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Longitudinal Intra-Individual Variability in Neuropsychological Performance Relates to White Matter Changes in HIV

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Abstract

Objectives—Recent studies suggest that intraindividual variability (IIV) of neuropsychological performance may be sensitive to HIV-associated neurologic compromise. IIV may be particularly dependent upon the integrity of frontal-subcortical systems, and therefore may be a meaningful phenotype in HIV. We examined the relationship between change in IIV and white matter integrity among HIV seropositive (HIV+) and HIV seronegative (HIV−) individuals.

Method—The sample consisted of 38 HIV+ participants and 26 HIV− control participants who underwent neuroimaging and a neuropsychological evaluation at baseline and at 2-year follow-up evaluation.

Results—Among HIV+ participants, increases in IIV (greater dispersion) were related to lower fractional anisotropy (FA) values in the anterior thalamic radiations (ATR) and the superior longitudinal fasciculus (SLF). Changes in mean-level global cognitive functioning were not significantly related to white matter integrity. Additionally, there was a significant group x IIV interaction effect in the SLF demonstrating that the relationship between IIV and white matter integrity was specific to HIV.

Conclusions—Overall, findings suggest that IIV may be more sensitive, relative to mean-level global cognitive functioning, in the detection of neurologic compromise among HIV+ individuals.

Keywords

human immunodeficiency virus; intra-individual variability; diffusion tensor imaging

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Competing Interests:
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INTRODUCTION

Cognitive impairment is a common complication of HIV infection, with a point prevalence of 40–50% among HIV seropositive (HIV+) individuals (Heaton et al., 2011; Sanmarti et al., 2014).

Extant studies of HIV-Associated Neurocognitive Disorder (HAND), with but a few exceptions, have typically focused on mean-level cognitive function. Examples include assessing if a group's mean performance of test scores differs relative to other groups, or if a person's average of multiple tests scores within a domain (i.e. composite score) correlates with another variable of interest. However, over the last few years there has been increased interest in the incremental utility of examining the dispersion, or intra-individual variability (IIV) of neurocognitive scores. Traditionally, IIV has been measured by either examining variability across multiple trials within a single task (most commonly reaction time), termed inconsistency, or by measuring variability across multiple tests scores within a single testing occasion, termed dispersion (Stuss et al., 2003).

IIV has been proposed to be a particularly relevant metric of cognitive compromise in HIV due to the fact that there may not be a "prototypical pattern" of cognitive impairment, and impairments can present across various cognitive domains (Hines et al., 2015; Woods et al., 2009). Since cognitive impairments can present in various domains while sparing others, examining the spread/variability of neurocognitive scores may be a more sensitive marker of impairment, relative to examining the average of all cognitive scores (mean-level global performance). Indeed, studies have shown IIV to be a stronger correlate, relative to mean-level neurocognitive performance, of important HIV-related factors such as medication adherence and peak immunological dysfunction (Ettenhofer et al., 2010; Thaler et al., 2015). However, only one study to date has examined the neuroanatomical correlates of IIV in HIV. A cross-sectional study of both HIV+ and seronegative (HIV−) participants showed that greater IIV was related to reduced cortical grey matter thickness, particularly within the frontal cortex (Hines et al., 2015).

A review of structural and functional neural correlates of IIV, in the context of aging and neurodegenerative disorders, suggested that IIV was strongly associated with frontal gray and white matter changes (MacDonald, Li & Backman, 2009). These authors proposed that increases in IIV are particularly related to frontal-subcortical dysfunction, as fluctuation in attention and self-monitoring may lead to variable performance across multiple cognitive measures. Additionally, a recent diffusion tensor imaging (DTI) study of community dwelling younger (18–30) and older (61–82) adults, showed that white matter integrity (as assessed by fractional anisotropy; FA) was more strongly related to variability than to mean level of cognitive performance (Mella, de Ribaupierre, Eagleson & de Ribaupierre, 2013).

Given how HIV appears to exercise a particular affinity for the same frontostriatal structures implicated in IIV, it is reasonable to hypothesize that alterations in IIV may be particularly prominent in HIV-infected individuals (Grant, 2008; Hardy & Vance, 2009; Woods et al., 2009). In fact, within the context of HIV, it has been proposed that increased IIV is a marker for frontal-subcortical dysfunction (Morgan et al., 2011).

It is important to recognize that a certain amount of variability in neuropsychological testing is normal (Schretlen et al., 2003). Therefore, at a single time point it may be difficult to determine the degree that dispersion of neuropsychological scores represents normal variability versus a marker of neurologic dysfunction. The majority of studies examining IIV among individuals with HIV have been limited to cross-sectional samples (Ettenhofer et al., 2010; Hines et al., 2015; Morgan et al., 2011), which complicates attempts to distinguish normal variability from pathological variability. One proposed solution is to examine changes in the dispersion of scores over time. By examining longitudinal changes in IIV, we are more likely to differentiate trait variability (i.e. variability due to a person's natural strengths and weaknesses) versus pathological variability (i.e. variability due to neurologic insult, which should become more variable as the insult worsens). If variability is reflective of a person's natural strengths and weaknesses, then we would expect IIV to be relatively stable over time. However, if IIV is due to a neurologic insult, then IIV should increase (i.e. become more variable) as the insult worsens, or possibly become less variable if neurologic compromise is alleviated. This approach has shown promise, as a recent study of older adults found that increases in neuropsychological dispersion scores over time were associated with increased risk for incident mild cognitive impairment and dementia (Vaughan et al., 2013).

The current study examined the longitudinal relationship between change in IIV and white matter integrity among HIV+ and HIV− adults. We hypothesized that if IIV is a marker for frontal-subcortical functioning, then increases in IIV over time (e.g. increased dispersion in neuropsychological performance) will be related to reduced white matter integrity; and given that disruption in frontal-subcortical circuits have been commonly observed in HIV (Grant, 2008; Woods et al., 2009), this relationship will be particularly robust among HIV+ individuals. Additionally, we predicted that white matter integrity would have a stronger relationship with IIV, relative to mean-level global performance.

METHODS

Study Design

The sample consisted of 38 HIV+ participants recruited from local HIV clinics in the Greater Los Angeles area and 26 HIV− participants who were recruited via flyers posted at local medical care clinics, advertisements on the internet, and participant referral of friends and/or family members.

The Institutional Review Board at UCLA approved the study and all participants provided written informed consent prior to all study activities. Exclusionary criteria included a history of seizure disorder or other neurologic disorder, history of traumatic brain injury sufficient to warrant medical attention, positive urine toxicology screen for stimulants or hallucinogens, current substance use disorder of stimulants, hallucinogens, opiates, sedatives (based on the Structured Clinical Interview for DSM-IV diagnostic criteria), past dependence on stimulants, current prescription for psychotropic medication (except for anxiolytics and antidepressants), comorbid CNS infection (e.g. Hepatitis C), HIV-associated CNS opportunistic infection (e.g. toxoplasmosis) or neoplasm, and MRI contraindications.

Neuropsychological Measures

All participants underwent comprehensive neurocognitive testing at baseline and follow-up assessment. The average length of time between testings was 23 months (standard deviation = 8 months; range = 7 – 37 months). Neuropsychological variables included the immediate recall total and delayed recall trial from the Hopkins Verbal Learning Test-Revised (HVLT-R) and the Brief Visuospatial Memory Test-Revised (BVMT-R), selected subtests of the Wechsler Adult Intelligence Scale-IV (WAIS-IV; symbol search, digit symbol coding, block design, letter-number sequencing), parts A and B of the Trail Making Test (TMT), the word reading and color-word interference trials of the Stroop test, the Controlled Oral Word Association Test (COWA), and a semantic/animal fluency test. All test scores were converted into T-scores based on test manuals and published norms (Heaton, 2004). WAIS-IV subtests were corrected for age only. A global cognitive composite score was computed by averaging the T-scores for all 14 neuropsychological test variables.

Neuropsychological dispersion was assessed by calculating each participant's IIV at each time point. Consistent with previous studies, IIV was calculated as the standard deviation (S) of the 14 neuropsychological scores for each individual at baseline, and separately at the follow-up evaluation (Thaler et al., 2015; Morgan et al., 2011; Hilborn et al., 2009).

$$\mathscr{S}=\sqrt{\frac{1}{N-1}\sum_{i=1}^{N}(x_i-\overline{x})^2}$$

The number of neuropsychological scores examined is generally consistent with the previous studies of IIV in HIV (Morgan et al., 2011; Thaler et al., 2015).

Statistical analyses examined change in IIV, calculated as the difference between the two time points (IIV at follow-up – IIV at baseline). Therefore, higher change values can be interpreted as an increase in the dispersion/variability of scores over time. Additionally, we computed the change in mean-level global cognitive functioning (mean-level cognition at follow-up – mean-level cognition at baseline). Higher values of change in global cognition can be interpreted as improved performance over time.

Neuroimaging Data Acquisition and Processing

All participants underwent neuroimaging at baseline and follow-up. All imaging data was collected within a week of the neuropsychological measures. DTI scans were collected using a 3T Siemens Trio scanner (Siemens, Germany) located at the UCLA Center for Cognitive Neuroscience (CCN). DTI scans were acquired in 64 directions, using single shot spin-echo planar imaging (EPI) with 60 × 2.0 mm axial slices (no gap), FOV = 190 mm (AP) × 190 mm (RL), matrix = 190 × 190, TR = 9000 ms, TE = 93 ms, voxel size = 2.0 × 2.0 × 2.0 mm, b-shells = 0, 1000, and time of acquisition was 7 min 16 s.

All imaging data was immediately inspected for artifacts and acquisition errors (e.g. ghosting) as soon as dicoms files were converted to niftii images. The DTI data was then corrected for motion artifact and eddy current distortion and the output images from these

corrections were again visually inspected. Next, each DTI image was skull stripped and both the brain mask and resulting skull stripped brain image were inspected for accuracy. Any brain masks which were either too inclusive of non-brain (e.g. skull) or too exclusive of brain (e.g. excluding frontal pole) were recreated by rerunning the skull stripping step with adjusted parameters. The resulting, rerun brain mask and skull stripped brain image were again visually inspected for accuracy. This process was rerun until all skull stripped images met quality assurance criteria (i.e. no skull was included and no brain tissue was excluded). Tensors were then fit to these skull stripped diffusion images and the final output images were again visually inspected. This was done by overlaying the primary eigenvector image (V1) onto the fractional anisotropy map (FA) in color so that the principal direction of diffusion throughout the brain could be visually checked to be sure that the final images were in line with what was expected anatomically (e.g. corpus callosum eigenvectors were interhemispheric; corticospinal tracts vectors were superior-to-inferior).

DTI data were processed using standard protocols via FSL software package (FMRIB software Library; www.fmrib.ox.ac.uk.fsl; Jenkinson and Smith, 2001; Smith, 2002). Each participant's FA map was registered to the John Hopkins University (JHU) atlas (Zhang et al., 2010; Mori et al., 2005). The JHU labels were used to extract the FA values for each region. To reduce the number of analyses, we only examined white matter in regions that have previously shown to be related to IIV (Mella et al., 2013). As such, we examined the following 8 regions: anterior thalamic radiation (ATR), cingulum bundle, uncinate fasciculus, forceps major, forceps minor, inferior fronto-occipital fasciculus (IFOF), inferior longitudinal fasciculus (ILF), and the superior longitudinal fasciculus (SLF). FA values in these regions were inspected for normality. FA values in the IFOF, ILF and uncinate fasciculus did not meet assumptions of normality (Kolmogorov-Smirnov $p < 0.05$, and/or skewness/kurtosis values > 2). FA values in these regions were Blom transformed, which resulted in normal distributions (all skewness and kurtosis values < 0.3; all Kolmogorov-Smirnov p values > 0.05; Blom, 1958). To reduce collinearity, residualized baseline regional FA values (residualized relative to the follow-up regional FA value) were computed. Additionally, the dependent variables (regional FA values at follow-up) were inspected for outliers (i.e., values greater or less than 3 SDs outside the mean; Jones et al., 2015). Like all outlier criteria, 3 SDs is arbitrary and was selected it to reduce the impact of only the most extremely implausible values (values beyond what we would expect from 99% of the population) so that the distributions could be left as unaltered as possible. Outliers were trimmed and set to closest allowable value (mean ± 3 SDs). Of note, outliers were only present for FA in the forceps minor and forceps major regions.

Statistical Analyses

Demographic factors (e.g. age, education) and clinical factors (e.g., past drug use) between HIV+ and HIV− groups were compared using one-way analysis of variance (ANOVA). Group differences in categorical factors (e.g. gender, race/ethnicity, urinalysis results) were assessed using chi-square analyses. We used $p < .05$ as our cutoff for statistical significance for these demographic analyses.

Hierarchical regressions were utilized to examine the relationship between neuropsychological dispersion and white matter integrity. Regional FA values at follow-up/time 2 were entered as the outcome/dependent variable for each regression. Three blocks of predictors/independent variables were entered. The first block of predictors was entered in stepwise fashion, so that variables were only entered if they statistically improved the model. The following variables were entered into the first block of predictors: age at baseline, gender, years of education and months between the pre-post evaluations. Regional (residualized) FA at baseline, the main effect of group (HIV+ versus HIV−) and change in mean-level global cognitive composite score were force-entered into the second block. Change in IIV and a Group X IIV interaction term was forced-entered into the third block.

Overall, a total of 8 regression analyses were conducted. Statistical significance adjusted with Benjamini-Hochberg false discovery rate (FDR) correction. Statistical significance was determined if the FDR adjusted p-value (i.e. q value) was <0.05.

RESULTS

Baseline sample and clinical characteristics are displayed in Table 1. At baseline, the HIV+ and control group did not statistically differ in terms of age, education, and FA in any region. There was a higher proportion of females in the control group relative to the HIV+ group. The HIV groups also did not differ on past or current alcohol abuse/dependence, past cocaine abuse/dependence, past stimulus abuse/dependence, past opioid abuse/dependence, past hallucinogen abuse/dependence, past sedative abuse/dependence, or current and past marijuana abuse (all p's > 0.05). More HIV+ participants reported past marijuana dependence than HIV− participants ($\chi^2 = 4.66$, $p = 0.031$), however individuals with and without a past history of marijuana dependence did not significantly differ in terms of IIV or FA in any region (all $p > 0.10$).

Consistent with previous studies, the HIV+ group had a wider dispersion of neuropsychological scores, relative to the HIV− group ($t(62) = 2.03$, $p = 0.047$, Cohen's $D = 0.53$), but there was no significant group difference in mean-level global cognition. Relative to males, females had lower FA values in the ILF at baseline ($t(62) = 2.85$, $p = 0.006$; Cohen's $D = 0.81$), but there were no gender differences in any other region (all p values >.05). Gender was not significantly correlated with change in mean-level global cognition or IIV. Change in global cognitive functioning and change in IIV were only mildly correlated with each other ($r = -0.241$, $p = 0.037$, $r^2 = 0.058$), meaning that as mean-level global cognitive functioning declines, there is an increase in dispersion/IIV. Diagnostic indicators of multi-collinearity suggested that multi-collineraity was not problematic among predictors (tolerance > .0.2 and variation inflation factor < 5). Urine toxicology screening for all participants were negative for barbiturates, cocaine, amphetamine, MDMA and phencyclidine.

Paired-samples t-tests were computed to examine change in FA over the two time points. In general, there was no significant evidence of decline in FA between the two time points (all p values > 0.05); however the was a trend for worsening of FA in the SLF (p=0.096). Specifically, SLF FA decreased by 2.23% over the two time points.

Neuropsychological Dispersion and White Matter Integrity Between HIV+ and HIV− Participants

We examined if changes in IIV was related to white matter integrity, and if this relationship differed among HIV+ and HIV− individuals. The overall model significantly predicted FA in the SLF ($F(6,57) = 5.04$, $p < .001$, $r^2 = .387$), ATR ($F(6,57) = 4.75$, $p = .004$, $r^2 = .329$), forceps minor ($F(6,57) = 3.07$, $p = .022$, $r^2 = .241$), and the cingulum bundle ($F(6,57) = 3.15$, $p = .022$, $r^2 = .249$).

Lower FA values in the SLF at follow-up were significantly related to older age, greater duration between evaluations, and the Group X IIV interaction (Table 2). Simple slope analyses of the Group X IIV interaction revealed that increases in IIV (i.e. greater dispersion over time) were related to lower SLF FA values for the HIV+ group ($\beta = -0.202$, $p = .007$), however there was no significant relationship between IIV and SLF FA for the HIV− group ($\beta = -0.100$, $p = .376$; Figure 1).

As mentioned above, the overall model significantly predicted FA in the ATR, forceps minor and cingulum bundle. However, FA in these regions was only significantly related to age, and FA was not significantly related to the main effect of IIV, the Group X IIV interaction or any other variable. Specifically, older individuals had lower FA values in the ATR ($\beta = -0.515$, $p < .001$), forceps minor ($\beta = -0.339$, $p = .048$), and the cingulum bundle ($\beta = -0.429$, $p = .006$).

DISCUSSION

The present study examined the relationship between changes in neuropsychological dispersion/IIV and white matter integrity in HIV+ and HIV− participants. Longitudinal increases in neuropsychological dispersion, but not mean-level global cognitive performance, were related to white matter integrity, particularly among HIV+ participants.

Findings from the current study are generally consistent with previous neuroimaging studies of IIV. A review of the neuroanatomical correlates of IIV in healthy and clinical populations concluded that IIV is robustly associated with frontal lobe functioning (MacDonald et al., 2009). Specifically, increased IIV was associated with smaller volumes of grey and white matter structures within the frontal lobes, as well as D2 dopamine receptor binding (which is presumed to facilitate responsiveness of neuronal networks) within cortical regions (e.g., anterior cingulate cortex and orbital frontal cortex) important for cognitive functioning, particularly aspects of executive functioning (MacDonald et al., 2009). Similarly, increases in IIV are hypothesized to be particularly related to executive dysfunction, as lapses in attention and self-monitoring may lead to variable performance across multiple cognitive measures (Bellgrove, Hester & Garavan, 2004).

To date, there have been relatively few studies examining IIV in HIV+ samples. However, the findings have been relatively consistent with studies of IIV in the general population in terms of the role of frontal-subcortical functioning. A previous study by members of our group examined the relationship between cortical atrophy and IIV in a cross-sectional subsample of HIV+ and HIV− individuals drawn from the Multicenter AIDS Cohort Study

(Hines et al., 2015). They found that greater dispersion of neuropsychological performance was related to thinning of grey matter in different regions of the frontal, temporal and parietal cortices, with the frontal cortex being particularly involved. Another study showed that IIV was related to the interaction of age and HIV status, with older HIV+ participants showing the greatest amount of dispersion (Morgan et al., 2011). They suggested that increased dispersion may indicate disruption of frontal-striatal circuits important for cognitive functioning. In the current study, we found IIV to be related to white matter integrity in the SLF. Our findings complement the previous studies highlighting the relationship between IIV and frontal-subcortical functioning. The SLF is involved in frontal-posterior cortical connections, and has been shown to be important in aspects of executive function. (Karlsgodt et al., 2008).

Two unique aspects of the current study are the use of a longitudinal sample and a HIV− control group. A previous study examining neuroanatomical correlates of IIV in a cross-sectional sample of HIV+ and HIV− participants failed to find a significant HIV status by IIV interaction (Hines et al., 2015). In other words, the relationship between IIV and cortical thickness was similar among HIV+ and HIV− participants. It is likely that their cross-sectional sample may have limited the ability to detect a significant interaction between HIV status and IIV in relating to neuroimaging outcomes. Furthermore, it is important to note that there was no significant difference in mean-level global cognitive functioning between the HIV+ and HIV− participants. Both groups were generally in the intact range, performing approximately 0.5 standard deviations below the mean in terms of global cognitive performance. On one hand, this suggests that the significant interaction between IIV and HIV status is not merely a functioning of different levels of cognitive functioning, but is related to an HIV-specific mechanism, such as frontal-subcortical dysfunction. However, it is also possible that the relationship between IIV, mean-level cognitive performance and white matter integrity may differ among HIV participants with more a more severe level of cognitive impairment.

Limitations were present in the current study. The relatively small sample size precluded examination of potential moderators (e.g. age, HIV severity) on the relationship between IIV and white matter integrity. Another limitation was that the calculation of IIV was based on neuropsychological T-scores that were computed from separate normative samples, with some tests corrected for age, and other tests corrected for age and other demographic factors. To the best of our knowledge, this has been a limitation of the majority of IIV studies in the HIV literature (Thaler et al., 2015; Morgan et al., 2011). Considering that IIV was examined as a change in dispersion of neuropsychological performance over time, and our use of an HIV− control sample, there is less concern that our findings are driven by differences in the normative samples used to calculate T-scores. Similarly, this study examined IIV as a function of “dispersion” between separate neuropsychological tests, as opposed to examining item “inconsistency” within a single cognitive test (such as variation in reaction times across multiple items of a single test, the approach employed by Ettenhofer et al., 2010). Although IIV can be measured multiple ways, previous studies have suggested that inconsistency and dispersion are correlated, and both metrics relate to meaningful outcomes such as age and cognitive decline (Hultsch et al., 2002; Hilborn et al., 2009). Separately, the current study was unable to determine the directionality of the relationship. In other words,

the degradation of white matter tracts may be causing increased dispersion of cognition functioning, or increases in IIV may predate white matter changes. It is important to note that in general, FA did not show evidence of significant decline over the two evaluation points, which may suggest that white matter changes predate worsening of IIV. This would be consistent with previous studies of white matter and cognitive functioning (Price et al., 2012; Silbert et al., 2012). Additionally, a longer time frame may have increased the ability to detect decline in FA, and may explain why some of the FA regions were not significantly related to changes in IIV or global cognition. Future longitudinal studies may also benefit by utilizing alternate forms of cognitive tests, in order to adjust for possible practice effects. While the current study provided support for the contention that IIV is related to white matter integrity, future longitudinal studies are needed to examine the utility of IIV as an early marker of HIV-associated dementia and other meaningful clinical markers.

Overall, this study provides support for the use of IIV as a marker of neurologic compromise. Specifically, IIV may be a more sensitive phenotype, relative to mean-level global cognitive functioning, of frontal-subcortical disruption among HIV+ individuals.

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Public Significance Statement

Cognitive impairment is a common complication of HIV infection. Studies of HIV-Associated Neurocognitive Disorder have typically focused on mean-level cognitive function. The current study provides support that intra-individual variability may be a more sensitive marker, relative to mean-level global cognitive functioning, of neurologic disruption among HIV+ individuals.

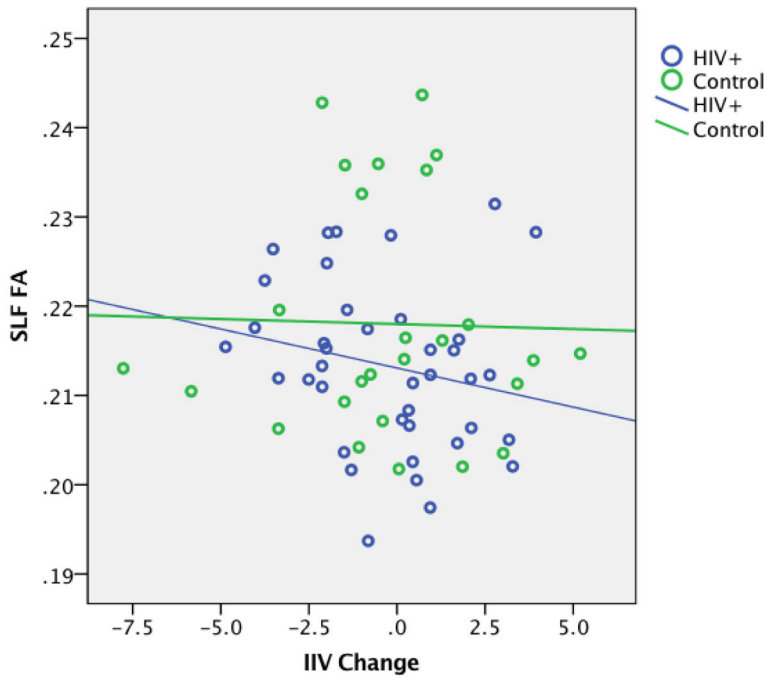

Figure 1.

Group by IIV Interaction. SLF = superior longitudinal fasciculus; FA = fractional anisotropy IIV= intra-individual variability.

Table 1

Mean Baseline Sample Characteristics

	HIV ***n*** **= 38**	**Control n = 26**	***t*/Mann-Whitney U**	**Cohen's *D***
Age	53.9 (9.3)	49.9 (14.0)	1.27	0.33
Years of education	13.3 (1.9)	14.1 (2.5)	1.33	0.36
% Female	14%	42%	361.0	0.42*
Absolute CD4 Count	588.1 (240)	-	-	-
Nadir CD4 Count	230.6 (172)	-	-	-
Peak Viral Load (log)	10.25 (3.38)	-	-	-
CNS Penetrance Efficiency of Current ARV Regimen	Median: 8.0 Range: 4 – 17		-	-
% with Current Major Depression	3%	0%	481.0	-
Global Cognitive Composite	44.7 (5.3)	45.3 (6.2)	0.42	0.10
Intraindividual Variability of Global Cognition	10.6 (2.7)	9.4 (2.2)	2.03	0.48*
Anterior Thalamic Radiations FA	0.21 (0.02)	0.21 (0.02)	0.13	0.34
Cingulum FA	0.20 (0.02)	0.19 (0.02)	1.32	0.34
Forceps Major FA	0.21 (0.02)	0.20 (0.02)	0.76	0.18
Forceps Minor FA	0.17 (0.04)	0.17 (0.04)	0.26	0.06
Inferior Fronto-Occipital Fasciculus FA	0.21 (0.02)	0.20 (.03)	1.27	0.31
Inferior Longitudinal Fasciculus FA	0.20 (0.02)	0.19 (0.03)	1.17	0.31
Superior Longitudinal Fasciculus FA	0.20 (0.03)	0.20 (0.03)	0.47	0.11

* $p<0.05$

Table 2

Results of Regression Analyses: IIV and White Matter Integrity in HIV+ Participants and Controls.

	FΔ	R^2Δ	Beta	Sig
SLF				
Overall Model	5.04	0.387		<0.001
Block 1	11.74	0.278		<0.000
Age			−0.349	0.016
Duration Between Evaluations			−0.318	0.016
Block 2	0.47	0.016		0.720
Block 3	4.22	0.092		0.020
HIV x IIV			0.293	0.016

Only significant predictors are shown; SLF = superior longitudinal fasciculus; IIV = intra-individual variability of neuropsychological performance.