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Apathy is associated with white matter abnormalities in anterior, medial brain regions in persons with HIV infection

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Abstract

Apathy is a relatively common psychiatric syndrome in HIV infection, but little is known about its neural correlates. In the present study, we examined the associations between apathy and diffusion tensor imaging (DTI) indices in key frontal white matter regions in the thalamocortico-striatal circuit that has been implicated in the expression of apathy. Nineteen participants with HIV infection and 19 demographically comparable seronegative comparison subjects completed the Apathy subscale of the Frontal Systems Behavioral Scale as a part of a comprehensive neuropsychiatric research evaluation. When compared to the seronegative participants, the HIV+ group had significantly more frontal white matter abnormalities. Within HIV+ persons, and as predicted, higher ratings of apathy were associated with greater white matter alterations in the anterior corona radiata, genu, and orbital medial prefrontal cortex. The associations between white matter alterations and apathy were independent of depression and were stronger among participants with lower current CD4 counts. All told, these findings indicate that apathy is independently associated with white matter abnormalities in anterior, medial brain regions in persons infected with HIV, particularly in the setting of lower current immune functioning, which may have implications for antiretroviral therapy.

Keywords

Diffusion tensor imaging; apathy; HIV/AIDS; Prefrontal cortex; depression

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Neurobehavioral dysfunction may develop in HIV seropositive (HIV+) individuals as a direct (e.g., effect of the virus in the CNS) or indirect (e.g., reaction to loss) consequence of the disease. Of these psychiatric disturbances, depression has received the most attention, although other alterations such as apathy have long been recognized as clinical manifestations of HIV-Associated Neurocognitive Disorders (HAND; e.g., Navia et al., 1986). It is only in the past decade that research has emerged on the prevalence, correlates, and neural underpinnings of apathy in the setting of HIV infection (Castellon, Hinkin, & Myers, 2001; Castellon, Hinkin, Wood, & Yarema, 1998; Paul, Flanigan et al., 2005; Rabkin et al., 2000). There is increasing evidence that apathy is associated with negative outcomes in HIV+ persons, including functional impairment and decreased quality of life (Barclay et al., 2007; Kamat et al., 2012; Tate et al., 2003), thus emphasizing the importance of investigating this psychiatric syndrome in the context of HIV infection.

Apathy is conceptualized as a lack of motoric, emotional, and cognitive motivation (Marin, Fogel, Hawkins, Duffy, & Krupp, 1995). Its symptoms include reduced drive, poor initiation and impaired control of self-directed purposeful behavior (e.g., Levy & Dubois, 2006; Stuss, van Reekum, & Murphy, 2000). This syndrome results from damage to specific frontal-subcortical structures and circuits, which are involved in the initiation, monitoring, and regulation of behavior (Cummings, 1993; Levy, 2012). While certain aspects of apathy and depression overlap (e.g., anhedonia) across clinical groups (including HIV infection), these two constructs are considered to be separable on behavioral (e.g., Levy et al., 1998; Starkstein et al., 2006) and neuropathological (e.g., Hoare et al., Lavretsky et al., 2007; Paul et al., 2005) bases.

Despite currently available efficacious antiretroviral therapy, there is continued evidence that HIV neuropathology remains common and is not specific to any one brain region (e.g., Everall et al., 2009; Jernigan et al., 2011). Findings from magnetic resonance imaging (MRI), structural imaging, and increasingly, diffusion tensor imaging (DTI) studies suggest that relative to HIV seronegative individuals, HIV+ persons evidence decreased integrity in major white matter tracts in the frontal lobes, internal capsule, inferior longitudinal fasciculus, occipital lobes, and optic radiation (e.g., Chen et al., 2009; Filippi et al., 2001; Gongvatana et al., 2009; Pfefferbaum et al., 2007; Pomara et al., 2001; Ragin et al., 2005; Stebbins et al., 2007; Thurnher et al., 2005; Wu et al., 2006). Frontostriatal circuits involving the basal ganglia as well as frontal cortical white and gray matter appear to be particularly vulnerable (e.g., Archibald et al., 2004; Aylward et al., 1993; Langford, Hurford, Hashimoto, Digicaylioglu, & Masliah, 2005). These circuits, including the orbital-medial stream, connect various frontal and basal ganglia regions involved in affect regulation and goal-directed behavior (Bonelli & Cummings, 2007; Levy & Dubois, 2005; Tanaka, Matsumoto, Mansouri, & Buckley, 2013; Tekin & Cummings, 2002). Consequently, injury to these circuits is known to produce symptoms of apathy (Levy & Dubois, 2005; Tekin & Cummings, 2002). This circuitry perspective on apathy is supported by findings that akinetic mutism and abulia, syndromes that share behavioral features of apathy, are also associated with pathology in thalamocortico-striatal circuits as well as frontal and cingulate cortices (e.g., Grunsfeld & Login, 2006; Demirtas-Tatlidede et al., 2013; Tengvan, Johansson, & Sorensen, 2004).

To date, there have been two neuroimaging studies that have examined the CNS correlates of apathy in HIV-infected individuals. In one structural MRI study of 12 asymptomatic HIV + individuals, Paul and colleagues (2005) reported a significant correlation, independent of depression and disease duration, between apathy and reduced volume in the nucleus accumbens, a structure whose damage in humans and monkeys has been associated with apathy (Brown et al., 2012; Phillips et al., 1987). Volume of the caudate nucleus, which plays a critical role in the dorsolateral and orbitofrontal circuits, was not significantly associated with apathy ratings (Paul et al., 2005). Using a voxel-wise DTI approach, Hoare et al. (2010) demonstrated that relative to HIV+ participants without apathy, HIV+, apathetic individuals had significantly lower fraction anisotropy values (an indicator of loss of axonal organization) in the genu of the corpus callosum, the superior corona radiata, and the anterior thalamic radiation. The anatomical regions implicated in these two studies of apathy in HIV-infected persons are consistent with those involved in the expression of this syndrome in various other disease groups including Alzheimer's disease (AD; Choi, Lim, Monteiro, & Reisberg, 2005), Parkinson's Disease (PD; Reijnders et al., 2010), and amyotrophic lateral sclerosis (ALS; Tsujimoto et al., 2011).

Taking into account general models of fronto-basal ganglia circuits related to apathy (Levy & Dubois 2006; Stuss et al., 2000; Tekin, & Cummings, 2002), as well as findings of the neural correlates of apathy in HIV (Hoare et al., 2010; Paul, et al., 2005), we developed several white matter regions of interest (ROI) to investigate brain circuits related to apathy in HIV. These white matter ROIs included the white matter adjacent to the orbito-medial frontal cortex, as well as the anterior and superior corona radiata, and genu of the corpus callosum.

We specifically hypothesized that higher levels of self-reported apathy will be uniquely associated with lower white matter integrity in the ROIs selected. Strongest associations were expected in the white matter adjacent to the orbital medial prefrontal cortex, as theorized across the apathy literature (e.g., Levy & Dubois, 2006; Stuss et al., 2000). In addition, we examined the degree to which the relationship between white matter abnormalities and apathy is independent of depression. We also examined the effect of disease severity (i.e., duration of infection, AIDS status, viral load, and nadir as well as current CD4 levels) on the correspondence between apathy and changes in white matter integrity. We hypothesized that HIV-associated white matter changes in the selected ROIs would not correspond with other frontal systems disturbances such as executive dysfunction and disinhibition, which are thought to be driven by pathology in other prefrontal regions (Cummings 1993; Kringelbach & Rolls, 2004).

Methods

Participants

Participants included 19 HIV+ individuals recruited from HIV treatment centers and community organizations and 19 seronegative comparison subjects who were recruited from community advertisements and word-of-mouth (e.g., friends and family of the seropositive participants). These 38 participants were enrolled at the University of California San Diego (UCSD) Translational Methamphetamine AIDS Research Center (TMARC). Individuals

with histories of current substance dependence or abuse, neurological diseases (e.g., seizure disorders, closed head injuries with loss of consciousness greater than 30 minutes, central nervous systems neoplasms, opportunistic infections) or severe psychiatric illnesses (e.g., schizophrenia) that might affect cognitive functioning were excluded from the study. Additionally, to be eligible, participants must not have had any metal or devices in their body that contraindicated MRI. Given its association with neural injury and apathy, comorbid Hepatitis C Virus infection was also used as a criterion for exclusion in the current study. HIV status was determined by the Med Mira Rapid HIV antibody test. In the HIV+ participants, CD4+ T cell counts were measured by flow cytometry at a Clinical Laboratory Improvement Amendments-certified medical center laboratory. HIV RNA levels were measured in plasma and CSF by reverse transcriptase PCR (Roche Amplicor, v. 1.5, lower limit of quantification 50copies/mL). CD4 nadir was obtained by self-report, with confirmation by documented prior measurements in a subset of individuals. Date of nadir was also obtained by self-report. The study was approved by the institutional review board and informed consent was obtained from each participant prior to enrollment. The demographic, clinical, neurocognitive, and psychiatric characteristics of the study sample are presented in Table 1. Participants were well matched on all demographic variables ($p > .10$). The seronegative group had lower rates of lifetime and current Major Depressive Disorder ($p < .01$).

Neuropsychiatric Assessments

Subjects were administered the 46-item self-report version of the Frontal Systems Behavior Scale (FrSBe; Grace & Malloy, 2001) that elicited the frequency of occurrence of a series of behaviors associated with frontal brain systems. The measure yields scores for three subscales: Apathy, Disinhibition, and Executive Dysfunction. Participants provided ratings on a Likert-type scale that ranges from 1 (“almost never”) to 5 (“almost always”) for each question, with higher ratings indicating more abnormal behavior (e.g., neglecting personal hygiene, leaving things unfinished). Based on the manual guidelines, raw scores were converted to demographically (i.e., age, education, and gender) adjusted T- scores, scaled so higher scores signify greater pathology. A T-score cut point of 65 is recommended to identify patients with more severe symptoms and greater clinical significance.

Trained interviewers administered the Composite International Diagnostic Interview (CIDI) to the participants. This measure is a computer-assisted interview and provides an assessment of alcohol, drug, and mental disorders using DSM-IV criteria (Wittchen et al., 1991), and was used to obtain diagnoses of current and lifetime major depressive disorder (MDD) and psychoactive substance abuse and dependence disorders.

Diffusion Tensor MRI Acquisition

MRI data were acquired using a 1.5T General Electric magnet. An axially acquired whole brain 2D spin echo, echoplanar imaging protocol was applied (Number of shots = 1, number of echoes = 1, TR=9.7s, TE=minimum, FOV=24 cm, matrix=96 × 96, 2.5 mm × 2.5 mm inplane resolution, 46 interleaved slices, no spaces, thickness = 2.5 mm, b = 0, 1000 s/mm², 51 gradient directions, with field maps). The B₀ distortions were corrected using field maps. The single diffusion-off image was co-registered to each subject's T1 high-resolution image

using localized Pearson correlation with AFNI's align_epi_anat routine (Saad et al., 2009). The DTI series was co-registered to the diffusion-off image. Corrections for eddy currents were made using FSL's eddy_correct routine. Diffusion eigenvectors and eigenvalues were derived from FSL's dtifit routine. FA, Mean Diffusivity (MD), Axial Diffusivity (AD), and Radial Diffusivity (RD) values were calculated from the eigenvalues derived from the dtifit routine.

White matter ROIs were selected within the thalamo-cortico-striatal loop associated with apathy according to apathy circuit models, as well as regions previously related to apathy in other HIV studies (Cummings, 1993; Hoare et al., 2010; Levy Dubois &, 2006; Paul et al., 2005). An ROI approach is an alternative to the voxel-wise method and helps protect against the Type I error by using a priori selected regions based on their theorized involvement in both HIV infection and the apathy syndrome. The ROIs included bilateral regions in the orbital-medial prefrontal cortex (OMPFC) as well as the anterior and superior corona radiata (ACR, SCR). An ROI was also placed in the genu of the corpus callosum. Two raters, blind to one another, defined these ROIs using the Oishi et al (2011) atlas. Each rater drew the ROIs on an MNI averaged 152 brain warped into Talairach space. The degree of between-rater similarity in the ROIs was assessed using Dice indices (Donner & Zou, 2002), which were as follows: ACR = .88, SCR = .85, OMPFC = .82, Genu = .85. The intersection maps of the two raters were used to derive the final Talairached ROIs, which were further processed to produce masks in each subject's native space. First, gray-white matter segmentation was performed on the T1 anatomical images. Each individual's T1 was warped into Talairach space, and using this transformation matrix, the Talairached MNI masks were reverse-warped into native space for each subject. Finally, the intersection of the reverse-warped masks with the white matter tissue segmentation was formed.

Statistical Analyses

Group differences between HIV+ and seronegative participants on demographic, neuropsychiatric, and imaging variables were examined using Wilcoxon Rank Sum test or χ^2 tests. The significance threshold was set to $p = .05$ for all analyses.

First, we calculated the correlation between apathy and DTI indices separately for the HIV+ (n=19) and seronegative comparison (n=19) groups in all the ROIs. This permitted us to characterize the pattern of the association between apathy and white matter changes across the two groups. Next, in each group, to determine whether the correspondence between white matter change and apathy was influenced by a history of major depressive disorder, we conducted a multivariate multiple regression analysis (Stata MVREG procedure; StataCorp, 2011). Here, apathy and depression history were entered as predictors of FA values for those ROIs where a moderate or large (Cohen's $d > .5$) HIV effect was detected. Multivariate multiple regression differs from ordinary multiple regression in that several outcome variables (in this case, FA values for each ROI) are jointly regressed onto a set of predictors (here, apathy ratings and depression history). The least squares regression coefficients relating the predictor set to a dependent variable are the same as those estimated when separately regressing each dependent variable onto the predictors. Multivariate multiple regression, however, permits a test of the multivariate null hypothesis that the

dependent measures taken as a set are not significantly related to the predictor set. Moreover, this procedure allows for the estimation of between-equation covariances, and thus differences in the coefficients across the equations predicting each ROI can be tested with the Wald test (e.g., Hanssen et al., 2002). Specifically, this method allowed us to directly test the null hypothesis that the coefficient of apathy as a predictor of the FA values in the OMPFC did not differ from the coefficient of apathy as a predictor of FA values in another ROI (e.g., the ACR). Similar multivariate multiple regression models using MD, AD, and RD in the ROIs with robust HIV effects were conducted in the HIV+ group. Multivariate multiple regression was also performed to detect whether current HIV disease characteristics moderated the association between apathy and FA values in the ROIs.

Finally, we examined the specificity of the white matter changes in the selected regions to apathy relative to other frontal systems disturbances. To do so, the correlations between FA values in the seven ROIs and the three FrSBe scales (i.e., apathy, disinhibition, and executive dysfunction) in the sample of HIV+ participants were examined. We also tested whether HIV+ persons with or without MDD differed in the extent of white matter alterations in the ROIs.

Results

Demographic and Clinical Findings

The demographic, clinical, neurocognitive, and psychiatric characteristics of the study sample are presented in Table 1. Participants were generally well matched on all demographic variables ($p > .10$). The HIV seropositive group had higher rates of lifetime MDD ($p < .05$). Individuals with HIV infection reported significantly higher levels of apathy relative to the seronegative comparison participants ($t(1,37) = 4.13, p < .001, d = 1.3$). Using the FrSBe cut point of $T = 65$ (Grace & Malloy, 2001), none of the HIV- participants reported clinically elevated levels of apathy. In contrast, 8 of the 19 (42%) HIV+ persons were apathetic.

Neuroimaging Findings

HIV infection and frontal white matter abnormalities—Group differences in white matter abnormality in the ROIs were examined. As shown in Table 2, moderate to large effect sizes (d 's = .54 – 1.28) were noted such that the HIV+ group had lower FA values in bilateral ACR, genu, and the left OMPFC. Small, non-significant differences in FA were noted in right OMPFC and bilateral SCR (d 's = 0.0 – .25). The pattern of the HIV serostatus differences was generally consistent when considering mean, axial, and radial diffusivity, although the effect sizes were somewhat weaker (see Table 2).

Next, within the HIV+ group ($n=19$), the association between FA values in the seven ROIs and HIV disease variables (e.g., current CD4 count, AIDS status, nadir CD4 count, and duration of illness) was examined. In general, individuals with AIDS ($n=12$) had lower FA values in the frontal white matter regions selected. Using the Wilcoxon Rank Sum test, significant differences based on AIDS status were noted in the genu ($\chi^2=4.83, p=.03$), the left OMPFC ($\chi^2=5.21, p=.02$) and right OMPFC ($\chi^2=6.01, p=.01$). Correlational analyses

using Pearson's r demonstrated moderate to strong significant associations between current CD4 count and frontal white matter changes. Specifically, higher CD4 counts were moderately correlated with FA values in the left ACR, genu, left OMPFC, and left SCR (r 's = .50 – .61). Similar associations were noted for nadir CD4 count and FA values in the genu and bilateral OMPFC (r 's = .50 – .59). Estimated duration of HIV infection was not significantly associated with white matter changes in any of the seven regions.

Apathy and frontal white matter abnormalities—We examined the correlations between apathy and FA values in the seven ROIs in the two HIV serostatus groups. Within the HIV+ cohort, strong, negative correlations were observed between apathy severity and FA values in the left ($r=-0.60$, $p<.01$) and right ($r=-0.44$, $p=.05$) ACR, genu ($r=-0.53$, $p=.02$), left OMPFC ($r=-0.43$, $p=.06$), left ($r=-0.45$, $p=.05$) and right ($r=-0.41$, $p=.08$) SCR. FA values in the right OMPFC were not associated with apathy in the HIV+ group ($p>.2$). There were no significant associations between white matter abnormality and apathy ratings observed in the seronegative comparison group (all p 's $>.20$).

Multivariate multiple regression: We used multivariate multiple regression to determine whether apathy correlated with ROIs in the HIV+ group once depression was taken into account. For this analysis, FA in the ROIs that were individually correlated with apathy (bilateral ACR, genu, and left OMPFC) were included as outcome variables in the multivariate multiple regression model. Lifetime diagnosis of major depressive disorder was entered as a covariate to account for depressive symptomatology as well as any residual apathy secondary to the historical depressive episode. Overall, the multivariate multiple regression model approached significance ($F(4, 14) = 3.04$, $p=.05$). To determine whether apathy significantly contributed to the variance explained in the multivariate multiple regression model, we tested the null hypothesis that all coefficients related to apathy in the design matrix were zero when depression was dropped from the model. This null hypothesis was rejected ($F(4, 16) = 3.41$, $p=.03$) indicating a significant association between apathy and FA for the four regions together. Next, we tested the significance of depression by forcing its coefficients to be zero while apathy was dropped from the model. The null hypothesis was not rejected ($F(4,16) = .87$, $p = .50$). Together, these findings support the overall unique importance of apathy as a predictor of white matter FA in the multivariate multiple regression model. When current diagnosis of MDD was entered as a covariate, the pattern of results was unchanged. In general, higher apathy was associated with lower FA values in the four, pre-determined ROIs. However, as demonstrated by the Wald tests, the magnitude of this association differed across the regions. The standardized parameter estimates are presented in Table 3. Specifically, relative to the left OMPFC, the relationship between apathy and FA values was significantly stronger in the left ACR ($F(1,16) = 9.11$, $p=.01$) and the genu ($F(1,16) = 5.47$, $p=.03$). The coefficient for apathy as a predictor of FA values in the left OMPFC did not differ from that in the right ACR. Compared to the right ACR, the coefficient of apathy was larger for the model predicting the FA values in the genu ($F(1,16) = 4.3$, $p=.05$) as well as the left ACR ($F(1,16) = 4.3$, $p=.05$). The coefficients for the genu and the left ACR were not significantly different ($F(1,16) = 2.62$, $p=.12$).

When the multivariate multiple regression model using the same regions (i.e., bilateral ACR, genu, and left OMPFC) was examined in the HIV– group, neither the overall model nor the individual regressions were significant (all p 's $>.3$).

Similar multivariate multiple regression models in the HIV+ group were conducted using MD, AD, and RD values in those regions where a robust HIV effect was detected as the outcome variables. The regions included in each model are indicated in Table 2. As before, apathy and depression history were entered as the predictors. Apathy rating fell short of being a significant predictor of MD in the overall model, even though the full model approached being significant ($F(4, 14) = 3.08, p=.05$). An examination of the individual models revealed that apathy was a significant, independent predictor of MD values in the genu ($\beta=.54, p=.03$) only (see Table 3). The multivariate multiple regression model predicting RD values was significant ($F(3, 15) = 4.25, p=.02$), and apathy showed a trend towards being an independent predictor of RD values ($F(3, 14) = 3.09, p=.06$). In the individual models, apathy ratings were uniquely associated with RD values in the genu only ($\beta=.57, p=.02$). The analyses with AD values as outcome variables demonstrated that neither the MANOVA nor the individual models were significant (all p 's $>.1$). Across the MD, RD and AD models, depression history did not explain a significant amount of variance in the DTI indices. Table 3 presents a summary of results for the individual ROI models in which apathy was a significant predictor of white matter changes.

Impact of HIV disease characteristics on the relationship between apathy and frontal white matter abnormalities

To characterize the nature of the relationship between apathy and white matter changes in the context of current immunovirologic status, a multivariate multiple regression analysis with FA values in bilateral ACR, genu, and left OMPFC predicted by apathy was conducted in the HIV+ individuals ($n=19$) with current CD4 count added as a covariate. The interaction between apathy and CD4 count was also entered in the analysis. The model was significant ($F(3, 14) = 4.37, p=.02$). A significant main effect for apathy was observed ($F(1, 14) = 8.6, p=.02$), as well as the interaction between apathy and CD4 count ($F(1, 14) = 5.8, p=.03$). An examination of the individual models indicated that the interaction of apathy and CD4 count was a significant predictor of white matter abnormality (i.e., lower FA) in the left ACR, genu, and the left OMPFC. However, Wald tests demonstrated that the coefficients for this interaction term did not differ across the regions (p 's $>.1$). Similar analyses were performed using MD values in the genu, bilateral OMPFC, and left SCR. The overall model was not significant ($p>.1$).

Follow up post-hoc analyses were conducted to examine the relationship between apathy and FA values in the context of current CD4 count. HIV+ participants were split into two groups using the median value of the CD4 count, and consisted of nine participants each. Those with a CD4 count of less than 340, i.e., suggestive of poor immune function, were in the “low CD4” group, while the remaining participants were in the “high CD4” group. This is consistent with the World Health Organization recommendations of using a CD4 count of 350 as a cutoff for antiretroviral treatment initiation (De Cock, Crowley, Lo, Granrich, & Williams, 2009; WHO, 2009). We observed strong, significant correlations between apathy

and FA in the left ACR, genu, and left OMPFC only in the low CD4 group (r 's = $-.68$ to $-.75$), such that higher ratings of apathy were associated with greater white matter abnormalities. All the correlations between the variables of interest in the high CD4 group, i.e., those who had relatively intact immune functioning, were non-significant and relatively weaker than the low CD4 group (r 's $<.5$). The pattern of results was unchanged when a CD4 cutoff of 350 instead of 340 was used. Figure 1 illustrates the pattern observed in the left OMPFC.

Specificity of the white matter regions to apathy—First we examined whether executive dysfunction and disinhibition, two frontal systems disturbances, were correlated with white matter abnormalities in the regions selected in the HIV+ participants. As demonstrated in Table 4, compared to executive dysfunction and disinhibition, apathy ratings were more strongly associated with white matter changes in the seven ROIs. FA values in the left SCR showed comparable, fairly high associations with ratings of executive dysfunction ($r = -.49$, $p = .03$) and apathy ($r = -.42$, $p = .07$). Ratings of disinhibition were consistently unrelated to white matter abnormalities in the ROIs (p 's $>.3$). Similarly, lifetime (i.e., past and current) diagnosis of MDD was also observed to be unrelated to white matter changes in the selected regions (p 's $>.4$).

Discussion

The present investigation of the correspondence between HIV-associated white matter microstructure and the expression of apathy was guided by models of brain circuitry implicated in the development of this neuropsychiatric syndrome. The results of our study support our hypothesis that apathy, but not other neuropsychiatric symptoms, is related to HIV-associated alterations in specific fronto-basal ganglia white matter connections.

Commensurate with prior research (e.g., Castellon et al., 1998; Kamat et al., 2012), HIV-seropositive participants reported higher ratings of apathy relative to seronegative comparison subjects. DTI as implemented in this study, appears to be sensitive to HIV-related microstructural white matter disturbance in the white matter regions selected, as the HIV+ persons showed greater abnormality than seronegative comparison participants. The most robust FA changes were observed in the bilateral ACR, genu, and left OMPFC. There may also be HIV-associated injury to the bilateral SCR and the right OMPFC as suggested by the group differences seen in MD, AD, and RD in these regions. The white matter pathology noted in HIV+ participants appears to be driven by immunovirological factors, most notably CD4 counts. Previous reports have linked these HIV disease markers to structural and white matter abnormalities (e.g., Cohen et al., 2010; Fillipi et al., 2001; Gongvatana et al., 2009; Jernigan et al., 2011).

Consistent with the findings of Hoare et al. (2010) in a South African cohort of Clade C HIV-infected individuals, we observed that apathy ratings were strongly associated with overall HIV-associated frontal white matter changes in the selected regions, independent of any history of comorbid major depressive disorder. To extend the literature and better characterize the neuroanatomical correlates of apathy in HIV infection, we examined whether certain regions are more closely involved in the expression of apathy. The strongest

association was expected between apathy and white matter abnormality in the OMPFC. Although the OMPFC did demonstrate a strong, significant association with apathy, it was not as strong as that noted in the ACR and genu. It is possible that the white matter directly underlying the cortical structures that regulate goal-directed behavior may not be as central to the apathy syndrome or may not be as susceptible to HIV-associated CNS pathology as white matter circuit tracks. Alternatively, differences in neuroarchitecture might explain the varying strength of correlations between apathy and white matter changes across the three regions. Future studies using more sophisticated methodology such as tract based spatial statistics (TBSS) may clarify the present findings. Given the neuroanatomical connections of the ACR and genu, two superior and medial structures, their involvement in apathy expression is not surprising. For instance, the ACR contains white matter tracts that connect the anterior cingulate circuit to the striatum and other regions involved in behavior regulation (McCandliss, 2011), while fibers from the prefrontal and orbitofrontal cortex extend within the genu and connect to other cortical regions (Catani & de Schotten, 2012). The strong link between diffusion abnormalities (i.e., MD, AD, RD) in the genu and apathy further substantiate the apparent relevance of this region in the regulation of goal-directed behavior. In contrast, within the HIV- group, there were no significant associations between apathy ratings and white matter integrity. This suggests that it is only in HIV+ individuals that CNS pathology exists and corresponds to apathy symptomatology.

At present, little is known about the impact of HIV disease characteristics on the relationship between neural damage and apathy severity. Current CD4 count is a marker of current immune functioning (e.g., Sousa et al., 2002), and is a commonly used clinical marker of HIV disease or treatment response. Accordingly, to characterize the relationship between current neuropsychiatric disturbance, neural integrity, and immunologic status, we examined whether current CD4 count moderated the correspondence between apathy ratings and frontal white matter abnormalities. It was observed that those individuals with current CD4 counts less than 340 demonstrated a robust correlation between apathy and white matter abnormalities. This association was absent in the HIV+ persons with relatively better immune functioning (i.e., those with CD4 counts of 340 and higher). Low CD4 count, which suggests poor immunologic function, has previously been shown to be associated with atrophy in frontostriatal regions (Chiang et al., 2007). These neuropathological findings are complemented by our result that there was a significant interaction between CD4 count and apathy such that the association between apathy and white matter damage differed depending on the CD4 count. Our preliminary findings suggest that important factors such as antiretroviral regimen history and medication adherence warrant consideration, as they may impact current CD4 count thereby modifying the magnitude of HIV-associated CNS damage. This potential mechanism raises the possibility of mitigating the neuropsychiatric burden in HIV+ patients via improved antiretroviral treatment.

Extending the literature, we observed that disinhibition, a behavioral syndrome associated with frontal systems disturbance, was not related to white matter abnormality in the selected regions. The same was true for symptoms of executive dysfunction, with the exception of the significant association noted between these ratings and white matter changes in the SCR. Although it has long been established that injury to frontal cortex and anterior cingulate produce symptoms of executive dysfunction, disinhibition, and apathy, recent theories of

frontal lobe dysfunction describe distinct brain circuits that underlie these three forms of frontal lobe disorder (e.g., Bonelli, & Cummings, 2007). The utility of apathy as a behavioral marker of HIV-associated CNS damage to frontal systems is bolstered by the unique correspondence between the selected regions and the severity of apathy symptoms vis-à-vis ratings of disinhibition and executive dysfunction. As such, these findings supporting the relationship between apathy and the anterior, medial structures targeted in this study are highly consistent with brain circuitry models used to explain specific neuropsychiatric disorders (Bonelli & Cummings, 2007; Levy & Dubois, 2006). Future studies in HIV-infected cohorts specifically examining the neural correlates of disinhibition and executive dysfunction are needed, given the potential relevance of these behavioral syndromes to everyday functioning outcomes.

Major depressive disorder status was also not related to white matter changes in the ROIs. Imaging studies across clinical groups (e.g., HIV, dementia, and aging cohorts) suggest that apathy and depression have separable neuropathological substrates (e.g., Hoare et al., 2010; Lavretsky et al., 2007; Paul, Brickman et al., 2005; Starkstein et al., 2009). Our findings are commensurate with these reports, and provide further support for the neuroanatomical distinction between the psychiatric constructs of apathy and depression.

Neuropathological studies in HIV have demonstrated that HIV-related toxicity induces myelin and axonal damage, ultimately resulting in neuronal apoptosis and dendritic simplification (Archibald et al., 2004; Ozdener, 2005). In the present study, we observed a correspondence between apathy ratings and HIV-associated alterations in both FA and MD. These DTI indices may reflect the myelin content, extent of axonal damage, and gliosis (Schmierer et al., 2006). Thus, it appears that apathy may be associated with these neuropathological processes. However, this correspondence should be interpreted with caution. Increasingly, RD and AD have been utilized as markers of myelin loss and axonal degeneration respectively (Song et al., 2002). Although our data suggest a stronger link between apathy and abnormal RD but not AD in the genu, potentially indicating a demyelination process, these findings are not conclusive. A thorough investigation of the underlying neural structural characteristics is recommended (Wheeler-Kingshott & Cercignani, 2009). As such, the exact pathological processes resulting in the observed microstructural frontomedial white matter abnormalities and consequent dysregulation of goal-directed behavior in HIV-infected participants remain to be investigated.

As with all cross-sectional clinical investigations, this study has limitations. Future longitudinal studies should examine the trajectory of white matter alterations in the context of fluctuations in neuropsychiatric disturbance. Our sample size is small and power issues did not permit thorough examination of all possible covariates (e.g., ART status) that might influence the correspondence between apathy and HIV-associated white matter alterations. We also observed medium effect sizes for HIV-associated white matter abnormalities as measured by mean, axial, and radial diffusivity in the ACR, OMPFC, and SCR (see Table 2). However, these group differences did not reach statistical significance due to limited power. Future investigations would benefit from examining white matter abnormalities in these regions using larger sample sizes. We utilized a self-report measure (i.e., FrSBe) of apathy as opposed to a clinical interview such as the Neuropsychiatric

Inventory (Cummings et al., 1994). The accuracy of self-reported ratings may be affected by depression, bias, and/or mild anosagnosia and this limitation tempers the strength of our conclusions.

Collectively, our findings suggest a unique association between apathy and HIV-associated white matter alterations in frontal and basal ganglia regions, which appears to be driven by poor current immune functioning. Our results raise the possibility that closer monitoring and treatment of HIV disease may alter the burden of CNS pathology and consequently minimize the expression of apathy. This is particularly clinically relevant given the documented negative functional outcomes associated with apathy in HIV-infected individuals (e.g., Barclay et al., 2007; Kamat et al., 2012; Tate et al., 2003). Overall, these findings support the assessment of apathy in HIV-infected individuals seen in clinical settings as it may serve as a proxy of the neuropathologic burden in these patients.

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Figure 1. Scatterplot demonstrating the different patterns of association between apathy ratings and Fractional Anisotropy values in the left OMPFC across the “High” and “Low” CD4 groups.

Table 1

Demographic and clinical findings in the sample of HIV– and HIV+ participants

	HIV–	HIV+	Cohen's <i>d</i>	<i>p</i> -value
Demographic variables				
Age (years)	38.3 (11.3)	42.9 (11.4)	–.41	.21
Gender (%male)	90	84.2	-	.60
Education (years)	14.2 (2.3)	13.8 (2.3)	.23	.63
Ethnicity (%Caucasian)	65	58	-	.70
Neuropsychiatric variables				
Apathy T-score	40.1 (7.1)	60.2 (20.4)	–1.32	<.01
Clinical elevation in apathy (T-score >65)	0	42.1	-	<.01
Proportion with Current MDD (%)	5	36	-	<.01
Proportion with Lifetime MDD (%)	20	63.2	-	<.01
Proportion with Lifetime Substance use disorders (%)	32	32	-	.64
Proportion NP impaired (%)	20	42.1	-	.15
HIV disease variables				
Duration of illness (months)	-	70.4 (7.7, 70.4)		
Proportion with AIDS (%)	-	63.2		
Current CD4 count (median, IQR)	-	340 (215, 500)		
Nadir CD4 (median, IQR)	-	175 (40, 250)		
Proportion on CART (%)	-	75		
Log ₁₀ Plasma Viral Load for those on CART	-	1.6 (1.6, 1.7)		
Plasma viral load (%undetectable of those on CART)	-	80		

Note: CART = Combination Antiretroviral Therapy

Table 2

Group differences in 4 DTI indices calculated for the seven regions of interest

	HIV- (n=19)		HIV+ (n=19)		Cohen's <i>d</i>
	Mean	SD	Mean	SD	
Fractional anisotropy					
ACR-L	0.37	0.03	0.34	0.05	0.73*
ACR-R	0.36	0.03	0.34	0.04	0.56*
Genu	0.47	0.09	0.38	0.11	0.89*
OMPFC-L	0.3	0.03	0.27	0.03	1.00*
OMPFC-R	0.29	0.04	0.28	0.04	0.25
SCR-L	0.4	0.03	0.4	0.04	0.00
SCR-R	0.39	0.03	0.39	0.05	0.00
Mean Diffusivity					
ACR-L	0.83	0.05	0.86	0.07	0.49
ACR-R	0.85	0.07	0.9	0.18	0.36
Genu	1.02	0.28	1.2	0.29	0.63*
OMPFC-L	0.81	0.07	0.86	0.11	0.54*
OMPFC-R	0.83	0.08	0.88	0.1	0.55*
SCR-L	0.73	0.04	0.75	0.04	0.50*
SCR-R	0.73	0.05	0.79	0.2	0.41
Axial Diffusivity					
ACR-L	1.16	0.05	1.19	0.1	0.38
ACR-R	1.2	0.07	1.24	0.17	0.31
Genu	1.56	0.25	1.7	0.27	0.54*
OMPFC-L	1.07	0.07	1.1	0.11	0.32
OMPFC-R	1.1	0.07	1.14	0.11	0.43
SCR-L	1.06	0.04	1.09	0.06	0.59*
SCR-R	1.04	0.06	1.12	0.2	0.54*

	HIV- (n=19)		HIV+ (n=19)		Cohen's <i>d</i>
	Mean	SD	Mean	SD	
Radial Diffusivity					
ACR-L	0.66	0.06	0.69	0.07	0.46
ACR-R	0.67	0.07	0.73	0.18	0.44
Genu	0.75	0.3	0.97	0.32	0.70*
OMPFC-L	0.67	0.08	0.73	0.11	0.62*
OMPFC-R	0.69	0.09	0.75	0.11	0.59*
SCR-L	0.56	0.04	0.57	0.04	0.25
SCR-R	0.56	0.05	0.63	0.2	0.48

Note:

* ROIs that were included as outcome variables in the multivariate multiple regression model for each DTI index with apathy entered as a predictor and depression status as a covariate.

ACR = anterior corona radiata

OMPFC = orbital medial prefrontal cortex

SCR = superior corona radiata

Table 3

Regression coefficients and associated p values for apathy as a predictor of FA, MD, RD, and AD.

DTI index	Region	Coefficient (β)	p -value
Fractional Anisotropy	Left Anterior corona radiata	-.59	<.01
	Right Anterior corona radiata	-.46	.02
	Genu	-.53	<.01
	Left Orbital medial prefrontal cortex	-.40	.03
Mean Diffusivity	Genu	.54	.03
	Left Orbital medial prefrontal cortex	.08	.76
	Right Orbital medial prefrontal cortex	.33	.19
	Left Superior Corona radiata	.30	.18
Radial Diffusivity	Genu	.57	.02
	Left Orbital medial prefrontal cortex	.11	.67
	Right Orbital medial prefrontal cortex	.35	.16
	Left Superior Corona radiata	.01	.95
Axial Diffusivity	Genu	.40	.11
	Right Superior Corona radiata	.38	.13

Note: Full model included apathy as the predictor with lifetime (past and current) major depressive disorder diagnosis as the covariate.

Table 4

Pearson's correlation between the three FrSBe scales and FA values in the HIV+ participants (n=19)

	Apathy	Disinhibition	Executive dysfunction
Left Anterior corona radiata	-.51*	-.1	-.31
Right Anterior corona radiata	-.48*	-.05	-.27
Genu	-.57*	-.06	-.17
Left Orbital medial prefrontal cortex	-.45*	-.23	-.18
Right Orbital medial prefrontal cortex	-.28	-.07	.05
Left Superior corona radiata	-.42	-.25	-.49*
Right Superior corona radiata	-.39	-.12	-.40

Note:

*
 $p < .05$

ACR = anterior corona radiata

OMPFC = orbital medial prefrontal cortex

SCR = superior corona radiata