Title

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HIV infection is associated with attenuated frontostriatal intrinsic connectivity

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Abstract

Objective—HIV-associated cognitive impairments are prevalent, and are consistent with injury to both frontal cortical and subcortical regions of the brain. The current study aimed to assess the impact of HIV infection on functional connections within the frontostriatal network, circuitry hypothesized to be highly vulnerable to HIV infection.

Method—Fifteen HIV-positive and 15 demographically matched control participants underwent 6 minutes of resting-state functional magnetic resonance imaging (RS-fMRI). Multivariate group comparisons of age-adjusted estimates of connectivity within the frontostriatal network were derived from BOLD data for dorsolateral prefrontal cortex (DLPFC), dorsal caudate and mediodorsal thalamic regions of interest. Whole-brain comparisons of group differences in frontostriatal connectivity were conducted, as were pairwise tests of connectivity associations with measures of global cognitive functioning and clinical and immunological characteristics (nadir and current CD4 count, duration of HIV infection, plasma HIV RNA).

Results—HIV – associated reductions in connectivity were observed between the DLPFC and the dorsal caudate, particularly in younger participants (< 50 years, N = 9). Seropositive participants also demonstrated reductions in dorsal caudate connectivity to frontal and parietal brain regions previously demonstrated to be functionally connected to the DLPFC. Cognitive impairment, but none of the assessed clinical/immunological variables, was associated with reduced frontostriatal connectivity.

Conclusions—In conclusion, our data indicate that a diagnosis of HIV is associated with attenuated intrinsic frontostriatal connectivity. Intrinsic connectivity of this network may therefore serve as a marker of the deleterious effects of HIV infection on the brain, possibly via HIV-associated dopaminergic abnormalities. These findings warrant independent replication in larger studies.

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Keywords

Magnetic Resonance Imaging; Resting-state; Dorsolateral Prefrontal Cortex; Caudate Nucleus; Thalamus; Dopamine

Introduction

HIV infection is associated with cognitive impairment in as many as 50% of patients (Heaton et al., 2010), despite the demonstrated effectiveness of anti-retroviral medications in combating the disease. Deficits in executive functioning, working memory and verbal fluency are frequently observed in HIV patients, suggesting injury to frontostriatal circuitry in the brain (Woods, Moore, Weber, & Grant, 2009). The HIV virus is believed to cross the blood-brain barrier shortly after infection, and may cause neuronal damage via multiple mechanisms (Kaul & Lipton, 1999). These pathogenic effects may be direct, through the shedding of neurotoxic viral proteins, such as GP120 and Tat (Nath, 2002), as well as indirect, through the initiation of neuroinflamatory cascades involving infected microglia, macrocytes and lymphocytes that culminate in cellular apoptosis (Burdo, Lackner, & Williams, 2013; Heyes, Saito, & Markey, 1992).

Cognitive impairment in HIV has historically been characterized as resulting from subcortical pathology, in accordance with the presentation of HIV-associated dementia (HAD), and evidence of atrophy in the basal ganglia in HIV positive patients (Jernigan et al., 1993). The widespread availability of highly active anti-retroviral (HAART) medication has seen a relative reduction in the incidence with which HIV patients present with frank motor deficits or dementia, with a concomitant increase in the representation of impairment in higher order cognitive abilities such as executive functioning (Heaton et al., 2010; Heaton et al., 2011). This implicates HIV in injury to multimodal association regions of the brain, which is also suggested by abnormal levels of brain activation in the dorsolateral prefrontal (DLPFC) and parietal cortices in HIV positive participants compared to healthy controls during the performance of working memory, attention, risky decision-making, and executive functioning tasks (Chang et al., 2001; Chang et al., 2004; Connolly et al., 2014; Ernst, Chang, Jovicich, Ames, & Arnold, 2002; Melrose, Tinaz, Castelo, Courtney, & Stern, 2008). Similar disruptions in local magnetic field potentials within the lateral PFC have been reported in HIV patients using magnetoencephalography (MEG), both at rest (Becker et al., 2012) and during the performance of visual attention (Wilson, Fox, et al., 2013) and fine motor control (Wilson, Heinrichs-Graham, et al., 2013) tasks.

That HIV-associated deficits in higher order cognitive processes may also result from injury to the striatum is suggested by models of corticostriatal neural circuits (Alexander, DeLong, & Strick, 1986; Nakano, Kayahara, Tsutsumi, & Ushiro, 2000; Parent & Hazrati, 1995; Selemon & Goldman-Rakic, 1985). Reports of atrophy of the caudate in HIV (Ances, Ortega, Vaida, Heaps, & Paul, 2012; Jernigan et al., 1993; Jernigan et al., 2005) are likely to be particularly relevant in this regard, given the presence of bidirectional white matter fibers from the dorsal aspect of the caudate to the DLPFC, as well as the association of atrophy of this structure with the severity of HIV-associated cognitive deficits (Hestad et al., 1993;

Kieburtz et al., 1996). Abnormal functional connectivity of the caudate to the prefrontal cortex in response to task demands has also been documented in seropositive participants (Melrose et al., 2008).

Resting-state fMRI (RS-fMRI) represents a promising tool for assessing HIV-associated abnormalities in fronto-striatal functional connectivity. RS-fMRI measures the intrinsic temporal covariation of blood oxygen level dependent (BOLD) signal acquired under minimally demanding conditions in which participants are typically instructed to close their eyes or fixate on a visually presented cross (Cole, Smith, & Beckmann, 2010). The popularity of RS-fMRI can be attributed to various factors: (a) it provides a measure of intrinsic connectivity networks of the brain that is highly reliable across both participants and scans (Damoiseaux et al., 2006; Dijk et al., 2010; Shehzad et al., 2009), (b) minimal task demands enhance compliance in difficult-to-scan populations, and (c), it is sensitive to brain abnormalities across a range of clinical disorders (Rosazza & Minati, 2011), including both chronic and acute HIV (Thomas, Brier, Ortega, Benzinger, & Ances, 2014; Thomas, Brier, Snyder, Vaida, & Ances, 2013; Wang et al., 2011).

The aim of this study was to assess the extent to which HIV infection in the post-HAART era is associated with disruptions in the intrinsic functional connectivity of regions comprising the frontostriatal network, and to identify possible clinical moderators of altered connectivity within this network. The thalamus was included given the observation in animal models of the basal ganglia of bidirectional thalamo-cortical and thalamo-striatal projections (Cheatwood, Reep, & Corwin, 2003; Kamishina, Yurcisin, Corwin, & Reep, 2008), supporting the role of the mediodorsal nucleus of the thalamus, in particular, as a relay station between association regions within the frontal cortex and basal ganglia (Alexander et al., 1986). We predicted that both HIV infection and global cognitive impairment would be associated with reductions in connectivity within the frontostriatal circuitry. We also anticipated that the effect of HIV infection on intrinsic connectivity would be most pronounced in older patients, given evidence that HIV infection may amplify the detrimental effects of aging on cognitive performance and brain health (Brew, Crowe, Landay, Cysique, & Guillemin, 2009).

Methods

Sample selection

Participants were recruited as part of the Translational Methamphetamine AIDS Research Center (TMARC) project, an ongoing multidisciplinary investigation of the effects of methamphetamine abuse, HIV infection, and their comorbidity on a range of cognitive, clinical and neuroimaging outcomes. The University of California San Diego's Human Research Protections Program approved the human rights and protection aspects of the study, and all participants provided written, informed consent. HIV status and seronegative status for Hepatitis C virus (HCV) were confirmed by MedMira Multiplo rapid test (MedMira Inc., Nova Scotia, Canada). Current CD4 T lymphocyte counts (cells/ml) were determined by flow cytometry at a medical center laboratory certified by Clinical Laboratory Improvement Amendments (CLIA), or CLIA equivalent. HIV RNA levels were measured in plasma by reverse transcriptase PCR (Roche Amplicor, v. 1.5, lower limit of

quantitation 50 copies/ml). CD4 nadir was obtained by self-report for all cases, with the exception of a single individual whose measured CD4 count was lower than self-reported CD4 nadir, and for whom the laboratory measure was substituted.

Eligible participants were at least 18 years of age, without a prior head injury resulting in loss of consciousness for more than 30 minutes; previous cerebrovascular events, as determined by comprehensive neurological exam, or a seizure disorder, a demyelinating disease or any other non-HIV neurological disorder. Exclusion criteria included HCV co-infection or a lifetime diagnosis of schizophrenia or other psychotic disorder, as assessed with the Composite International Diagnostic Interview (CIDI version 2.1) (Kessler & Ustun, 2004) using DSM-IV criteria (American Psychiatric Association, 2000). Chronic renal or pulmonary disease, as well as any medical or neurological condition that could be a neuropsychiatric confound was also exclusionary. Individuals with contra-indications for MRI, or who changed dosage within the last 30 days of medications known to affect the hemodynamic response (e.g., antidiabetics, antihypertensives, antibiotics, and thyroid medications) were not eligible to participate. For this report, individuals meeting lifetime DSM-IV criteria for substance abuse (other than for alcohol, marijuana and nicotine, but including methamphetamine) in the prior year or dependence within the preceding five years were excluded, as were participants who tested positive for illicit drug use or alcohol on the day of scan, determined by urine toxicology screen and Breathalyzer, respectively. Lifetime abuse of, or dependence on, marijuana and abuse in the case of alcohol in the prior 12 months was not exclusionary. Nicotine use was assessed through breath carbon monoxide levels and the presence of cotinine in urine on the day of scan.

A global deficit score (GDS) was calculated for each participant based on demographically corrected standard scores (T – scores) from a comprehensive battery of neuropsychological tests administered within an average of 68 days of the scan (range: 19–180 days; see the supplementary document for a description of the individual tests (Table S2) and the calculation of the GDS). The battery and its GDS summary score have previously demonstrated sensitivity to the effects of HIV on neuropsychological performance (Carey et al., 2004). Premorbid IQ was assessed using the reading subscale of the WRAT-4 (Wilkinson & Robertson, 2006)+ Caseletto 2014. Depression symptoms were assessed immediately prior to the scan by means of the Beck Depression Inventory II (BDI) (Beck, Steer, & Brown, 1996). Given overlap of some of the BDI items with somatic symptoms of HIV infection (Kalichman, Rompa, & Cage, 2000), in addition to the total score, cognitive and affective symptoms of depression were assessed using the seven item BDI Fast Screen (BDI-FS) subscale (Beck et al., 1996).

Data acquisition

Whole-brain T_2^*-weighted gradient echo echo-planar images (36 slices, TR = 2s, TE = 30ms, FOV = 240×240mm, 3.75×3.75mm voxels, slice thickness= 4mm, inter-slice gap = 0.4mm) and corresponding fieldmaps were acquired in the axial plane on two 3T GE Discovery MR 750 (Milwaukee, WI) MRI scanners at the Keck fMRI Center at UCSD. A six minute resting-state scan sequence was employed, prior to which participants were instructed to clear their minds of all thoughts, and focus on a white cross presented on a screen at the end

of the scanner bore (visible through a head-coil-mounted mirror). Brain segmentation and group-level registration into Talairach space were facilitated through the acquisition of high-resolution whole-brain T1-weighted fast spoiled gradient (FSPGR) anatomical images (TR=8.1 s, TE=3.17 ms, 1mm isotropic voxels, flip angle=8°, FOV = 256×256mm, 172 sagittal slices).

Data preprocessing

RS-fMRI BOLD data were preprocessed using AFNI (Cox, 1996) (http://afni.nimh.nih.gov/). The first 4 volumes of the EPI sequence were discarded to allow for stabilization of tissue magnetization, after adjusting for magnetic field inhomogeneities through application of echoplanar fieldmaps (Greve, Brown, Mueller, Glover, & Liu, 2013). Standard preprocessing procedures were applied to the EPI data, including the removal of outliers in the voxel time-series, followed by the simultaneous correction for motion and registration into Talairach space, and spatial smoothing using a seven millimeter full width at half maximum (FWHM) Gaussian kernel. Mean, linear, quadratic and cubic temporal trends, as well as the 6 rigid-body motion parameter estimates and their first-order derivatives were subsequently removed from the EPI time-series for each participant. The influence of physiological sources of artifact was addressed through regressing out both the mean BOLD signal from lateral ventricle seeds, as well as a localized estimate of signal from subject-specific white matter (WM) masks. The supplementary documentation contains a more detailed description of the data preprocessing pipeline.

In order to be included in the analysis at least five minutes (150/176 volumes) of BOLD data had to be retained per participant, after removing volumes characterized by a high degree of motion (=>0.3 mm relative to the immediately preceding time-point) or for which more than 10% of voxel intensities were identified by 3dToutcount as outliers. In cases of motion, data from both the high motion time-point as well as the preceding time-point were censored, an approach that is analogous to the scrubbing procedure pioneered by Power and colleagues (Power et al., 2014).

Definition of seed regions

Region of interest (ROI) masks for the DLPFC, dorsal caudate and the mediodorsal thalamus were extracted from the areal segmentations contained within the Talaraich atlas (Lancaster et al., 2000) provided with AFNI (see Figure 1). To isolate the dorsal caudate, the region superior to Z = 6mm in the caudate body was extracted, as per the protocol described by Di Martino and colleagues (Di Martino et al., 2008). The DLPFC mask was constructed from the union of the regions corresponding to BA 9 and BA 46 (Potkin et al., 2009). Subject-specific grey matter segmentation masks were subsequently intersected with the ROI masks in order to accommodate anatomical variability in the frontostriatal network. Bilateral masks were employed for the inter-ROI correlations in the absence of specific hypotheses regarding hemispheric differences in the effect of HIV infection on fronto-striatal connectivity.

Data analysis

Connectivity between ROIs was estimated by averaging the residual time series after preprocessing across voxels within each of the masks, and subsequently computing pairwise Pearson's correlation coefficients between these mean time series. Multiple linear regression statistical procedures were conducted to test for group differences in connectivity between ROIs, with terms included to model age and age x serostatus interaction effects. A categorical age variable was constructed, by dichotomizing age in years at 50, in keeping with conventions (Barclay et al., 2007) and given evidence of a bimodal age distribution in the sample. Although all connectivity estimates are reported as Pearson's correlation coefficients in this paper, to aid interpretability, the Fisher Z transform was applied to these coefficients prior to the application of inferential test statistical procedures, to minimize the risk of violating distributional assumptions.

Where differences in connectivity between particular ROIs were observed, these were further explored by means of whole-brain analyses of group differences in voxel-wise correlations, using AFNI's 3dRegAna. This involved conducting separate voxel-wise linear regression analyses for each of the ROIs implicated. Group differences were assessed in the magnitude of Fisher Z transformed correlations coefficients calculated between the average BOLD time-series for the ROI and the time-series for all voxels across the entire brain. These analyses were corrected for mean-centered differences in age, as well as for any moderating effect of age on observed differences between groups in connectivity. A liberal family-wise correction for multiple statistical tests (voxel alpha < 0.005, cluster extent = 858μl) was employed given the exploratory nature of these tests and in recognition that standard family-wise thresholding in fMRI research may be too conservative (Lieberman & Cunningham, 2009).

Bivariate tests were conducted of differences between HIV positive and control participants on demographic characteristics, including age and education in years, as well as scores for depression (BDI total and BDI-FS scores), premorbid IQ, and cognitive impairment (see Table 1). Potential confounds of differences in frontostriatal connectivity between the serogroups were identified as those clinical/demographic variables associated with both serostatus and the connectivity measure, with a lenient statistical threshold (alpha = 0.2) employed to increase the power of these tests.

Tests for an association between pairwise inter-ROI frontostriatal connectivity estimates and nadir and current CD4 counts, as well as HIV duration (in months) were conducted using Spearman's rank correlation coefficients, to account for non-normal distribution of the data. Additionally, Welch t-tests were employed to test whether ranked intrinsic connectivity estimates differed across participants as a function of a dichotomous measure of cognitive status, constructed using a cut-point of 0.5 on the GDS (see supplementary documentation). The inflated probability of false positive findings resulting from multiple testing of clinical predictors of connectivity was adjusted for using Benjamini and Hochberg's false discovery rate algorithm (Benjamini & Hochberg, 1995). This method imposes an expected proportion of false discoveries that are considered acceptable amongst the total set of uncorrected statistically significant findings, according to a conventional threshold (5% in this study). The interpretability of the size of group differences was facilitated through presentation of

Cohen's *d* effect size estimates that have been adjusted to correct for small sample bias (Hedges & Olkin, 1985).

All statistical tests and procedures to validate distributional assumptions were conducting using the R statistical platform (version 2.15.2; R Development Core Team (2012)). Non-parametric tests of differences between groups employed routines implemented in the Coin R package, with Mann-Whitney exact t-tests generating Z scores representing the magnitude of group differences (Torsten, Kurt, Mark, & Achim, 2008). Compliance with distributional assumptions of normality and homoscedasticity was determined qualitatively through visual inspection of quantile-quantile plots, by examination of the spread of model fit statistics relative to their residuals, as well as by means of the Shapiro-Wilk test (Shapiro & Wilk, 1965) prior to conducting any of the regression analyses.

Results

Sample characteristics

RS-fMRI data was initially acquired for this study from thirty-six participants, 6 of whom were excluded from the analysis (one HIV and two control participants due to scanner artifact and two control and one HIV participant due to insufficient BOLD data following censoring). Comparable average subject motion was observed within groups prior to censoring ($t = -0.82$, $p = 0.42$), with a high average proportion of time-points retained from the RS-fMRI sequences across all participants (97.6%). The 15 HIV participants and 15 healthy controls included in this study were comparable with respect to age, gender, education, ethnicity, proportion of cognitive impairment, and premorbid IQ (see Table 1). Although total depression scores on the BDI-II were significantly higher in the seropositive participants than controls (Mean (SD) = 10.13 (9.63), 2.87 (3.98), respectively; Cohen's *d* effect size (ES), 95% confidence interval (CI) = −1.03 (−1.81,−0.26)), these differences were not apparent when excluding data from items that may be confounded by somatic symptoms of HIV infection.

Equivalent proportions of participants in the HIV and control groups were classified as older adults (>= 50 years; 33.67% versus 40%, respectively, $\chi^2 = 0.14$, $p > 0.1$). Groups were comparable with respect to the proportion classified as cognitively impaired (GDS > 0.5, 26.7% in both groups). Older HIV seropositive participants were more highly educated and possessed higher estimates of premorbid IQ than their younger counterparts, with no such age effect observed amongst the control participants (see Table S.1 in the supplementary material).

With regards to clinical status, seropositive participants had been diagnosed with HIV for a median of three years prior to the scan, and the majority (85.7%) of the 14 seropositive participants for whom data on treatment status was available at the time of analysis were on antiretroviral medication (ARV) when imaged. Plasma viral load was undetectable (< 50 copies per ml) in 11 (73%) of the HIV participants. Older HIV participants had been infected for longer than younger seropositive individuals ($Z = -2.24$, $p = 0.03$), though age was not associated with any marker of immunological status. Minimal substance use since the last study visit was observed across the entire sample, with the exception of tobacco

(43.3%), alcohol (66.6%), and marijuana (23.3%). No group differences were detected for use of these substances over this time-period, or for anti-anxiety drugs, ecstasy, cocaine, hallucinogens, heroin, inhalants, methamphetamines, poppers, and sedatives (all p's > 0.05). A greater proportion of seronegative (46.7%) than seropositive (13.3%) participants were diagnosed with lifetime alcohol abuse (χ^2= 3.97, p < 0.05), though no group differences were observed with respect to lifetime alcohol dependence (χ^2= 2.14, p > 0.1), current alcohol abuse or dependence, or measures of lifetime alcohol consumption and duration since last use.

Comparisons of frontostriatal intrinsic connectivity

Table 2 contains connectivity estimates between all three ROIs, stratified by serogroup. A linear regression model indicated that connectivity between the DLPFC and dorsal caudate was significantly lower in the HIV than control participants, (t = −2.45, p < 0.02, ES = −0.87 (−1.63, −0.11)), after adjusting for effects of age across the entire sample, as well as any group-specific differences in the effect of age on connectivity. No evidence of an effect of serostatus was detected for connectivity between the DLPFC and mediodorsal thalamus (t = −0.16, p > 0.05, ES = −0.06 (−0.78, 0.67)). Differences in dorsal caudate – thalamic connectivity were not estimable using linear regression modeling, as the distribution of the model's residual errors failed to meet assumptions of normality or homoscedasticity, and the connectivity estimates were resistant to transformation. However, no effect of HIV status was observed for connectivity between these structures when group differences were tested using the non-parametric Mann-Whitney test (Z = 0.44, p > 0.05, ES = 0.16 (−0.57, 0.88)).

A trend effect of age on connectivity between the DLPFC and dorsal caudate was observed in the regression model, with reductions in individuals over 50 years of age compared to their younger counterparts (t = −2.02, p = 0.05, ES = −0.72 (−1.47, 0.03)). The relationship between age and connectivity did not differ by HIV serogroup (t = 1.44, p = 0.16). Nevertheless, connectivity estimates between these regions were larger in the 10 younger control participants than in the other groups combined (Mean, standard deviation (SD) of correlation coefficients: 0.42 (0.20) versus 0.19 (0.26), respectively, Mann-Whitney Z = 2.64, p < 0.01, see Figure 2). Dorsal caudate-DLPFC connectivity was not associated with scores on the BDI-II (total or FS subscale), years of education, or performance on the WRAT (all p's > 0.2).

Based on differences in dorsal caudate-DLPFC connectivity for the HIV and control participants, whole-brain analyses of group differences in voxel-wise correlations were conducted for both structures separately, to identify additional regions of the brain in which connectivity to these structures varied as a function of serostatus, after adjusting for any effects of age or age x serostatus interactions. Differences between serogroups in connectivity were only observed for the dorsal caudate, with reduced connectivity observed in the HIV positive participants in a cluster in the dorsal anterior cingulate cortex (ACC) as well as the precuneus/superior parietal cortex (see Table 3 and Figure 3).

Differences in HIV duration, plasma viral RNA occupancy, and nadir and current CD4 count did not predict variability for any of the inter-regional connectivity estimates within the HIV positive cohort, after correction for multiple comparisons (see Table 4). Further

analyses prompted by the higher prevalence of lifetime alcohol abuse in the seronegative participants did not detect an association between a history of alcohol abuse and either cognitive impairment ($\chi^2 = 0.13$, $p > 0.1$) or DLPFC – dorsal caudate connectivity ($Z = -0.29$, $p > 0.1$).

The comparison of participants on cognitive status across the entire sample revealed that DLPFC-dorsal caudate connectivity was lower in the eight participants who were cognitively impaired than those who were unimpaired (Mean (SD) = 0.14 (0.1) and 0.31 (0.25), respectively; t-test on ranks: $t = -2.62$, degrees of freedom (df) = 25.78, $p = 0.02$; ES (95%CI) = −0.93 (−1.7, −0.16); see Figure 4). Amongst the 22 unimpaired participants, HIV infection was associated with lower connectivity estimates ($Z = 2.00$, $p < 0.05$).

Discussion

This is the first study to utilize intrinsic BOLD connectivity in order to investigate the effect of HIV infection in the post-HAART era on the integrity of the frontostriatal network, thus complementing an existing database of neurocognitive, histopathological and in-vivo imaging evidence suggesting that HIV compromises anatomical and functional frontostriatal pathways in the brain (Melrose et al., 2008; Woods et al., 2009). Our data suggest that the consistent observation from task-based fMRI paradigms of an association between HIV infection and fronto-striatal abnormalities (Plessis et al., 2014) also applies within the realm of intrinsic functional connectivity. Specifically, HIV-associated reductions in connectivity were detected between the DLPFC and the dorsal caudate. This was largely due to a relative reduction in connectivity estimates between these regions in younger HIV participants compared to their seronegative counterparts. Indeed, we observed that seropositive participants in general displayed similar levels of connectivity between the DLPFC and dorsal caudate as older control participants, for whom attenuations of connectivity likely reflect documented aging-induced frontostriatal atrophy (Fjell & Walhovd, 2010).

The observation of reduced frontostriatal connectivity in HIV positive individuals is congruent with findings from studies employing task-based experimental fMRI paradigms (Melrose et al., 2008; Schweinsburg et al., 2012). These studies have recorded alterations in frontostriatal functional connectivity amongst seropositive participants despite comparable performance to seronegative control participants, prompting investigators to conclude that task-based fMRI may be sensitive to HIV-associated brain injury prior to the manifestation of cognitive deficits associated with the disease (Connolly et al., 2014; Ernst et al., 2002; Melrose et al., 2008). The observation in this study that an HIV-associated reduction in frontostriatal connectivity was most apparent in cognitively unimpaired participants suggests this may also be the case with respect to RS-fMRI. Larger prospective studies will be required before more definitive statements can be made regarding the relationship between intrinsic fronto-striatal functioning and HIV-associated cognitive impairment.

This study failed to replicate reports from a prior investigation of additive effects of age and HIV on intrinsic functional connectivity of the brain (Thomas et al., 2013), despite post-hoc findings suggesting stronger frontostriatal connectivity in healthy younger individuals. This was surprising, given that similar additive effects have been reported across other imaging

modalities (Becker et al., 2012; Ernst, Jiang, Nakama, Buchthal, & Chang, 2010), and have also implicated the caudate (Ances et al., 2012). In addition to insufficient power in this study to detect evidence of additive effects of HIV status and age on frontostriatal neurocircuitry, it is possible that higher levels of schooling and premorbid IQ in the older HIV positive individuals may have protected these participants from HIV-associated injury to frontostriatal brain circuitry. Support for the latter explanation is undermined, however, by failure to observe evidence in our sample of an association between these factors and intrinsic frontostriatal connectivity.

Data from this study do not support an association between frontostriatal connectivity and a variety of immunological status or clinical history indicators. Although the majority of associations tested yielded small effect estimates (see Table 4), prior simulations have concluded that even relatively robust effects of demographic and behavioural measures, such as age, may require samples in the hundreds to reliably detect an association with intrinsic functional connectivity (Biswal et al., 2010). Nevertheless, our null findings are consistent with those reported in larger studies of chronic HIV across a range of intrinsic functional networks (Thomas et al., 2014; Thomas et al., 2013).

In this investigation HIV infection was associated with additional reductions of dorsal caudate connectivity to the dorsal ACC and the precuneus/superior parietal cortex. Prior research indicates that both of these regions are functionally connected to the DLPFC. For instance, the cluster in the left precuneus occupies a region of the brain determined through a prior comparative study of resting-state connectivity in humans and monkeys to form part of a cognitive network that includes the DLPFC (Margulies et al., 2009). Furthermore, the dorsal ACC cluster maps onto a region identified as co-activating with the ipsilateral anterior DLPFC in a conjunction analysis of both task and resting-state fMRI datasets in healthy individuals (Cieslik et al., 2013). In that study the anterior DLPFC cluster was observed to be responsive to tasks involving inhibitory cognitive control processes, consistent with the notion that the DLPFC forms a core component of an intrinsic central executive network (Vincent, Kahn, Snyder, Raichle, & Buckner, 2008) that is disrupted in HIV positive individuals (Thomas et al., 2013).

Documented HIV-associated dopaminergic abnormalities provide one possible mechanism underlying the attenuated connectivity of the dorsal caudate with the central executive network observed in seropositive participants in this study. Dopamine depletion has been observed in HIV patients in both cerebrospinal fluid and the central nervous system (Berger, Kumar, Kumar, Fernandez, & Levin, 1994; Kumar et al., 2009; Larsson, Hagberg, Forsman, & Norkrans, 1991; Sardar, Czudek, & Reynolds, 1996), with neuronal loss in the substantia nigra, the primary site for dopamine synthesis in the brain, detected in HIV patients on autopsy (Itoh, Mehraein, & Weis, 2000; Reyes, Faraldi, Senseng, Flowers, & Fariello, 1991). Dopaminergic abnormalities may also account for our finding that frontostriatal connectivity was attenuated in cognitively impaired participants, given evidence in healthy individuals of greater D1 receptor binding in the caudate and/or the DLPFC in individuals with stronger connectivity in these networks during the performance of working memory and executive functioning tasks (Backman et al., 2011; MacDonald, Karlsson, Rieckmann, Nyberg, & Bäckman, 2012; Rieckmann, Karlsson, Fischer, & Bäckman, 2011).

There are several limitations that should be borne in mind in interpreting the results of this study. Sample sizes employed in this study were small, limiting power to detect between-group differences in frontostriatal intrinsic connectivity. In addition, despite care taken during data preprocessing to remove the influence of physiological and motion artifacts, residual effects from these sources may have influenced the intrinsic connectivity estimates observed in this study. Our dataset was also subject to the inherent ambiguities of RS-fMRI, stemming from its use of blood oxygenation as a proxy for neuronal activity, and an inability to determine whether observed correlations reflect direct or indirect anatomical connections in the brain (Buckner 2013). The majority of HIV participants in this study were receiving antiretroviral medication at the time of the scan. While this increases the relevance of our findings to the HIV population in the post-HAART era, it was not possible to disentangle the relative contribution of potential neurotoxic effects of antiretroviral medication and the HIV virus on disruptions on intrinsic connectivity. Finally, various factors that may potentially undermine the generalizability of the study results to the HIV positive community include the relatively high levels of schooling and premorbid IQ of older HIV positive participants, as well as the relatively high proportion of seronegative participants who were cognitively impaired.

Substance use may serve as a potential confound of our findings, as it affects the same frontostriatal circuitry investigated in this study (Feil et al., 2010). Excluding individuals who screened positive for substance abuse and dependence, with the exception of marijuana, alcohol, and tobacco, for which the serogroups were comparable, minimized this possibility. Moreover, although lifetime alcohol abuse was more prevalent in the seronegative participants, it is unlikely to have confounded the results from this study, given lack of evidence for an association between a diagnosis of lifetime alcohol abuse and frontostriatal connectivity or cognitive impairment. Finally, the study results were discussed in the context of dopaminergic abnormalities associated with HIV, in keeping with the vast majority of research on the neurochemical determinants of oscillatory behavior in the basal ganglia. The relationship between abnormalities in intrinsic connectivity in HIV and perturbations in other neurotransmitters that also may be relevant in explaining cognitive deficits in HIV, such as serotonin and noradrenalin (Arnsten, 2007), warrants further investigation.

Conclusion

We were able to confirm that HIV infection is associated with abnormalities of intrinsic functional connectivity within the frontostriatal network. The observation that HIV status and cognitive impairment was associated with attenuated connectivity between the DLPFC and the dorsal caudate, and that the dorsal caudate was less well connected to the central executive network in HIV participants compared to controls, were discussed in terms of dopaminergic abnormalities associated with HIV infection. These findings suggest the potential of intrinsic functional connectivity as a marker of HIV-associated neuronal injury, even in the absence of corresponding cognitive impairment, and warrant independent replication in larger studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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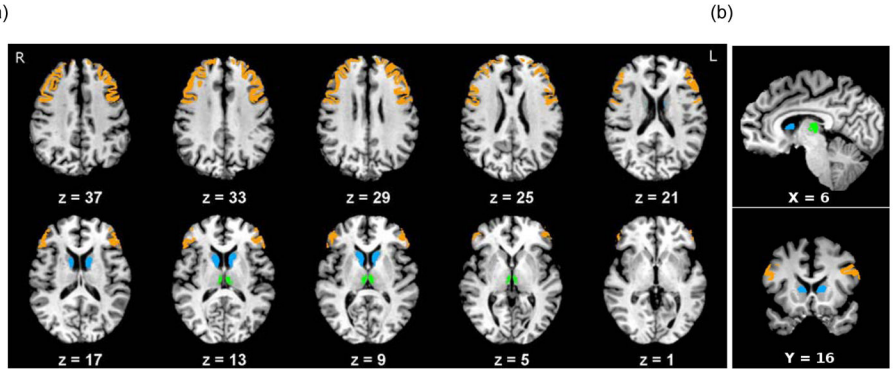

Figure 1.

DLPFC, dorsal caudate and mediodorsal thalamic masks from a representative subject.

(a) Mosaic of axial slices, (b) coronal/sagital slices.

DLPFC = orange, dorsal caudate = blue, mediodorsal thalamus = green. Coordinates are in Talairach space

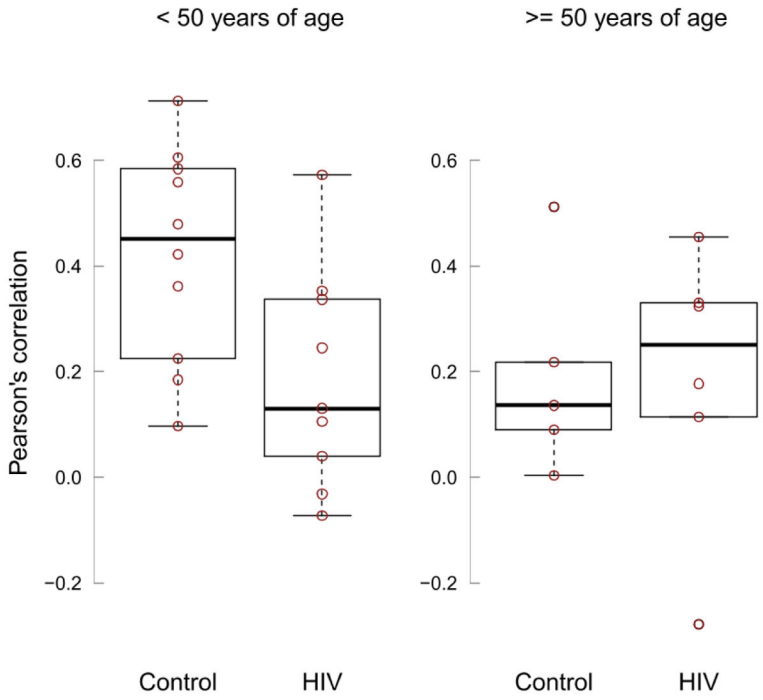

Figure 2.

Participant-level estimates of connectivity between the DLPFC and dorsal caudate, stratified by HIV status and age.

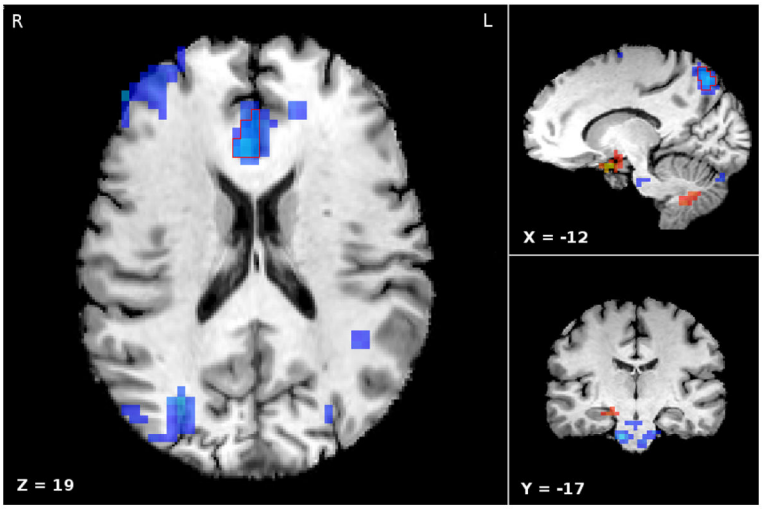

Figure 3.

Decreased (blue) and increased (red) whole-brain dorsal caudate connectivity as a function of HIV status, superimposed on a representative T1 MRI image in Talairach space. The overlay represents t-test statistics signifying group differences (range: −4.860 to 4.659), after adjusting for age and serostatus x age interactions. Significant clusters of reduced connectivity in seropositive subjects (voxel alpha < 0.005, cluster extent = 858μl) outlined in red. Subthreshold differences in connectivity ($p < 0.05$, cluster extent >= 429μl) provided for context.

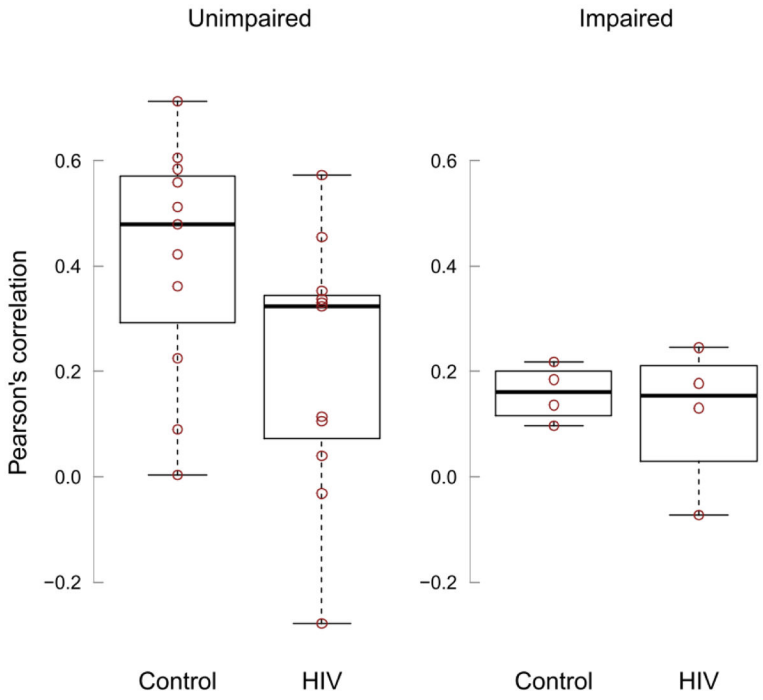

Figure 4.

Participant-level estimates of connectivity between the DLPFC and dorsal caudate, stratified by HIV and cognitive impairment status.

Table 1

Demographic and clinical characteristics of study sample[a]

	HIV (N = 15)	Control (N = 15)	Statistic[b]	ES (95%CI)[c]
Demographics				
Age	40.6 (14.46)	39.73 (12.55)	Z = −0.353	−0.13 (−0.85, 0.6)
Male N(%)	12 (80)	13 (86.7)	$\chi^2 = 0.24$	0.17 (−0.57, 0.91)
Right Handed N(%)	13 (86.7)	15 (100)	$\chi^2 = 2.143$	0.53 (−0.24, 1.3)
Education (years)	13.8 (2.18)	13.73 (1.33))	Z = −0.54	−0.19 (−0.92, 0.54)
Ethnicity N(%)				
African American	4 (26.7)	2 (13.3)		
Asian	1 (6.7)	0 (0)		
Caucasian	7 (46.7)	8 (53.3)		
Hispanic	3 (20)	5 (33.3)		
Neurocognition and affect				
GDS	0.32 (0.28)	0.29 (0.26)	Z = −0.230	−0.08 (−0.81, 0.65)
% impaired on GDS	26.7	26.7	$\chi^2 = 0$	0
WRAT-4 standard scores[d]	99.27 (10.65)	105.87 (13.05)	Z = 1.623	0.6 (−0.14, 1.35)
BDI-II total score	10.13 (9.63)	2.87 (3.98)	Z = −2.567[e]	−1.03 (−1.81,−0.26)
BDI-II FS score	3.13 (4.47)	1.13 (1.81)	Z = −1.42	−0.52 (−1.26, 0.22)
Indicators of clinical and treatment status				
ART currently prescribed (%)[e]	85.7%			
ART never used (%)[f]	14.3%			
AIDS status (%)	33.3%			
Indicators of HIV course				
Duration of infection (months)	80.4 (90.47)			
CD4 nadir	309.87 (192.85)			
CD4 current	548.07 (255.29)			
HIV RNA plasma (range)[g]	2.11 (0.98)			

[a] Continuous data presented as means (standard deviations)

[b] Results from Mann-Whitney or Chi-squared tests with Monte-Carlo estimation of the exact distribution (number of replications = 9999) under the null hypothesis for continuous and categorical variables, respectively.

[c] Cohen's *d* effect size estimates were derived from the between group test statistics using formulae provided in Fritz et al. (2012), and corrected for small-sample bias using the compute.es package in R (Del Re, 2013).

[d] WRAT-4 standard scores, with mean of 100 and standard deviation of 15

[e] $p < 0.01$

[f] Medication was prescribed within 6 months of scan session. Data on medication status was not available for one participant

[g] Viral load is reported in log base 10 copies per ML

GDS = global deficit score; WRAT-4 = Wide Range Achievement Test (reading subscale); BDI-II = Beck's Depression Inventory, 2nd edition; ART = Antiretroviral Therapy

Table 2

Pair-wise frontostriatal-thalamic intrinsic connectivity estimates[a]

Region	HIV (N = 15)	Controls (N = 15)
DLPFC – dorsal caudate	0.187 (0.22)	0.346 (0.22)
DLPFC – mdthalamus	0.152 (0.23)	0.228 (0.18)
Dorsal caudate - mdthalamus	0.266 (0.16)	0.293 (0.22)

[a] Mean (SD) Pearson's correlations of voxel time-series between regions

ROI = region of interest; DLPFC = dorsolateral prefrontal cortex; mdthalamus = mediodorsal thalamus

Table 3

Clusters of reduced connectivity to dorsal caudate in HIV seropositive versus seronegative participants

Label	BA[a]	X	Y	Z	Cluster extent (3.5 mm^3 voxels)	t-statistic
Controls > HIV						
Left precuneus/inferior parietal cortex	7	−12.2	−71	45	51	−4.386
Anterior cingulate	32	−1.8	34	17	22	−3.672

[a]BA = Brodmann Area

Table 4

Association of clinical variables with inter-regional connectivity estimates[a]

	DLPFC-dcaudate	DLPFC-mdthalamus	dcaudate-mdthalamus
CD4 nadir	rho = −0.075	rho = 0.018	rho = −0.154
CD4 current	rho = −0.093	rho = −0.132	rho −0.096
Infection duration	rho = −0.057	rho = −0.361	rho = 0.114
Detectable plasma HIV RNA	t(df) = 1.62 (12.9)	t(df) = 1.66 (6.70)	t(df) = 2.71 (9.33)

[a] $p > 0.1$ for all 9 tests, after false discovery rate correction

DLPFC = dorsolateral prefrontal cortex; dcaudate = dorsal caudate; mdthalamus = mediodorsal thalamus