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Cortical Brain Atrophy and Intra-Individual Variability in Neuropsychological Test Performance in HIV Disease

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Abstract

Objective—To characterize the relationship between dispersion-based intra-individual variability (IIV_d) in neuropsychological test performance and brain volume among HIV seropositive and

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Compliance with Ethical Standards:

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Informed consent: Informed consent was obtained from all individual participants included in the study.

Data Analysis: The data were analyzed by L.J. Hines, J.T. Becker and V. Maruca, with assistance from J. Sanders.

seronegative men and to determine the effects of cardiovascular risk and HIV infection on this relationship.

Methods—Magnetic Resonance Imaging (MRI) was used to acquire high-resolution neuroanatomic data from 147 men age 50 and over, including 80 HIV seropositive (HIV+) and 67 seronegative controls (HIV−) in this cross-sectional cohort study. Voxel Based Morphometry was used to derive volumetric measurements at the level of the individual voxel. These brain structure maps were analyzed using Statistical Parametric Mapping (SPM2). IIV_d was measured by computing intra-individual standard deviations (ISD's) from the standardized performance scores of five neuropsychological tests: Wechsler Memory Scale-III Visual Reproduction I and II, Logical Memory I and II, Wechsler Adult Intelligence Scale-III Letter Number Sequencing.

Results—Total gray matter (GM) volume was inversely associated with IIV_d. Among all subjects, IIV_d -related GM atrophy was observed primarily in: 1) the inferior frontal gyrus bilaterally, the left inferior temporal gyrus extending to the supramarginal gyrus, spanning the lateral sulcus; 2) the right superior parietal lobule and intraparietal sulcus; and, 3) dorsal/ventral regions of the posterior section of the transverse temporal gyrus. HIV status, biological, and cardiovascular disease (CVD) variables were not linked to IIV_d -related GM atrophy.

Conclusions—IIV_d in neuropsychological test performance may be a sensitive marker of cortical integrity in older adults, regardless of HIV infection status or CVD risk factors, and degree of intra-individual variability links with volume loss in specific cortical regions; independent of mean-level performance on neuropsychological tests.

Keywords

Imaging; Cognition; HIV; Voxel-Based Morphometry; Intra-Individual Variability

Introduction

Despite advances in treatment of HIV infection in the era of combination antiretroviral therapy (cART), cognitive impairments remain quite common (Brew 2004; Navia et al. 1986; Sacktor et al. 2001; Sacktor et al. 1999). These deficits, in turn, are associated with impairment in activities of daily living and functional independence (Heaton et al. 2004; Marcotte et al. 2004; Osowiecki et al. 2000). The relationship between neuropathological changes and cognitive decline among HIV-infected individuals has been well documented (Kieburtz et al. 1996; Thompson et al. 1996; Lin et al. 2005; Moore et al. 2006). Whereas early studies suggested HIV predominantly affected the basal ganglia and other subcortical regions, more recent findings suggest the pattern of neuropsychological deficits is changing with cART to include evidence of more cortical dysfunction (Becker et al. 2012c; Becker et al. 2009; Cysique et al. 2004; Everall et al. 2005; Hultsch et al. 2002; Kuper et al. 2011; Thompson et al. 2005). HIV status has a significant effect on grey matter volume, with atrophy in the posterior and anterior temporal lobes, the parietal lobes, and the cerebellum (Becker et al. 2012c). Age also has a significant effect on grey and white matter volume; age-related grey matter (GM) atrophy is primarily in the superior temporal and inferior frontal regions (Becker et al. 2012c). Cortical thinning in HIV disease has also been identified in primary sensory and motor cortices (Thompson et al. 2005), anterior cingulate

gyri, and the temporal lobe (Kuper et al. 2011). Prefrontal and parietal cortical thinning is correlated with neuropsychological impairment in AIDS patients (Thompson et al. 2005).

Recent studies have documented the relationship between cardiovascular risk factors occurring in older HIV+ patients (Becker et al. 2012c). Factors associated with age-related neuropsychiatric syndromes and neurodegenerative diseases such as cardiovascular disease, metabolic dysregulation, Alzheimer's disease, and subcortical small vessel ischemic disease have become increasingly important in understanding the etiology of neurocognitive dysfunction occurring in older HIV+ patients (Becker et al. 2012c; Becker et al. 2011; Becker et al. 2004).

The pattern of neuropsychological deficits in HIV disease has been described as variable, or "spotty" (Butters et al. 1990), with impairment reported across various cognitive domains, including memory, attention and working memory, language (fluency), psychomotor processing, and executive functioning (Woods et al. 2006; Dawes et al. 2008). Aside from relatively consistent deficits in psychomotor functioning, there does not appear to be a single "prototypical pattern" of neuropsychological impairment associated with HIV infection (Dawes et al., 2008), possibly due to the variable underlying neuropathology (Everall et al. 2005).

Recent studies have addressed the qualitative aspects of the neuropsychological profile of HIV infection by examining *within-person* variability in cognitive functioning, otherwise termed intra-individual dispersion (IIV_d) (Morgan et al. 2011; Morgan et al. 2012; Ettenhofer et al. 2010; Levine et al. 2008). While much neuropsychology research has focused on mean differences in performance across groups of individuals, IIV_d addresses within-person variations in performance (Hilborn et al. 2009; Holtzer et al. 2008; Schretlen et al. 2003; Rapp et al. 2005). Within-person differences in neuropsychological (NP) test performance have been observed across tasks at a single time point (dispersion), or on a single task across multiple time points (inconsistency) (Hultsch et al. 2002; Hultsch et al. 2000; Hilborn et al. 2009). In this study of IIV_d we examine *dispersion* in performance across neuropsychological tests administered in a single session in order to capture the variable pattern of performance in individuals with HIV disease. Prior studies examining IIV_d in HIV-infected individuals found greater dispersion in older HIV seropositive adults relative to older HIV negative and younger HIV positive individuals, irrespective of the mean level of performance and confounding demographic and medical variables (Morgan et al. 2011). Greater dispersion among HIV-infected older adults relative to HIV-infected younger adults was found to mirror the pattern of greater dispersion in advancing age in normal aging, implying a possible synergistic effect of HIV and age on expression of IIV_d (Morgan et al. 2012). Greater HIV-associated dispersion is associated with poorer medication adherence and decreased independence in basic and instrumental activities of daily living (Morgan, Woods, & Grant, 2012). In addition, greater IIV_d predicts future medication adherence, even after controlling for critical covariates (Thaler et al. 2015). Furthermore, reaction time variability (inconsistency) in HIV-infected individuals is significantly associated with poor medication adherence (Ettenhofer et al. 2010), and inconsistent medication adherence (Levine et al. 2008).

Increased IIV_d is also associated with early signs of longitudinal decline in cognition (Christensen et al. 1999; Hilborn et al. 2009), and is linked to genetic risk for dementia (Wetter et al. 2006). Patients with Alzheimer's disease or vascular dementia, and older adults with cognitive and functional decline have increased IIV_d (Anstey et al. 2007; Hilborn et al. 2009; Holtzer et al. 2008; Rapp et al. 2005). Even in the absence of any diagnosed condition, older age is associated with greater IIV_d (Christensen et al. 1999). As such, IIV_d may serve as a more sensitive measure of early cognitive changes than mean test performance, may antedate clinical cognitive decline in dementia, and may serve as an indicator of compromised neurologic mechanisms prior to functional changes (Christensen et al. 1999; Hilborn et al. 2009; Holtzer et al. 2008).

Although there are no studies of anatomical correlations with dispersion, the existing studies of *inconsistency* suggest that the frontal lobes are strongly associated with IIV_d. Greater inconsistency is linked to changes in frontal gray matter (GM), and white matter (WM) including atrophy, demyelination, and WM hyperintensities (West et al. 2002; Bunce et al. 2007; Stuss et al. 2003), although regional specificity is unclear. Greater inconsistency has been observed in persons with frontotemporal dementia compared to those with Alzheimer's disease, implying differential relevance of the frontal lobes versus the medial temporal lobe (Murtha et al. 2002). Individuals with circumscribed frontal lobe lesions have greater IIV_d than individuals with non-frontal lesions (Stuss et al. 2003). Lesions in the dorsolateral prefrontal cortex and in the superior medial frontal cortex were associated with the most pronounced variability.

Existing studies of inconsistency have suggested that IIV_d may be a marker of deficient attentional control (Stuss et al. 2003) and an index of the efficiency of the frontal cortex in maintaining executive control (Bellgrove et al. 2004). In older adults, *decreased* IIV_d has been linked to *increased* functional activation in the supramarginal gyrus, a structure implicated in sustained attention, deep semantic encoding, and memory retrieval success (MacDonald et al. 2008). While greater IIV_d may be related to alterations in structure/function in select anatomical regions of the brain, it may also reflect compromised regulation and coordination of brain functional networks (Kelly et al. 2008).

The aim of this study was to evaluate the relationship between brain structural integrity and IIV_d in a sample of older men (N = 147; age ~50 years) recruited from the Multicenter AIDS Cohort Study (MACS). We hypothesized that greater IIV_d would be associated with reduced frontal lobe grey matter volume, and that IIV_d-associated reduction in grey matter volume would be greater in individuals with HIV disease (i.e., an interaction). We further hypothesized that this reduction in GM volume would be related to age-associated cardiovascular risk factors. To address these aims, we assessed the relationship between IIV_d and gray matter volume in the HIV + group, and evaluated how any volume reductions might be related to specific clinical features.

Materials and Methods

Standard Protocol Approvals, Registrations, and Patient Consents

The ethical standards committees on human experimentation at each of the sites of the Multicenter AIDS Cohort Study (MACS) approved this study. Written informed consent was obtained from all participants prior to their undergoing research procedures.

Participants

The MACS is a 4-site study of the natural and treated history of HIV infection among gay and bisexual men. Study participants were enrolled in 3 waves: 1984/1985 (1,813 HIV+ and 3,141 HIV–), 1987/1990 (382 HIV+ and 286 HIV–), and 2001/2003 (688 HIV+ and 662 HIV–). The current study consisted of a subset of MACS participants age 50 years with no self-reported history of heart disease (heart attack, heart surgery, other heart illness) or cerebrovascular disease, and weight <300 pounds who completed detailed evaluations of cardiovascular disease (CVD) risk factors (Kingsley et al. 2008; Becker et al. 2014) as well as MRI scans (Becker et al. 2014; Becker et al., 2009). The CVD visit was completed between April 2004 and January 2006; MRI scanning took place in 2007 and 2008 (see additional information on MACS methods in Becker et al. 2014; Becker et al., 2009; and Kingsley et al. 2008). Each of the volunteers who were enrolled in the MRI study completed neuropsychological tests that conform to those described in the revised research criteria for HIV Associated Neurocognitive Disorder (HAND) (Antinori et al. 2007; Kingsley et al. 2008). Study-specific neuropsychological testing took place within three months of the date of the MRI scan (Becker et al., 2011).

The 147 men who were recruited into the MRI study were selected in terms of age, education and race (Caucasian vs. Other) in order to have equivalent values across HIV-groups (80 HIV+, 67 HIV–). 79% of the 80 infected men in this study met criteria for Acquired Immune Deficiency Syndrome. The mean peak viral load was $\log_{10}$ 4.57, with a nadir CD4+ cell count of 229.2. The average duration of infection was 19.9 years (range: 6.4 – 26.1). At the time of scanning, none of the infected men had detectable HIV RNA in plasma. Demographic characteristics of the subjects are shown in Table 1.

Neuropsychological Assessment

Each of the volunteers who were enrolled in this study completed study-specific neuropsychological testing that conformed to those described in the revised research criteria for HAND (Antinori et al. 2007). Variables from the standard battery of neuropsychological tests administered longitudinally in the MACS since 1991 (Miller et al. 1991) were not included in the study analysis so as not to introduce unknown effects of repeat assessment on construct validity (Martin and Hofer 2004; Allaire and Marsiske 2005).

We selected four memory performance variables (Wechsler Memory Scale-III Visual Reproduction I and II, Logical Memory I and II) and a measure of psychomotor speed and attention (Wechsler Adult Intelligence Scale-III Letter Number Sequencing) from the MRI study neuropsychological battery. These measures assess the pattern of neuropsychological deficits associated with cortical dysfunction in HIV Disease (Cysique et al. 2004; Thompson

et al. 2005; Becker et al. 2009; Kuper et al. 2011), and are relevant to the revised research criteria for HAND (Antinori et al. 2007). The number of tests included in the calculation of the dispersion variable (IIV_d) is similar to existing studies (e.g., Christensen et al. 1999; Hilborn et al. 2009; Holtzer et al. 2008; Rapp et al. 2005). Although other NP tests were available from the MRI study, we limited our selection to these five in order to ensure a common normative data sample, which reduces any influence of differing demographic corrections on study findings. Raw scores from the tests were transformed to standardized T-scores derived from published norms (David Wechsler 1987; D Wechsler 1997).

Two variables were created for the analyses. We calculated the mean and standard deviation of the T-scores for *each participant* based on the five tests (see above) similar to existing studies of IIV_d (Hilborn et al. 2009; Holtzer et al. 2008; Morgan et al. 2011; Morgan et al. 2012). The standard deviation, or IIV_d , reflects the degree of dispersion across the five performance variables for each individual, in which higher values refer to greater across-task variability, and smaller values reflect a flatter, more consistent profile of abilities. The mean score was used as a covariate in the analyses (Morgan et al. 2012; Schmiedek et al. 2009). The standard deviation was the measure of IIV_d , which was used both as an independent and a dependent variable.

Magnetic Resonance Imaging

The anatomical imaging sequence was developed by the Alzheimer's Disease Neuroimaging Initiative for use with 3T scanners (<http://www.adni-info.org/images/stories//mritrainingmanualv1.pdf>). The Magnetization Prepared Rapid Acquisition Gradient Echo (MP-RAGE) sequence was: FOV = 256 mm; slices=160; TR=2300 ms; TE=2.91ms; TI=900 ms; Flip angle=9 degrees; thickness=1.2mm.

The MRI data were first processed through a non-parametric non-uniform intensity normalization (Sled et al. 1998) to reduce between-scan and between-site differences in the images. This was followed by a bias correction (within SPM2) in order to help improve spatial registration.

We created a template image using a random subset ($n = 40$) of the HIV-negative control subjects, and estimated the prior probabilities of each tissue class (e.g., GM, WM, CSF) for use in the segmentation routines. All study images were first spatially normalized to the study-specific template. The normalized images were then segmented using a mixed model cluster analysis, which assigned each voxel a value reflective of a tissue type based on prior probabilities from the template. The segmented images were modulated by multiplying these files by the inverse of the Jacobian determinant of their spatial transformation matrix, yielding values related to tissue volume (as opposed to density). The resulting images were smoothed using a 10 mm isotropic Gaussian filter, rendering the data more normally distributed for use in the parametric statistical analysis of SPM2. We chose Voxel Based Morphometry (VBM) because it allows for an unbiased examination of the effects of interest (i.e., HIV and IIV_d) on brain structure. Other approaches, for example region-of-interest analyses, require that we select specific brain regions *a priori*, and we were not in a position to make such specific predictions about structure: function relationships. For a more complete description of the modulated VBM approach, see the discussions by Good,

Ashburner and colleagues (Ashburner and Friston 2000; Good et al. 2001). The initial processing of the scans was run as a semiautomated script in SPM2 (<http://dbm.neuro.uni-jena.de/vbm/vbm2-for-spm2>).

Modulated GM images were analyzed using SPM2 with subject group, IIV_d, mean performance, total intra-cranial volume and clinical site as subject-specific covariates. The default threshold for reporting statistical significance was set using a False Discovery Rate of $p < .05$ (Genovese et al. 2002), with an extent threshold of 100 voxels. Following the identification of the specific areas of IIV_d-related regional atrophy (having controlled for mean performance), eigenvariates were extracted from within SPM2 at the cluster level within the regions identified for the comparison of the normal subjects and the patients with HIV disease. The regions of significant differences were projected onto the template brain.

Cardiovascular Disease Evaluation

Subclinical CVD was assessed using electron beam tomography or Multidetector Computed Tomography to measure coronary artery calcium (CAC) and ultrasound examination of the carotid artery to measure carotid IMT, plaque and stiffness/distensibility. Laboratory measures included total cholesterol, low and high-density lipoproteins, glucose, insulin, glycosylated hemoglobin, and standardized blood pressure and heart rate measures. Glomerular filtration rate (GFR), a measure of kidney function, was estimated using a standard protocol. The CVD variables are shown in Table 1.

The CVD variables were reduced to categorical variables (present/absent, normal/abnormal) based on standard criteria or the distribution of values within the HIV- group. These included hypertension (resting BP >130/90, or self-report of HTN, or use of anti-hypertensive medications) and diabetes (self-report or use of anti-diabetic medications).

Demographic Variables

A Center for Epidemiological Studies Depression Scale (CES-D) (Radloff 1977) score was obtained from each subject, and those scoring above 16 were classified as “depressed” for the purpose of this analysis. Education was classified as High School or less, 13–15 years, and college or greater. We classified use of illicit drugs (crack, cocaine, uppers) as none, or any within the past 5 years (including current).

Statistical Analysis

Statistical analyses included the use of t-tests and chi-square analyses (as appropriate) for testing unadjusted associations. Multiple regression analyses were used to examine the relationships among the various predictor variables and whole brain measures of GM/WM/CSF as well as individual regional eigenvariates. A regression-based approach was used to assess the ways in which age-related biological and clinical variables alter the strength of, or explain the relationships between predictor (GM volume) and the criterion (IIV_d) variable.

Results

There are three main findings from this analysis. First, *total* volume of GM, WM, and CSF were significantly associated with IIV_d, indicating that increased variability was associated with abnormal brain structure. Second, among all subjects, IIV_d-related GM atrophy occurred primarily in three distinct cortical regions. Third, HIV status, biological, and CVD variables were not linked to IIV_d-related gray matter atrophy.

We completed three separate multiple regression analyses in which we regressed GM, WM, and CSF volume (expressed as a proportion of total intracranial volume) on age, metabolic variables, depression, drug use variables, mean test performance, and IIV_d. As can be seen in Table 2, IIV_d was consistently associated with total GM, WM, and CSF volumes, whereas HIV status was not. With regard to GM, other than IIV_d, only age was a significant predictor. With regard to WM, a range of variables predicted overall volume, including depression, abnormal triglycerides, abnormal low-density lipoproteins, abnormal total cholesterol, the presence of a metabolic syndrome, and elevated glucose. Finally, the volume of CSF, a nonspecific measure of brain atrophy (as it includes components from both the GM and WM compartments) revealed significant associations with age, total cholesterol, and IIV_d. It is of some interest that mean performance on the five neuropsychological measures was associated with smaller CSF volumes, i.e., a healthier brain was associated with better test performance.

Figure 1 shows the results of the VBM analysis of the relationship between IIV_d and GM (controlling for mean performance) projected onto the Colin27 template (Holmes et al.). There was no significant interaction between IIV_d and HIV group.

IIV_d-related GM atrophy is focused primarily in three distinct cortical regions, including the inferior frontal gyrus of both left and right hemispheres (Figure 1, a, b), with atrophy of the left inferior frontal gyrus extending to the supramarginal gyrus, spanning the lateral sulcus and dorsal/ventral regions of the posterior section of the transverse temporal gyrus (Figure 1, a); and the superior parietal lobule and intraparietal sulcus of the right hemisphere (Figure 1, c; the coordinates of the peak differences in these regions are shown in Table 3).

We regressed eigenvariates from the three cortical regions on age, race, education, HIV status, diabetes, and hypertension among all study participants; none of the effects were statistically significant (See Table 4). In an effort to understand predictors of IIV for the purpose of building hypotheses for future studies, we followed this analysis with a series of linear regression models to examine the relationships among total GM and WM volumes (adjusted for total intracranial volume (TIV)), IIV_d, age, HIV status and relevant covariates. We regressed IIV_d on all of the independent variables, and found that only WM and GM volumes were significant predictors ($p < .05$) (see Figure 2). We then regressed GM volume on WM volume, age, and HIV serostatus: only age and WM volume were related to GM atrophy (see also Raji, et al., 2012). Finally, HIV serostatus, but not age, was linked to total WM volume associated with IIV_d.

Discussion

These findings make several important points. First, greater IIV_d is associated with cortical atrophy, regardless of HIV status or CVD risk. Second, the degree of IIV_d is associated with the GM volume in specific cortical regions, and is independent of mean performance on the NP tests. Third, age and HIV serostatus may act independently on IIV_d through changes in GM and WM volume.

This is the first study to use structural imaging techniques to examine within-person, across-task IIV_d in neuropsychological test performance. Other studies have linked changes in IIV_d to various neurodegenerative conditions (Christensen et al. 1999; Hilborn et al. 2009; Holtzer et al. 2008), including HIV disease (Morgan et al. 2011; Morgan et al. 2012; Ettenhofer et al. 2010). The relationship between CNS integrity and within-person variability on measures of *reaction time* has been well established (Anstey et al. 2007; Sowell et al. 2003; Stuss et al. 2003); for a review see (MacDonald et al. 2009). Reaction time variability is associated with global cognition, medication adherence rates, and immunocompetence (current CD4+ cell count) in HIV-infected individuals (Ettenhofer et al. 2010). While there are a few studies of the anatomical basis of IIV_d abnormalities in reaction time, (Anstey et al. 2007; MacDonald et al. 2009), ours is the first to examine the underlying neural correlates of within-person, *across-task* IIV_d in neuropsychological test performance in HIV disease.

In the present study, greater whole brain GM volume was associated with less IIV_d, but total GM volume did not significantly differ between our HIV-infected and non-infected participants. These findings are consistent with prior studies indicating IIV_d is a non-specific marker of alterations in central nervous system structure and function rather than an indicator of a specific disease-related process (Kelly et al. 2008).

IIV_d was not significantly correlated with mean neuropsychological test performance ($r = -.069$; $p = .409$), suggesting that IIV_d measures a construct distinct from performance accuracy. Further, IIV_d was significantly associated with total GM volume ($\beta = -.38$, $p < .001$), whereas mean performance was not ($\beta = .20$), suggesting that IIV_d may be a more sensitive measure of early functional changes associated with GM atrophy than is overall test performance. We would predict, therefore, that over time the participants with greater IIV_d will be the most likely to show progressive decline in test performance and increased brain regional atrophy. Our findings are preliminary, and are limited because cross-sectional data cannot address progressive decline. Additional research will be necessary to determine how the severity of HAND, antiretroviral medication regimen and compliance, and CNS penetration of medications affect these findings (e.g., (Letendre et al.)). Additionally, our study population is comprised of a specific cohort of men >50 years of age. Age was not significantly associated with IIV_d, but was related to GM atrophy ($\beta = -.41$), and may have had a synergistic effect on the association between HIV on IIV_d (Morgan et al. 2011). Future studies employing neuroimaging in longitudinal and between (age) group analyses are necessary to obtain a greater understanding of the relationship between IIV_d, age, and brain structure.

The regression analyses (see Fig. 2) revealed important links between IIV_d and brain volumes that should stimulate further studies. We found that IIV_d was independently associated with the integrity of the GM and WM, and that age and HIV serostatus had only indirect impact on performance variability. Indeed, HIV status acted through two mechanisms – one due to its direct effects on WM volume, and the other an indirect effect on GM volume, mediated by the loss of WM. Since the earliest days of the HIV epidemic, white matter damage has been one of the hallmarks of the neuropathology (Budka 1991). Furthermore, WM volume can be affected by a range of non-HIV-related factors, including CVD (See Table 2); indeed, IIV_d is significantly linked to WM integrity (and the micro-structural level) in patients with relapsing-remitting multiple sclerosis (Mazerolle et al. 2013). Therefore, we predict that with a larger sample size, and perhaps with longitudinal data, we would be able to disentangle these non-HIV related effects from those related to the infection.

The regional GM atrophy associated with IIV_d included the superior parietal lobule and intraparietal sulcus of the right hemisphere, and inferior frontal regions of both the left and right hemispheres, with atrophy of the left hemisphere extending to the supramarginal gyrus and lateral sulcus (Figure 1). These areas differ from those related to HIV disease, which include the posterior and anterior temporal lobes, parietal lobes, cerebellum (Becker et al. 2011), bilateral primary sensory and motor cortices (Thompson (Thompson et al. 2005), anterior cingulate, and temporal cortices (Kuper et al. 2011). However, regions of IIV_d-associated GM atrophy are similar to the previously identified regions of age-related GM atrophy that indicated bilateral inferior frontal atrophy (Becker et al. 2012c).

Damage to frontal gray matter is associated with increased IIV_d, whether related to age or to disease. The critical regions include the right and left middle frontal gyri (Bellgrove et al. 2004), the dorsolateral prefrontal cortex, and the superior medial frontal cortex (Stuss et al. 2003). Our findings converge with these prior investigations with our finding of IIV_d-associated atrophy of the inferior frontal lobes. However, our study did not examine the relationship between IIV_d and performance on executive functioning measures (Hultsch et al. 2002; Morgan et al. 2012; Stuss et al. 2003). Future neuroimaging studies are needed to examine the relationship between IIV_d, neuroanatomical correlates of IIV_d, and their association with deficits in specific domains of cognitive functioning (e.g., executive functioning, attention).

IIV_d is likely mediated by executive functions with the result that increased IIV_d leads to reduced efficiency in sustaining cognitive control processes (Levine et al. 2008; Stuss et al. 2003; D Wechsler 1997). Interestingly, the posterior-cortical regions of IIV_d-associated decreased volume (including parietal regions; supramarginal gyrus) support research on existing models of neuroanatomical networks in attention and executive functioning (Fernandez-Duque and Posner 2001; Posner and Petersen 1990; Kelly et al. 2008).

IIV_d is not necessarily related to select anatomical regions of the brain, but may reflect compromised regulation and coordination of functional networks (Kelly et al. 2008). This is important because of the increasing evidence of the progressive breakdown in neuronal networks during the course of progressive neurodegenerative diseases (e.g., Zamrini et al.

2011). In the context of HIV disease, not only is it possible to identify HIV-infected individuals based on the pattern of neuronal networks, but also network abnormalities “normalize” in the face of effective antiretroviral therapy (Sacktor et al. 1999; Becker et al. 2012b; Cysique et al. 2004; Sacktor et al. 2001). Thus, the finding that IIV_d is not particularly well localized to an individual area of the brain relative to analyses of dispersion (Stuss et al. 2003) and inconsistency (Bellgrove et al. 2004) is not entirely unexpected; we found associations between IIV_d and brain structure across a wider area of brain regions. The frontal lobes generally appear to be critical for the maintenance of inter-test variability is not unexpected given the extensive inter-regional connections and the supervisory and modulatory roles played by frontal lobe systems on cognition and behavior (Becker et al. 2012b; Becker et al. 2012a). Thus, we can speculate that IIV_d may, in fact, be the cognitive manifestation of (at least the) early stages of breakdown of neuronal networks.

The present study has limitations that should be taken into consideration with regard to interpretation and directions for future investigation. First is in respect to the measurement properties of our dispersion variable. Unlike *inconsistency*, a comprehensive review of methodological and statistical approaches to computing the *dispersion* index is not available (MacDonald et al. 2009). Tests included in our computation of IIV_d assess attention, psychomotor speed, memory encoding, and memory retrieval, and are not representative of all domains of neuropsychological functioning. Future studies are needed to delineate the influence of cognitive domains assessed on outcomes of the current investigation and existing studies of dispersion. Second, we chose to limit tests included in our performance variable to those from a common normative data set, yielding five measures from two neuropsychological tests (Wechsler Memory Scale-III, Wechsler Adult Intelligence Scale-III). Demographic corrections that differ between tasks (ie, age only, or age and education; age, education, and race) yield variability across scores within a battery of neuropsychological tests for the purpose of *improving* utility and diagnostic accuracy in the clinical setting. In turn, greater dispersion results as a function of measurement properties rather than an indicator of cognition, cortical functioning, or neuroanatomical networks. Additional research is necessary to determine the influence of discrepant demographic corrections on generalizability and interpretation of extant and future investigations of dispersion. Third, our computation of IIV_d included five test scores. Existing studies examining dispersion in neurocognitive test performance have included from 3 to 14 tasks assessing a range of neuropsychological domains (Christensen et al. 1999; Hilborn et al. 2009; Holtzer et al. 2008; Lindenberger and Baltes 1997; Rapp et al. 2005), including HIV-specific investigations of dispersion across 12 neuropsychological tasks by Morgan and colleagues (Morgan et al. 2011; Morgan et al. 2012). The exact influence of number of measures included in the computation of the dispersion variable on interpretation and generalizability of dispersion remains unclear. Based on the central limit theorem, one would assume that as the number of tests included in the computation of a standard deviation (or IIV_d) increases, the skewness of the distribution will decrease and the distribution will become normalized (Ratcliff 1979); potentially diminishing the sensitivity of the construct. Conversely, limiting the number of test scores in the computation of IIV may influence the stability of the measurement construct, and thus generalizability of findings across investigations. Importantly, future studies are needed to clarify the relative

contributions of these measurement constructs on study outcomes and interpretation. Here, we chose to use a relatively simple index of dispersion based on demographically adjusted T-scores, in a cross-sectional study, in order to minimize the influence of those potential confounds on study findings.

While IIV_d has been identified in age-related neurodegenerative diseases, studies using structural/functional neuroimaging techniques combined with measures of IIV_d are needed to determine whether the specific regions of IIV_d-associated GM atrophy identified here are consistent across other diagnostic groups. These findings will facilitate an understanding of the neural underpinnings of IIV_d in neuropsychological test performance.

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Fig. 1.

Results of the VBM analysis of gray matter projected onto coronal, sagittal, and axial views of the Colin27 single-subject template of the cortical surface from SPM2. The effects of Intra-individual variability in all subjects are shown in three primary cortical regions, including the inferior frontal gyrus of both left and right hemispheres (a, b), with atrophy of the *left* inferior frontal gyrus extending to the supramarginal gyrus, spanning the lateral sulcus, and dorsal/ventral regions of the posterior section of the transverse temporal gyrus (a); and the superior parietal lobule and intraparietal sulcus of the right hemisphere (c). The analysis included both IIV_d and HIV status as independent variables, with total intra-cranial volume and mean neuropsychological test performance as covariates. False discovery rate= $p < .05$, with an extent threshold of 100 voxels

Fig. 2.

Results of regression-based analyses of the relationships among outcome and predictor variables. The numbers above the lines are the standardized regression coefficients from the individual analyses. These results show the mediation of GM and WM volumes (adjusted for TIV) significantly linked to intra-individual variability, including partial mediation of the effect of WM on intra-individual variability through GM. Greater WM volume was linked to greater GM volume, which itself was associated with intra-individual variability. HIV serostatus was uniquely and independently associated with WM volume, whereas age was associated with GM volume

Table 1

Subject characteristics

	HIV–	HIV+	Statistics ^a
<i>N</i>	67	80	
Age	60.81 (6.5)	59.57 (3.9)	1.38, –.11
Education	16.4 (2.3)	15.5 (2.5)	2.24, –.18 *
CES-D	9.82 (11)	8.70 (8.5)	.636, –.05
Race ^b	80.6 (54)	72.5 (58)	1.32, .095
Crack use ^c	16.4 (11)	22.5 (18)	.825, .076
Cocaine ^c	16.4 (11)	26.3 (21)	2.07, .119
Uppers ^c	7.5 (5)	16.3 (13)	2.62, .852
<i>Cardiovascular Health Variables</i>			
Hypertension ^d	42 (28)	43 (34)	.008, .007
Diabetes ^d	16 (11)	10 (8)	1.33, –.095
Systolic Blood Pressure	128.3 (16.8)	128.7 (13.3)	–.15, .01
Diastolic Blood Pressure	77.1 (10.4)	78.1 (9.2)	.619, .05
Total cholesterol	192.7 (39.2)	196.3 (54.7)	–.55, .04
High Density Lipoproteins	52.0 (15.2)	48.2 (15.7)	1.49, –.23
Low Density Lipoproteins	112.2 (34.9)	111.8 (33.9)	.07, –.006
Triglycerides	15.5 (15.4)	19.2 (25.5)	–.95 .09
Glucose	111.5 (62.8)	101.1 (18.4)	1.29, –.12
Hemoglobin A1C	5.99 (1.7)	5.53 (8.4)	2.01, –.17 *
<i>Neuropsychological summary variables</i>			
Intra-Individual Variability	2.27 (0.89)	2.17 (1.11)	0.59, –.05
Mean Performance	12.1 (2.2)	11.2 (2.4)	2.26, –.18 *
<i>Neuroimaging Variables</i>			
Gray Matter Volume ^e	40.8 (2.15)	40.5 (1.87)	–.88, .07
White Matter Volume ^e	25.41 (1.3)	26.00 (1.7)	–2.25, .18 *
Cerebrospinal Fluid Volume ^e	34.09 (2.7)	33.2 (3.0)	1.86, .15 *

^a *t* and *r* or χ^2 and Phi^b White/non-white (percent (*N*))^c Never/last 5 years (percent (*N*))^d Yes/no (percent (*N*))^e As of proportion of Total Intracranial Volume* $p < .05$

Table 2Results of Multiple Regression Analyses of Whole Brain Tissue Segments^{a,b}

	Gray Matter	White Matter	Cerebrospinal Fluid
Age	-.41		.40
IIV _d	-.38	-.35	.45
Mean Performance			-.23
HIV Disease	-.02	-.02	-.02
Depression		-.25	
Triglycerides		.23	
Low Density Lipoprotein		.33	
Total Cholesterol		-.43	.26
Fasting Glucose		-.30	
Metabolic Syndrome		-.38	
Stimulant Use		.21	

^aResults presented in standardized beta coefficients (β).^bAll effects, except HIV Disease, are significant ($p < .05$). Age, IIV_d, Mean Performance and HIV serostatus were all forced into the models in the first step. All other variables were entered in a forward stepwise method.

Table 3

Coordinates (in MNI space) of peak voxels in regions showing significant Gray Matter atrophy related to Intra-individual variability

Region	X	Y	Z	Peak Z
Left	-50	3	15	5.24
Right	17	-72	50	4.52
Parietal	57	24	16	3.97

Table 4

Standardized regression coefficients (β) for three cortical regions a, b, and c (see Figure 1)

	a	b	c
HIV Status	-.09	.02	-.08
Age	-.26 *	-.10	-.36 *
Education	.08	.02	.07
Race	-.25 *	-.30 *	-.20 *
Diabetes	-.06	-.04	-.15
Hypertension	-.05	-.10	-.02

*
p<.05