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Intraindividual Variability in HIV Infection: Evidence for Greater Neurocognitive Dispersion in Older HIV Seropositive Adults

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Abstract

Objective—Both the prevalence and incidence of HIV infection among older adults are on the rise. Older adults are at increased risk of HIV-associated neurocognitive disorders, which has historically been characterized as an inconsistent or "spotty" pattern of deficits. Dispersion is a form of intraindividual variability (IIV) that is defined as within-person variability in performance across domains and has been associated with poorer neurocognitive functioning and incipient decline among healthy older adults. To our knowledge, no studies have yet examined dispersion in an aging HIV-infected sample.

Methods—For the current study we examined the hypothesis that age and HIV infection have synergistic effects on dispersion across a battery of clinical and experimental cognitive tasks. Our well-characterized sample comprised 126 HIV-seropositive individuals (HIV+) and 40 HIV-seronegative comparison individuals (HIV−), all of whom were administered a comprehensive neuropsychological battery.

Results—Consistent with our hypothesis, an age by HIV serostatus interaction was observed, with the older HIV+ group demonstrating a higher level of dispersion relative to older HIV− and younger HIV+ individuals, even when potentially confounding demographic and medical factors were controlled.

Conclusion—Our results demonstrate that older HIV+ adults produce greater dispersion, or intraindividual variability in performance across a range of tests, which may be reflective of cognitive dyscontrol to which this population is vulnerable, perhaps driven by the combined effects of aging and HIV infection on prefrontostriatal systems.

Keywords

HIV; aging; neuropsychological assessment; variability

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INTRODUCTION

Over the past decade, two factors have primarily contributed to the growing proportion of HIV-seropositive individuals aged 50 and older, a group that currently accounts for more than a quarter of all HIV-infected individuals in the United States according to the Centers for Disease Control (CDC, 2009). Introduction of combined antiretroviral therapies (cART) in the mid-1990s has significantly decreased the mortality rates of individuals infected at younger ages, allowing them to survive longer into adulthood (CDC, 2007). In addition, the incidence of HIV infection in older adults has continued to rise (CDC, 2007). Although improvements in the treatment of medical aspects of HIV infection have enhanced physical health outcomes, the prevalence of HIV-associated neurocognitive disorders (HAND) remains high, affecting up to 50% of all HIV-infected individuals (Antinori et al., 2007; Heaton et al., 2010). Furthermore, increased age at seroconversion may be associated with greater risk for development of neurocognitive impairment (Bhaskaran et al., 2008). As the proliferation of older HIV-infected adults continues, the nature of the HIV epidemic may be evolving, particularly with regard to the expression of HAND.

Notably, older HIV-seropositive adults have been shown to be at increased risk for HAND, including the most severe form, HIV-associated dementia (HAD; Becker et al., 2004; Larussa et al., 2006; Valcour et al., 2004a; Valcour et al., 2004b). Evidence suggests that HIV-seropositive older adults are at particular risk for impairment in the domains of executive functioning, psychomotor speed, and episodic memory (e.g., Cherner et al., 2004; Sacktor et al., 2007; Sacktor et al., 2010; Woods et al., 2010). Conceptually, the higher rate of HAND among older adults may result from the increased impact of HIV and aging in combination on prefronto-striato-thalamo-cortical circuits and temporolimbic regions. Both HIV and aging preferentially affect these circuits independently (Burke & Barnes, 2006; Langford et al., 2005) and together may produce an additive or perhaps synergistic effect on their structure and function (e.g., Chang et al., 2004; c.f. Valcour et al., in press). Some have suggested that HIV-related CNS effects may increase the risk for clinical manifestation of neurodegenerative disorders such as Alzheimer's disease (AD) as HIV-infected individuals age (e.g., Brew et al., 2009), and although there is some evidence of increased neuropathological markers of AD among HIV-infected older adults, such as increased amyloid deposition (e.g, Achim et al., 2009), recent neurocognitive evidence does not support a shift to HAND being expressed with an AD-like presentation (Scott et al., in press). Alternatively, comorbidities of aging known to increase risk for cognitive impairment (Salthouse, 1996) may be predisposed or accelerated in the context of HIV infection, including cardiovascular disease (e.g., hypertension, hyperlipidemia), cerebrovascular events, and metabolic dysregulation (Magalhaes et al., 2007; McMurtray et al., 2007; Valcour et al., 2006). Consistent with this possibility, older HIV-seropositive adults have demonstrated psychomotor slowing and executive dysfunction associated with increased risk for subcortical small vessel ischemic disease (Sacktor et al., 2010; Prins et al., 2005) and hyperglycemia or increased carotid intima-media thickness (Becker et al., 2009).

Regardless of the underlying pathophysiologic mechanisms of the higher rate of HIV-associated neurocognitive impairment in older HIV-seropositive adults, its negative implications are considerable, particularly with regard to declines in daily functioning. Although some studies of older HIV-infected adults have shown intact functional status (e.g., medication management; Hinkin et al., 2004), particularly among those deemed to be "successful cognitive agers" (Malaspina et al., in press), risk for adverse functional outcomes among older HIV+ persons is strongly linked to neurocognitive status (Barclay et al., 2007). For example, older adults with HIV-associated neurocognitive impairment demonstrate lower adherence rates (Ettenhofer et al., 2009) and poorer medication management (Thames et al., 2010) relative to other age and serostatus comparison groups.

To date, examinations of the combined effects of HIV and aging have been exclusively conducted with paradigms using measures of central tendency, or average performance across groups. Increasingly, researchers in the cognitive aging literature have focused on outcomes based on variability within-persons, or intraindividual variability (IIV), which can be examined by measures of inconsistency, defined as performance by a single person on a single task across time (various intervals), or dispersion, reflecting the performance of a single person across multiple tasks on a single occasion (Hultsch, MacDonald, & Dixon, 2002; Hilborn, Strauss, Hultsch, & Hunter, 2009). Studies have repeatedly demonstrated increased inconsistency with advancing age, often reported with concomitant cognitive dysfunction (e.g., Burton, Strauss, Hultsch, Moll, & Hunter 2006; Hultsch et al., 2002; MacDonald, Hultch, & Dixon, 2003). Furthermore, increased IIV has been shown to be associated with genetic risk for dementia (Wetter et al., 2006) as well as a harbinger of decline in longitudinal studies of cognition (e.g., Christensen et al., 1999; Hilborn et al., 2010).

With respect to dispersion, examination of the profile of performances across measures is a common interpretive approach within neuropsychology because distinct prototypical patterns of neurocognitive dysfunction have been linked to specific disorders. It is also understood that neurologically intact individuals have relative strengths and weaknesses that manifest as some degree of variability across measures (Schretlen et al., 2003). Notably, a growing body of research has shown that dispersion increases with advancing age, typically defined as age 65 and over (Christensen et al., 1999; Hultsch et al., 2002; Hilborn et al., 2009), and increases in dispersion have been associated with poorer cognitive outcomes and greater decline over time (e.g., Christensen et al., 1999; Rapp et al., 2005). The preponderance of studies finding increased IIV, including dispersion, in the context of aging and/or neurological compromise suggests that level of dispersion may be an indicator of cognitive integrity (Hilborn et al., 2009), with some suggesting that greater variability may be a marker of underlying neuropathology (e.g., MacDonald, Li, & Backman, 2009; Wetter et al., 2006). Consistent with the robust findings of greater variability (across the types of IIV) with advancing age, increased IIV has been strongly associated with frontal systems dysfunction in neuroimaging studies, as evidenced by lesion studies of both frontal grey and white matter, and patterns of blood-oxygen level-dependent (BOLD) activation in frontal regions (see MacDonald et al., 2009 for a review).

IIV may be particularly relevant to HIV infection in which the pattern of HAND has historically been described as “spotty” or inconsistent across domains (Butters et al., 1990). For example, Dawes and colleagues (2008) used cluster analysis to compare the patterns of the emergent clusters to the prototypical neuropsychological profile, which is based on group averages, among a large HIV seropositive sample. Their analysis revealed six clusters, a finding suggestive of considerable variability in performance across domains among HIV-seropositive individuals and may be related to the variable neuropathologic presentation of HIV infection (e.g., Everall et al., 2009). Although to our knowledge dispersion has yet to be examined in older HIV-seropositive persons, increased IIV has been demonstrated among younger groups of HIV infected individuals in prior studies. In one study, an exploratory factor analysis conducted by Levine and colleagues (2008) to evaluate a model of attention in HIV infection revealed a latent cognitive factor primarily comprising variables related to performance over time on a single task, labeled “stabilize,” which included reaction time variability and response omissions and was separate from reaction time latency. A more recent study by Ettenhofer and colleagues (2010) showed significant associations between reaction time variability and poorer cognitive outcomes as well as levels of important HIV disease characteristics (e.g., lower current and nadir CD4 cell count). Notably, both studies showed that greater reaction time variability was uniquely and significantly related to poor medication adherence (i.e., as compared to reaction time latency, which did not show a

relationship to adherence in either study), suggesting that IIV may be a sensitive marker of HIV-associated neurocognitive deficits that, in turn, manifest as functional decline. Accordingly, dispersion, another type of IIV, warrants study in the context of aging with HIV infection given the robust association between increased IIV and poorer outcomes in aging among non-infected adults, as well as the variable nature of the presentation of HIV-associated neurocognitive impairment across domains.

The present study aimed to extend prior findings of increased IIV in HIV infection (as evidenced by inconsistency and heterogeneous patterns of performance) by investigating dispersion in relation to HIV serostatus and aging. Given that both factors have independent and potentially additive or synergistic neuropathologic effects on brain regions and cognitive functions, the primary hypothesis of the current study was that older HIV-seropositive adults would demonstrate higher levels of dispersion in cognitive performance relative to targeted comparison groups, including similarly-aged individuals in an older healthy comparison group and younger HIV-seropositive individuals.

METHOD

Participants

The total sample of 166 participants comprised 126 HIV-seropositive individuals (HIV+) and 40 HIV-seronegative comparison individuals (HIV-), all of whom were enrolled in a study funded by the National Institutes of Mental Health (NIMH) to study memory in HIV infection. For the parent study, HIV serostatus was determined by enzyme-linked immunosorbent assays and confirmed by a Western blot test, and individuals were excluded if they reported a history of conditions known to affect cognitive functioning, including neurological disorders (e.g., seizure disorders, closed head injuries with loss of consciousness greater than 15 minutes, stroke, non-HIV-associated dementias, and central nervous system neoplasms or opportunistic infections), severe psychiatric illnesses (e.g., psychotic disorders), and medical complications (e.g., advanced liver disease). Additional exclusion criteria for both the HIV− and HIV+ groups included meeting *Diagnostic and Statistical Manual-IV* (DSM-IV; American Psychiatric Association, 1994) criteria for substance abuse or dependence within 6 months of evaluation, screening positive for illicit drugs (other than cannabis) on a urine toxicology screen conducted on day of evaluation, and an estimated verbal IQ (VIQ) score below 70 on the Wechsler Test of Adult Reading (WTAR). For the current sub-study, individuals were also excluded if they met DSM-IV criteria for current Major Depressive Disorder (MDD) or Generalized Anxiety Disorder (GAD).

The demographic and psychiatric characteristics of the HIV+ and HIV− study samples are provided in Table 1. The samples were comparable with regard to age, years of education, proportion of Caucasian participants in the sample, and estimated VIQ, but there was a higher proportion of male participants in the HIV+ sample ($p < .0001$). The medical characteristics of the groups, including HIV disease and treatment variables, are displayed in Table 2.

A continuous age variable was used for the primary regression analysis, but for the purpose of planned *post hoc* comparisons the HIV+ and HIV− samples were divided into age groups based on a cutpoint of < 50 (younger) versus ≥ 50 (older) years of age. This age cutpoint is consistent with the guidelines recommended by the NIMH for neuroAIDS research given the characteristics of the HIV epidemic in the United Status (Centers for Disease Control and Prevention, 2007). The mean ages of the stratified HIV serostatus groups were as follows: HIV− Older ($n = 14$, $M = 56.4$, $SD = 6.9$); HIV+ Older ($n = 37$, $M = 54.1$, $SD = 4.64$); HIV− Younger ($n = 26$, $M = 36.4$, $SD = 9.5$); HIV+ Younger ($n = 89$, $M = 41.3$, $SD =$

5.34). Comparison of the younger and older groups within the HIV+ and HIV− samples revealed that the age groups were comparable with regard to demographic (excluding age) and psychiatric factors (*p*s > 0.05). Cardiovascular risk characteristics (i.e., proportion of individuals with hypertension, hypercholesterolemia, diabetes mellitus type II, or "vascular risk" defined as having any one of those conditions) were also comparable in both HIV serostatus samples, with the exception of significant differences observed between the HIV− younger and older groups on rate of hypertension (younger = 3.9%, older = 28.6%, $p = 0.04$). Within the HIV+ group, significant differences between the age groups were observed for several HIV disease characteristics, including the following among the older HIV+ individuals (displayed in Table 2): longer duration of infection ($p = 0.05$), lower nadir CD4 count ($p = 0.009$), higher proportion immunosuppressed ($p = 0.03$), and a higher rate of hepatitis C (HCV) co-infection ($p = 0.01$). The younger and older HIV+ groups were comparable with regard to other disease severity indices (i.e., current CD4, plasma and CSF viral load, and disease stage) and medication status, including antiretroviral therapy (ART) treatment regimen (i.e., combined, non-combined, no current treatment, and treatment naïve) and CNS penetration-effectiveness rank (CPE rank), which was included because poorer penetration of ART into the CNS has been shown to increase likelihood of continued viral replication in CSF, as evidenced by higher CSF viral load (Letendre et al., 2008).

PROCEDURE

Materials

All participants provided written, informed consent and completed comprehensive neuropsychological, psychiatric, and medical research evaluations that were administered as part of the larger investigation. For determination of relevant psychiatric diagnoses (i.e., current and lifetime MDD, GAD, and substance use disorders), participants were given the Composite International Diagnostic Interview (CIDI version 2.1; World Health Organization, 1998). Participants also completed the Profile of Mood States (POMS) questionnaire as a measure of current affective distress (McNair, Lorr, & Droppleman, 1981). The neuropsychological battery comprised standardized clinical and research tests, including the following: California Verbal Learning Test – 2nd Edition (CVLT-II; Delis, Kramer, Kaplan, & Ober, 2000), Logical Memory (LM) subtest of the Wechsler Memory Scales Third Edition (WMS-III; Psychological Corporation, 1997), Boston Qualitative Scoring System for the Rey-Osterreith Complex Figure Test (BQSS: Stern et al., 1999), Tower of London – Drexel (ToL; Culbertson & Zillmer, 2001), Trail Making Test (TMT; Reitan & Wolfson, 1985), Digit Span subtest of the Wechsler Adult Intelligence Scale – Third Edition (WAIS-III; Psychological Corporation, 1997), Self-Ordered Pointing Test (SOPT; Shimamura & Jurica, 1994; Morgan et al., 2009; Woods et al., 2010), Letter Fluency (letter C) and Animal Fluency (Benton, Hamsher, & Sivan 1994; Gladsjo et al., 1999), Action Fluency (Woods et al., 2005), Memory for Intentions Screening Test (MIST; Raskin, 2004; Woods et al., 2008), Boston Naming Test (BNT: Goodglass, Kaplan, & Barresi, 2001), Grooved Pegboard Test (GP: Klove, 1963), and the Wechsler Test of Adult Word Reading (WTAR; Psychological Corporation, 2001).

The primary criterion for the current study was an index of dispersion, or IIV, across cognitive domains in a single testing session. Calculation of the dispersion variable in the present study was undertaken using a procedure similar to that which has been employed in previous studies examining dispersion outcomes (e.g., Christensen et al., 1999; Hilborn et al., 2009). As in the case of these prior studies, standard summary measures from tests within each evaluated cognitive domain were selected for inclusion in the dispersion variable. The specific domains and the tests used in the present study were consistent with the recommendations provided in the recently updated nosology of HAND (Antinori et al., 2007). When multiple summary measures were available for a given test, measures were

selected based on their demonstrated sensitivity in HIV infection (i.e., HVLT-R and BVMT-R Learning, Grooved Pegboard Nondominant Hand Time; Carey et al., 2004). Raw scores from the measures of interest were converted into z-scores, and an intraindividual standard deviation (ISD) across the z-scores was computed. Although there is no standard number of indices that are typically computed into the dispersion variable, the total number included in the present dispersion variable was roughly comparable to prior published work (e.g., Christensen et al., 1999; Hilborn et al., 2009). Z-scores from the following 12 measures were included in the ISD to create the dispersion variable: CVLT-II Total Learning, LM-I, BQSS Presence Accuracy Immediate Summary; MIST Summary Score, ToL Total Moves, WAIS-III Digits Backward, SOPT Total Correct, BNT Total Correct, Grooved Pegboard Non-Dominant, and Total Correct for Letter, Animals, and Action Fluency trials. A high dispersion score indicated greater variability across measures in the battery, whereas a low dispersion score suggested that the individuals' scores were more consistent across measures. Some studies have used corrected measures of IIV that adjust for level of performance (e.g., mean-adjusted indices such as the coefficient of variation), but recent evidence suggests that such correction may complicate interpretation of results (e.g., Schmiedek, Lovden, & Lindenberger, 2009), and therefore the present study did not examine a mean-adjusted score. Furthermore, the methodological design of the current study established stratification on both the serostatus and age factors, allowing for appropriate *post hoc* comparison without correcting for mean performance, as well as inclusion of mean level of performance and/or global cognitive impairment status as a covariate in the regression models.

Data Analysis

Given that the Shapiro-Wilk *W* test indicated that the dispersion variable deviated from the normal distribution ($p = 0.001$), it was log-transformed (log10) to improve the normality of the distribution. Using multiple linear regression, HIV status, age group (< 50 versus ≥ 50 years of age), and their interaction were regressed on the log-transformed dispersion variable. Given that the HIV serostatus groups were not comparable with regard to sex (% male), it was also included as a predictor in the model to account for its influence. Targeted, planned group contrasts were conducted to examine the potential effect of HIV serostatus on dispersion within the younger age and older age groups (HIV+ Older versus HIV− Older and HIV+ Younger versus HIV− Younger), and to investigate potential differences in dispersion as a function of age within the HIV serostatus groups (HIV+ Younger versus HIV + Older and HIV− Younger versus HIV− Older).

RESULTS

As shown in Table 3, a significant HIV serostatus by age group interaction effect on dispersion was observed ($p = 0.03$). With the sample stratified by HIV serostatus, a significant association between age and dispersion was observed in the HIV+ group ($r = 0.21$, $p = 0.02$) but not in the HIV− group ($p > 0.10$). A planned comparison between the older serostatus groups revealed that the HIV+ older group had significantly higher dispersion scores ($M = -0.06$, $SD = 0.12$) relative to the HIV− older group ($M = -0.13$, $SD = 0.1$; *t-ratio* = 2.1, $p = 0.04$, Cohen's $d = 0.6$). Note that these groups were comparable with regard to demographic, psychiatric, and cardiovascular risk factors (ps > 0.05), and the small sample size of the HIV− older group (n = 14), though not ideal, increased risk for Type II rather than Type I error. In contrast, no significant difference in dispersion scores was observed as a function of HIV serostatus in the younger group (HIV− $M = -0.09$, $SD = 0.09$; HIV+ $M = -0.12$, $SD = 0.11$; *t-ratio* = −1.08, $p = 0.28$, Cohen's $d = 0.28$). These groups also differed with regard to age ($p = 0.001$) and sex (HIV− = 46.2% male; HIV+ = 91.0% male, $p < 0.001$), but simultaneous consideration of these factors with serostatus did

not alter the results. Within the HIV− sample, dispersion scores did not differ significantly as a function of age group (*t-ratio* = 1.33, $p = 0.19$, Cohen's $d = 0.42$), and these groups were demographically-comparable with the exception of the rate of current hypertension (younger=7.7%, older=35.7%, $p = 0.04$), consideration of which did not affect the findings. Notably, significant differences were observed between the younger and older age groups in the HIV+ sample (*t-ratio* = −2.78, $p = 0.006$, Cohen's $d = 0.53$). The younger and older HIV + groups were not comparable on some important HIV disease characteristics (i.e., duration of infection, nadir CD4) and rate of HCV co-infection (see Table 2), and therefore these factors were included in a simultaneous multiple regression model with the age group variable in order to evaluate whether age accounted for a significant amount of unique variance in the dispersion variable among HIV+ participants (i.e., only those characteristics that were not comparable between the groups were included in the model). As shown in Table 4, age group was the only significant predictor of dispersion in the HIV+ model ($p = 0.004$). The pattern of results did not change when proportion immunosuppressed (representing the proportion of the sample with a history of CD4 count < 200) was substituted for nadir CD4 in the model.

In addition to the above-detailed planned group comparisons, we also conducted several *post hoc* analyses to investigate whether consideration of several potentially relevant factors influenced our pattern of results. First, inclusion of mean performance or global neuropsychological impairment as a predictor in both regression models did not alter the significance of the predictors of interest (i.e., HIV serostatus by age interaction in the primary regression analysis, and age main effect in the HIV+ sample), although both metrics were significantly and independently associated with dispersion in our *post hoc* models (ps < 0.05). Second, although participants with current mood, anxiety, and substance use disorders were excluded, we evaluated whether a history of lifetime psychiatric diagnoses was associated with dispersion. There were no differences in dispersion as a function of any psychiatric diagnoses, and dispersion was not correlated with current affective distress (as measured by POMS Total Mood Disturbance).

DISCUSSION

Dispersion, a measure of intraindividual variability (IIV) across cognitive domains, has considerable potential as a sensitive and useful marker of cognitive integrity in aging HIV+ individuals given the known profile of "spotty" deficits that has been demonstrated in HIV (e.g., Dawes et al., 2008) and the well-established association between IIV and both impaired cognitive status and incipient cognitive decline in healthy older adults. Our findings revealed a significant interaction between HIV serostatus and on dispersion and, as expected, the older HIV+ group demonstrated the highest level of dispersion. In other words, individuals in the older HIV+ group showed the greatest degree of variability in performance across a range of cognitive tests as measured by intraindividual standard deviations (iSD) of those test scores. Importantly, dispersion is a novel outcome measure in the HIV population, and this finding supports the extension of its use from the cognitive aging literature to aging with HIV. These results also have potential implications regarding our understanding of the cognitive mechanisms of cognitive aging with HIV infection and may provide insight into the changing nature of the HIV epidemic in older adults with regard to the expression of HAND.

Planned contrasts revealed that the older HIV+ group demonstrated a significantly higher level of dispersion relative to the younger HIV+ group with a cutpoint of 50 years of age, which defines "older adults" within the context of HIV infection. These findings suggest that the observed greater dispersion among HIV+ older adults relative to HIV+ younger adults mirrors the robust association between increased IIV and advancing age in the

cognitive aging literature, with earlier onset. Another notable finding from the current study was the unique and significant association between age and dispersion in the HIV+ group even when HIV disease and medical cofactors on which the age groups were not comparable were included simultaneously in the model. Specifically, the older HIV+ group had longer duration of infection, lower nadir CD4 cell counts, and a higher proportion of individuals with comorbid HCV infection, all of which have been shown to be related to neurocognitive dysfunction in HIV+ individuals. The fact that the age effect on dispersion was not better explained by these factors is consistent with prior studies of the neurocognitive sequelae of HIV and aging in combination (Cherner et al., 2004; Sacktor et al., 2007; Woods et al., 2010), and suggests that an aspect of the aging process may be related to the increase in dispersion at older ages in the HIV+ group rather than simply to greater exposure to these factors. One factor that mitigates this possible conclusion is that our sample contained few older HIV+ individuals with short duration of infection (e.g., five years or less), meaning that our results may be influenced by survival bias. That is, given the fact that the older adults typically have a longer duration of infection, even after statistically controlling for the effects of infection duration in our model, we therefore cannot entirely rule out its contribution due to the restricted range in the older HIV+ group.

Although this is the first study to examine dispersion in relation to HIV infection and aging, prior studies demonstrating increased IIV (i.e., reaction time inconsistency) in HIV-seropositive individuals did not demonstrate an association between measures of IIV and age (Ettenhofer et al., 2010; Levine et al., 2008). Specifically, Ettenhofer and colleagues (2010) showed that greater reaction time variability was associated with cognitive dysfunction and HIV disease markers (current and nadir CD4 cell count, current and highest viral load), suggesting that reaction time variability is a measure that may be sensitive to HIV-associated neuropathology and neurocognitive decline, but this measure was not examined in relation to age, possibly due to the limited sample size of the study. Levine and colleagues (2008) did examine the relationship between their “stabilize” measure (a latent factor primarily representing reaction time variability) and age but found no significant association. This null finding may be related to the sample characteristics given that the average age of their sample was younger than our HIV+ sample (M = 40.9, SD = 7.*4 vs.* M = 45.1, SD = 7.8 respectively). Studies in healthy adults have reported that both forms of IIV, reaction time variability and dispersion, are elevated with advancing age, but perhaps the variable nature of the profile of HIV-associated neurocognitive dysfunction in older adults may be better detected with dispersion in early, milder stages. That is, aging may exacerbate the “spottiness” of the neurocognitive profile in individuals with HIV, and coupled with the fact that the presentation of such variability manifests in different profile patterns across individuals (e.g., Dawes et al., 2008), dispersion may better characterize this effect. Future studies should include both measures of IIV as well as both age groups in order to examine this question more fully.

Several possible explanations may underlie the identification of an age-related neurocognitive signal (i.e., dispersion) among HIV+ adults in their 50s that has typically been detected at much more advanced ages among healthy older adults. With the sample stratified by age group, a comparison across serostatus revealed that the HIV+ older group also showed significantly higher levels of dispersion relative to the HIV− older group, whereas the younger HIV+ and HIV− groups showed comparable levels of dispersion. That is, the majority of the individuals in the HIV− older group had not yet reached the age at which increased IIV has typically been observed in healthy older adults, which is typically 65 or 70 years of age in most studies, and the HIV+ sample showed increased dispersion at an earlier age (mean age of 54.1, SD = 4.6). Thus, one possibility is that accelerated aging underlies the observation of an earlier age effect on dispersion in HIV infected individuals. Notably, higher rates of aging-related comorbidities, such as hypertension, dyslipidemia,

and metabolic dysregulation, have also been observed at younger ages in HIV infection (Magalhaes et al., 2007; McMurtray et al., 2007; Valcour et al., 2006). Therefore, the neurovirulence of HIV infection, including direct viral neurotoxicity, neuroinflammation, and vasculopathy, coupled with earlier onset of comorbities of aging, which themselves have neurocognitive consequences, may result in a synergistic effect that manifests as cognitive symptoms (such as increased dispersion) at an earlier age in the context of HIV infection. The combined effects of aging and HIV-associated neuropathology likely converge on executive dysfunction given the observed preferential impact on frontal systems in aging with HIV infection in terms of fronto-striatal neuropathology (e.g., Langford et al., 2005) and neurocognitive findings observed on tests of executive functions (Cherner et al., 2004; Sacktor et al., 2007). Interestingly, increased IIV is purportedly related to a loss of executive control (e.g., West et al., 2002), the neural correlates of which have been associated with dysfunction in frontal cortex (MacDonald et al., 2009). HIV-associated executive dysfunction has been observed across age groups in HIV+ individuals as measured by individual test and domain scores (e.g., Reger et al., 2002), whereas degraded executive control expressed as increased variability across domains, or increased "spottiness" in the neurocognitive profile, was only apparent among HIV+ older adults. Therefore dispersion may represent a particular component of HIV-associated neurocognitive change that is expressed with aging. Nevertheless, without an external criterion of executive functioning, we cannot confidently rule out the possibility that the observed increase in dispersion was a function of deficits in basic attention or information processing speed.

Admittedly, interpretation of our findings as being related to accelerated aging is speculative based on the present study, and future work may address this hypothesis with consideration of important factors such as biomarkers, neuroimaging, and/or studies linking premortem neurocognitive findings to postmortem neuropathological examination. Indeed, although demonstration of aging effect on dispersion in HIV infection suggests that dispersion may be a particularly sensitive neurocognitive marker in aging with HIV infection, it is clearly not specific to HIV infection. Greater dispersion has been associated with other disorders such as Parkison's disease and dementia (Burton, et al., 2006; Hultsch, MacDonald, Hunter, Levy-Bencheton, & Strauss, 2000). Importantly, an alternative possibility that neuropathology related to chronic HIV infection in the CNS has lowered the threshold for behavioral manifestation of a neurodegenerative process cannot be entirely ruled out based on the results of the present study given that the older group did have greater exposure to HIV disease or other medical cofactors (i.e., HCV coinfection). The results of our cross-sectional study seem to suggest otherwise given that age effect in the HIV+ group was not better explained by these factors, but a longitudinal study design would be better suited to address this question.

There are limitations in the present study that temper the interpretation of our findings and suggest directions for future work. Our HIV− comparison sample had too few older adults as defined by the cognitive aging literature (i.e., aged 65 years and over) to demonstrate the age effect on dispersion in our study. Although there is ample evidence from the literature to support the inference that dispersion increases in the traditional older adult group (e.g., Christensen et al., 1999; Hilborn et al., 2010), future studies examining the effect of aging with HIV infection on dispersion should include this group so that the specific dispersion measure can be validated. Importantly, future studies could clarify the relative contributions of aging and duration of infection by including older HIV+ adults with shorter duration of infection, a group that is purportedly growing as the incidence of HIV infection increases in adults over the age of 50. Additionally, the current study is cross-sectional in nature, and demonstration of the association between dispersion and neurocognitive decline over time in HIV infection would strengthen the evidence in favor of the use of dispersion as a marker of

cognitive integrity and possibly its potential as a sensitive early indicator of underlying neuropathological changes that may not yet be detected by standard screening measures and/or examination of mean levels of performance on clinical measures. Such evidence would extend the findings of prior studies that have demonstrated increased IIV among HIV− individuals with advancing age in longitudinal studies (e.g., Christensen et al., 1999; Hilborn et al., 2010) and enhance the clinical utility of the use of dispersion for detection and predictor of individuals at risk for decline. Additional study of dispersion in HIV infection would also serve to clarify the ranges of variability in dispersion, given that some degree of 'normal' variability is expected and more information is required in order to delineate normal from abnormal levels of variability across age (e.g., Hilborn et al., 2009; Schretlen et al., 2008). Increased inconsistency was significantly associated with poorer medication adherence in the study by Ettenhofer and colleagues (2010), and therefore examination of the relationship between dispersion and instrumental activities of daily living (e.g., shopping, driving) are warranted and, if demonstrated, would also increase the clinical utility of the measure in terms of enhancing identification those at risk for future functional decline.

The present study did not include neuroimaging or neural biomarker data and therefore conclusions regarding neural correlates in the current study are necessarily inferential. An important direction of future study is examination of dispersion in HIV infection in relation to CNS biomarkers that have been predictive of HAND and cognitive dysfunction in HIV such as traditional neuroAIDS biomarkers such as monocyte chemoattractant protein-1 (MCP-1) in comparison to traditional cortical dementia markers such as CSF amyloid beta and tau (Clifford et al., 2009), as well as markers of glial activation and neuronal integrity (e.g., Ernst et al., 2004). Furthermore, examination of neuroimaging in older adults with HIV infection might reveal associations with frontal structural and metabolic abnormalities, particularly those that could shed light on the relationship with comorbidites of aging, such as cerebrovascular disease (e.g., Bunce et al., 2007).

In summary, the results of this study revealed increased levels of dispersion (i.e., increased intraindividual variability in performance across neurocognitive domains) among older HIV + adults, which may be related to dysfunction in executive control. This hypothesis is consistent with the possibility of additive, and potentially synergistic, effects of combined HIV infection and aging on frontal systems functioning, and therefore dispersion demonstrates promise as an potential early marker of cognitive integrity in this population even at the relatively younger ages that define "older" adults in HIV. Based on its robust association with clinical diagnoses and aging, as well as the nature of the presentation of HIV-associated neurocognitive deficits, continued investigation is warranted, and directions of future work include evaluation of associations between dispersion and prediction of current and incipient expression of HAND, structural and functional neural correlates of dispersion, as well as prediction of functional outcomes.

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Table 1

Demographic and Psychiatric Characteristics of the Study Participants

Variable	HIV− (*n* = 40)	HIV+ (*n* = 126)	*p*
Demographic Characteristics			
Age (years)	43.4 (2.1)	45.1 (7.8)	0.32
Education (years)	14.5 (1.9)	14.2 (2.4)	0.51
Sex (% male)	52.5	88.9	<0.0001
Ethnicity (% Caucasian)	52.5	60.3	0.38
Estimated verbal IQ [a]	105.3 (11.1)	105 (11.9)	0.91
Psychiatric Characteristics [b]			
Lifetime Major Depressive Disorder (%)	32.5	48.4	0.07
Lifetime Generalized Anxiety Disorder (%)	5.0	5.6	0.89
Lifetime Substance Use Disorders			
Alcohol dependence	22.5	33.3	0.20
Methamphetamine dependence	17.5	23.8	0.40
Cannabis dependence	7.5	10.3	0.60
Opioid dependence	0.0	3.2	0.57
Cocaine dependence	10.0	20.6	0.13
Other substance dependence [c]	5.0	6.3	0.75

Note.

[a] Based on the WTAR Verbal IQ Estimate;

[b] based on Fisher's Exact Test;

[c] other substance dependence = hallucinogens, inhalants, and sedatives

Table 2

HIV Disease Characteristics and Medical Comorbidities in the HIV+ Sample (n=126)

Variable	Total HIV+ (n=126)	Younger HIV+ (n=89)	Older HIV+ (n=37)	*p*
HIV Disease Characteristics				
HIV Infection Duration (years)[a,e]	15 [7, 21]	12 [6, 20]	17 [9, 21]	0.05
Current CD4 (cells/ml)[b,e]	535 [326, 779]	547 [357, 814]	448 [226, 660]	0.07
Nadir CD4 (cells/ml)	140 [42, 302]	199 [54, 350]	70 [28, 204]	0.009
Plasma HIV RNA (log_{10})[b,e]	2 [2, 2]	2 [2, 2]	2 [2, 2]	0.47
CSF HIV RNA (log_{10})[c,e]	2 [2, 2]	2 [2, 2]	2 [2, 2]	0.71
Disease Stage				
AIDS (%)	60.3	55.1	73.0	0.06
CDC A	42.1	44.9	35.1	
CDC B	23.8	25.8	18.9	
CDC C	34.1	29.2	46.0	
Immunosuppressed (%)	57.9	51.7	73.0	0.03
Medication Status				0.75
cART (%)	82.5	82	83.8	
Non-cART ART (%)	1.6	1.1	2.7	
No Current ART	10.3	10.1	10.8	
ART Naïve (%)	5.6	6.7	2.7	
CPE Rank[d,e]	1.5 [1, 2]	1.5 [1, 2]	1.5 [1, 2]	0.83
Medical Comorbidities				
Hepatitis C Co-infection (%)[b]	12.6	8.1	24.3	0.02
Vascular Risk (%)[f]	17.5	14.6	24.3	0.21
Hypertension (%)[g]	11.9	11.2	13.5	0.77
Hypercholesterolemia (%)[g]	4.0	3.4	5.4	0.63
Diabetes Mellitus Type II (%)[g]	4.0	2.3	8.1	0.15

Note: p-values based on chi-square or Fisher's exact test and Wilcoxon rank sums test for between-group differences; Immunosuppressed = nadir CD4 < 200; cART = combined antiretroviral therapy; CPE Rank = CNS Penetration-Effectiveness Rank;

a–d data were available only for a subset of the total HIV+ sample, as follows:

a n=121,

b n=124,

c n=88;

d n = 106;

e data presented as medians and interquartile ranges (IQR);

f vascular risk was defined as having one or more of the cardiovascular conditions listed above percentages;

g percentages reflect those with current diagnosis

Table 3

Predictors of Dispersion in the Total Sample (N=166)

Variable	Model	Parameter (*B*)	*p*-value
Adjusted R^2	0.04		
F	2.66		0.03
Sex		0.14	0.10
HIV Status		−0.08	0.31
Age		0.07	0.35
HIV Status*Age Group		−0.17	0.03

Table 4

Predictors of Dispersion in the HIV-Seropositive Sample (n=119)[1]

Variable	Model	Parameter (*B*)	*p*-value
Adjusted R^2	0.08		
F	3.56		0.009
Age Group [Older][2]		0.27	0.004
Nadir CD4		0.03	0.73
Infection Duration (Years)		0.17	0.08
HCV Serostatus [Negative]		0.02	0.81

Note:

[1] Sample was limited to n = 119 due to unavailability of HCV serostatus and/or infection duration data for 7 participants;

[2] Age groups based on cutpoint of < 50 years = younger and ≥ 50 years = older