto-parietal cortices among HIV-infected persons during a monetary decision-making task. *Hum Brain Mapp.* 2016; 37:2455–2467. [PubMed: 27004729]
- Meng JS, Okeda R. Neuropathological study of the role of mast cells and histamine-positive neurons in selective vulnerability of the thalamus and inferior colliculus in thiamine-deficient encephalopathy. *Neuropathology.* 2003; 23:25–35. [PubMed: 12722923]
- Mrozek S, Luzi A, Gonzalez L, Kerhuel L, Fourcade O, Geeraerts T. Cerebral and extracerebral vulnerability to hypoxic insults after diffuse traumatic brain injury in rats. *Brain Res.* 2016; 1646:334–341. [PubMed: 27302136]
- Muthuswamy J, Kimura T, Ding MC, Geocadin R, Hanley DF, Thakor NV. Vulnerability of the thalamic somatosensory pathway after prolonged global hypoxic-ischemic injury. *Neuroscience.* 2002; 115:917–929. [PubMed: 12435429]

- Navia BA, Jordan BD, Price RW. The AIDS dementia complex: I. Clinical features. *Ann Neurol*. 1986; 19:517–524. [PubMed: 3729308]
- Norman MA, Moore DJ, Taylor M, Franklin D Jr, Cysique L, Ake C, Lazarretto D, Vaida F, Heaton RK, Hnrc Group. Demographically corrected norms for African Americans and Caucasians on the Hopkins Verbal Learning Test-Revised, Brief Visuospatial Memory Test-Revised, Stroop Color and Word Test, and Wisconsin Card Sorting Test 64-Card Version. *J Clin Exp Neuropsychol*. 2011; 33:793–804. [PubMed: 21547817]
- Oguz I, Farzinfar M, Matsui J, Budin F, Liu Z, Gerig G, Johnson HJ, Styner M. DTIPrep: quality control of diffusion-weighted images. *Frontiers in Neuroinformatics*. 2014; 8:4. [PubMed: 24523693]
- Pasternak JF, Predey TA, Mikhael MA. Neonatal asphyxia: vulnerability of basal ganglia, thalamus, and brainstem. *Pediatr Neurol*. 1991; 7:147–149. [PubMed: 2059257]
- Pfefferbaum A, Rosenbloom MJ, Rohlfing T, Kemper CA, Deresinski S, Sullivan EV. Frontostriatal fiber bundle compromise in HIV infection without dementia. *AIDS*. 2009; 23:1977–1985. [PubMed: 19730350]
- Plessis SD, Vink M, Joska JA, Koutsilieri E, Bagadia A, Stein DJ, Emsley R. HIV infection results in ventral-striatal reward system hypo-activation during cue processing. *AIDS*. 2015; 29:1335–1343. [PubMed: 26091294]
- Power BD, Looi JC. The thalamus as a putative biomarker in neurodegenerative disorders. *Aust N Z J Psychiatry*. 2015; 49:502–518. [PubMed: 25943981]
- Rabkin JG, McElhiney M, Ferrando SJ, Van Gorp W, Lin SH. Predictors of employment of men with HIV/AIDS: A longitudinal study. *Psychosom Med*. 2004; 66:72–78. [PubMed: 14747640]
- Ragin AB, Wu Y, Storey P, Cohen BA, Edelman RR, Epstein LG. Diffusion tensor imaging of subcortical brain injury in patients infected with human immunodeficiency virus. *J Neurovirol*. 2005; 11:292–298. [PubMed: 16036809]
- Reitan RM, Wolfson D. The Halstead-Reitan neuropsychological test battery: Theory and clinical interpretation. 2nd. Neuropsychology Press; Tucson, AZ: 1993.
- Sanford R, Fernandez Cruz AL, Scott SC, Mayo NE, Fellows LK, Ances BM, Collins DL. Regionally specific brain volumetric and cortical thickness changes in HIV-infected patients in the HAART era. *J Acquir Immune Defic Syndr*. 2017; 74:563–570. [PubMed: 28129254]
- Sheehan DV, Lecrubier Y, Sheehan KH, Amorim P, Janavs J, Weiller E, Hergueta T, Baker R, Dunbar GC. The Mini International Neuropsychiatric Interview (M.I.N.I.): The development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. *J Clin Psychiatr*. 1998; 59:22–33.
- Sherman SM. Thalamic relays and cortical functioning. *Prog Brain Res*. 2005; 149:107–126. [PubMed: 16226580]
- Sporns O. Contributions and challenges for network models in cognitive neuroscience. *Nat Neurosci*. 2014; 17:652–660. [PubMed: 24686784]
- Sporns O, Tononi G, Kötter R. The human connectome: a structural description of the human brain. *PLoS Comp Biol*. 2005; 1:e42.
- Stern RA, White T. NAB Digits Forward/Digits Backward Test: Professional Manual. Psychological Assessment Resources, Inc (PAR); Lutz, FL.: 2009.
- Stubbe-Drager B, Deppe M, Mohammadi S, Keller SS, Kugel H, Gregor N, Evers S, Young P, Ringelstein EB, Arendt G, Knecht S, Husstedt IW. Early microstructural white matter changes in patients with HIV: a diffusion tensor imaging study. *BMC Neurol*. 2012; 12:23. [PubMed: 22548835]
- Su T, Caan MW, Wit FW, Schouten J, Geurtsen GJ, Cole JH, Sharp DJ, Vos FM, Prins M, Portegies P, Reiss P, Majoie CB, Study AGC. White matter structure alterations in HIV-1-infected men with sustained suppression of viraemia on treatment. *AIDS*. 2016; 30:311–322. [PubMed: 26691551]
- Summerfield C, Junque C, Tolosa E, Salgado-Pineda P, Gomez-Anson B, Martí MJ, Pastor P, Ramirez-Ruiz B, Mercader J. Structural brain changes in Parkinson disease with dementia: a voxel-based morphometry study. *Arch Neurol*. 2005; 62:281–285. [PubMed: 15710857]

- Vivithanaporn P, Heo G, Gamble J, Krentz HB, Hoke A, Gill MJ, Power C. Neurologic disease burden in treated HIV/AIDS predicts survival: A population-based study. *Neurology*. 2010; 75:1150–1158. [PubMed: 20739646]
- Wakim KM, Molloy CJ, Bell RP, Ross LA, Foxe JJ. White Matter Changes in HIV+ Women with a History of Cocaine Dependence. *Frontiers in Neurology*. 2017; 8
- Wang J, Wang X, Xia M, Liao X, Evans A, He Y. GRETNA: a graph theoretical network analysis toolbox for imaging connectomics. *Frontiers in Human Neuroscience*. 2015; 9
- Watts DJ, Strogatz SH. Collective dynamics of ‘small-world’ networks. *Natur*. 1998; 393:440–442.
- Wechsler D. Wechsler Adult Intelligence Scale–Third Edition: Administration and Scoring Manual. Harcourt Brace; San Antonio, TX: 1997.
- Winston GP. The physical and biological basis of quantitative parameters derived from diffusion MRI. *Quantitative Imaging in Medicine and Surgery*. 2012; 2:254–265. [PubMed: 23289085]
- Woods SP, Moore DJ, Weber E, Grant I. Cognitive neuropsychology of HIV-associated neurocognitive disorders. *Neuropsychol Rev*. 2009; 19:152–168. [PubMed: 19462243]
- Xia M, Wang J, He Y. BrainNet Viewer: a network visualization tool for human brain connectomics. *PLoS ONE*. 2013; 8:e68910. [PubMed: 23861951]
- Yang X, Tian F, Zhang H, Zeng J, Chen T, Wang S, Jia Z, Gong Q. Cortical and subcortical gray matter shrinkage in alcohol-use disorders: a voxel-based meta-analysis. *Neurosci Biobehav Rev*. 2016; 66:92–103. [PubMed: 27108216]

Figure 1. Structural connectome based on clustering coefficient for FA
 Line thickness and color show connectivity strength. Only edges with a correlation of r 0.50 are displayed. Node size shows degree of clustering. The HIV+ group had lower clustering coefficient relative to the HIV- group ($p=0.05$) reflected by fewer connections between nodes and lower connectivity strength. Connectome was created with the BrainNet Viewer (Xia et al., 2013) (<http://www.nitrc.org/projects/bnc/>).

Table 1

Sample characteristics

	HIV-positive N=35	HIV-negative N=35	Statistic	<i>p-value</i>
Demographics				
Male gender, n (%)	25 (71.0%)	22 (63.0%)	$\chi^2(1) = 0.58$	<i>p</i> =0.44
Age in years, M (SD)	41.97 (8.31)	41.34 (9.45)	<i>t</i> (68)= 0.30	<i>p</i> =0.77
Race, n (%)			$\chi^2(2)=1.43$	<i>p</i> =0.70
Black	27 (77.0%)	26 (74.0%)		
White	6 (17.0%)	7 (20.0%)		
Mixed/Other	1 (3.0%)	2 (6.0%)		
Hispanic ethnicity, n (%)	1 (3.0%)	0 (0.0%)	FET	<i>p</i> =1.00
Education in years, M (SD)	13.97 (2.08)	13.97 (2.42)	<i>t</i> (68)= 1.00	<i>p</i> =1.00
Neurocognitive functioning, M (SD)	47.1 (6.0)	49.6 (6.0)	<i>t</i> (68)= -1.68	<i>p</i> =0.10

FET=Fisher's Exact Test

Table 2

Global and nodal Z-scores in HIV-positive and HIV-negative individuals

	FA		MD	
	HIV-positive N=35	HIV-negative N=35	HIV-positive N=35	HIV-negative N=35
Global network metrics				
Clustering coefficient, Mdn (IQR)	5.12 (1.78)	5.19 (2.22)	6.45 (1.95)	6.64 (1.73)
Characteristic path length, Mdn (IQR)	3.24 (1.17)	3.58 (1.20)	4.05 (1.08)	4.01 (1.29)
Global efficiency, Mdn (IQR)	-3.15 (1.11)	-3.48 (1.12)	-3.96 (1.02)	-3.91 (1.22)
Connection strength, Mdn (IQR)	230 (20.4)	233 (22.0)	0.36 (0.05)	0.34 (0.04)
Nodal network metrics				
Nodal degree – L Thalamus, Mdn (IQR)	6.46 (1.58)	6.42 (1.98)	0.008 (0.002)	0.007 (0.001)
Nodal degree – R Thalamus, Mdn (IQR)	6.28 (1.30)	6.04 (1.31)	0.008 (0.002)	0.007 (0.002)

* =significant result, FA=fractional anisotropy, MD=mean diffusivity, Mdn=median, IQR=interquartile range