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Intra-individual Neurocognitive Variability Confers Risk of Dependence in Activities of Daily Living among HIV-Seropositive Individuals without HIV-Associated Neurocognitive Disorders

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Abstract

Although HIV-associated neurocognitive disorders (HAND) are the strong predictors of everyday functioning difficulties, approximately half of all functionally impaired individuals are labeled "neurocognitively normal" according to the standard neuropsychological measures, suggesting that novel predictors of functional problems in this prevalent subgroup are needed. The present study hypothesized that increased neurocognitive intra-individual variability as indexed by dispersion would be associated with poor daily functioning among 82 persons with HIV infection who did not meet research criteria for HAND. An intra-individual standard deviation was calculated across the demographically adjusted *T*-scores of 13 standard neuropsychological tests to represent dispersion, and functional outcomes included self-reported declines in basic and instrumental activities of daily functioning (basic activity of daily living [BADL] and instrumental activity of daily living [IADL], respectively) and medication management. Dispersion was a significant predictor of medication adherence and dependence in both BADL and IADL, even when other known predictors of functional status (i.e., age, affective distress, and indices of disease severity) were included in the models. As a significant and unique predictor of a performance on the range of daily functioning activities, neurocognitive dispersion may be indicative of deficient cognitive control expressed as inefficient regulation of neurocognitive resources in the context of competing functional demands. As such, dispersion may have clinical utility in detecting risk for functional problems among HIV-infected individuals without HAND.

Keywords: HIV; Everyday functioning; Neuropsychological assessment; Variability; AIDS dementia complex; Treatment compliance

Introduction

Declines in numerous aspects of everyday functioning are common among persons living with HIV infection. Although the magnitude and impact of such declines ranges from very mild to severe, approximately 50% of HIV-infected individuals qualify for social security disability benefits according to the Centers for Disease Control and Prevention (Centers for Disease Control, 2009). Prevalence estimates of daily living dysfunction among HIV-seropositive adults vary across functional domains; for example, approximately one-third experience broad declines in instrumental activities of daily living (IADLs; Woods, Iudicello, et al., 2008), as many as half are non-adherent to their antiretroviral regimens (Hinkin et al., 2004), and nearly two thirds are unemployed (Centers for Disease Control, 2009). Considering the notable psychosocial and fiscal impact of everyday functioning declines, there have been concerted research efforts over the past 25 years to identify salient, potentially modifiable clinical indicators of HIV-associated disability. To date, some of the most reliable predictors of everyday functioning difficulties include demographics (e.g., age; Hinkin et al., 2004), mood (e.g., depression; Rabkin, McElhiney, Ferrando, van Gorp, & Lin, 2004), substance dependence (e.g., Hinkin et al., 2007), and disease factors (e.g., Cysique, Murray, Dunbar, Jeyakuman, & Brew, 2010).

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Moreover, a substantial body of literature indicates that HIV-associated neurocognitive disorders (HANDs) are a significant risk factor for everyday functioning declines (*see* Gorman, Foley, Ettenhofer, Hinkin, & van Gorp, 2009, for a review). Specifically, up to half of those individuals who experience problems with daily functioning evidence impairment on standardized neuropsychological testing (e.g., Heaton et al., 2004), particularly in the domains of episodic memory (e.g., Woods, Iudicello, et al., 2008), executive functions (e.g., Hinkin et al., 2002), and information processing speed (e.g., Heaton et al., 2004). HAND is associated with dysfunction in a range of important activities of daily living, including medication management (e.g., Hinkin et al., 2002), vocational performance (van Gorp et al., 2007), automobile driving (e.g., Marcotte et al., 1999), and typical everyday activities such as managing finances, shopping, and cooking (e.g., Heaton et al., 2004). Importantly, the association between HAND and functional disability is largely independent of other established predictors, such as demographics, affective distress, substance use, HIV disease severity, and neuromedical comorbidities (e.g., Woods et al., 2009).

Despite the robust association between HAND and everyday functioning difficulties, the exclusive consideration of HAND tells only half the disability story. That is, approximately 50% of individuals with HIV-associated functional problems perform within normal limits on well-validated, comprehensive standardized neurocognitive test batteries (e.g., Heaton et al., 2004). Moreover, many of these individuals attribute their functional difficulties, at least in part, to neurocognitive problems (Woods, Iudicello, et al., 2008). Thus, although HAND is a relevant and significant predictor of functional outcomes in many cases, its utility is limited by the relatively large proportion of individuals without who nevertheless experience problems with functioning in their daily lives (e.g., Burgess, Alderman, Evans, Emslie, & Wilson, 1998; Scott et al., 2010). Although a variety of factors may account for the restricted sensitivity of HAND (e.g., presence of depression, limited psychosocial supports), it is also possible that some "neurocognitively normal" individuals may actually be experiencing neurocognitive deficits that are not fully captured by traditional assessment methods. For example, traditional methods for summarizing neurocognitive performance necessarily rely on the measurement of the average level of performance across a battery of tests, which informs cutpoints for the determination of impairment. In fact, one frequently used and well-validated method for quantifying general cognitive functioning, labeled the global deficit score (GDS; Carey et al., 2004), deliberately minimizes variability within the normal range, and instead weights impaired scores in an effort to maximize sensitivity. In contrast, a neurocognitive summary measure that is not based on the mean level of performance may help to identify individuals who are experiencing problems with daily living regardless of their global impairment status.

Intra-individual variability (IIV) is an index of performance variability within persons. Unlike measures of central tendency (i.e., average performance across groups), IIV treats variability evidenced by a single person across time or across tasks (i.e., cognitive domains) as an important signal. Given the diverse range of populations in which higher levels of IIV have been associated with cognitive deficits, elevated IIV has been proposed to be a behavioral maker of underlying neural alterations (*see* McDonald, Li, & Backman, 2009, for a review). More specifically, higher IIV has been linked to the integrity of frontal systems as evidenced by its associations with executive dysfunction (Bellgrove Hester, & Garavan, 2004; Strauss, Bielak, Bunce, Hunter, & Hultsch, 2007; West, Murphy, Armillo, Craik, & Stuss, 2002), frontal gray and white matter lesions (e.g., Bunce et al., 2007; Stuss, Murphy, Binns, & Alexander, 2003), and increased frontal activation during task performance (Bellgrove et al., 2004). These findings suggest that increased IIV may be a marker of underlying neuropathology that manifests behaviorally as diminished cognitive control, an aspect of executive functions that likely reflects the failure of top-down processes responsible for sustained regulation and allocation of cognitive resources (e.g., attention) across trials or across a battery of neuropsychological tests (McDonald et al., 2009).

Dispersion, a specific type of IIV, reflects variability in performance by a single person across multiple tasks representing different cognitive domains. Although there is little direct evidence regarding the neural correlates of dispersion specifically, dispersion and inconsistency (i.e., within-person variability across trials of a single task) have been shown to be positively correlated (Hultsch, MacDonald, & Dixon, 2002). Thus, cognitive (i.e., executive) dyscontrol may result in variable performance across tasks representing different cognitive domains in a similar manner to variable performance from trial to trial of the same task. Some degree of variability across domains is expected even among healthy individuals (Schretlen, Munro, Anthony, & Pearlson, 2003), but a burgeoning line of research shows that advancing age (viz., typically 65 years of age and over) is related to increases in dispersion (Christensen et al., 1999; Hilborn, Strauss, Hultsch, & Hunter, 2009; Hultsch et al., 2002), which in turn are associated with poorer cognitive outcomes and incident decline over time (e.g., Christensen et al., 1999; Rapp, Schnaider-Beeri, Sano, Silverman, & Haroutunian, 2005).

Dispersion may be particularly sensitive to HAND in which the pattern of deficits has long been described as variable across domains, or "spotty" (Butters et al., 1990), possibly due to the variable neuropathologic presentation of HIV infection (e.g., Everall, Hansen, & Masliah, 2009). A recent study revealed a syngergistic effect of HIV status and age on dispersion such that older HIV-seropositive adults showed higher levels of dispersion relative to older HIV and younger HIV+ individuals irrespective of the mean level of performance, even after potentially confounding demographic and medical factors were

controlled (Morgan, Woods, Delano-Wood, Bondi, & Grant, 2011). Two other studies have examined intra-individual inconsistency across trials of a single reaction time test in HIV. Levine and colleagues (2008) showed that inconsistency is a unique index that provides separate information from reaction time latency. More recently, Ettenhofer and colleagues (2009) demonstrated that increased inconsistency was significantly, negatively associated with cognitive outcomes and indices of immune functioning (e.g., lower current and nadir CD4 cell count). Importantly, both studies observed that greater reaction time variability (but not latency) was uniquely and significantly related to poor medication adherence (Ettenhofer et al., 2009; Levine et al., 2008). This combined evidence suggests that IIV may be a sensitive marker of neurocognitive changes in HIV that manifest as IADL dysfunction, possibly even among subsyndromal individuals (Morgan et al., 2011).

To our knowledge, dispersion has not yet been studied in relation to functional outcomes in HIV (or in any other population for that matter). Of particular interest, dispersion may capture HIV-related cognitive alterations that are not measured by traditional neuropsychological assessment methods and therefore dispersion may demonstrate robust sensitivity for the detection of functional problems. This is an especially intriguing idea, since daily functioning difficulties are observed among some individuals who would otherwise not meet criteria for HAND. In other words, one might reasonably expect that cognitive changes (i.e., cognitive dyscontrol expressed as dispersion) underlying these early daily functioning problems in HIV-infected individuals may be a harbinger of future cognitive and functional declines. This hypothesis draws from data showing an increased risk for conversion to dementia among older adults with mild cognitive impairment who also evidence difficulty with complex IADLs (e.g., Nygard, 2003; Perneczky et al., 2006). Furthermore, failure to identify early functional difficulties may be particularly problematic in clinical populations, including HIV infection, in which daily functioning demands and implications for dependence may be of greater consequence (e.g., medication non-adherence may lead to antiretroviral resistance). As such, the current study tested the hypothesis that higher levels of dispersion will be uniquely related to increased dependence in basic activity of daily living (BADL) and IADL, including medication adherence, among HIV-seropositive individuals without HAND.

Method

Participants

The study sample comprised 82 participants who were drawn from a National Institutes of Mental Health (NIMH) funded R01 on memory in HIV infection. Inclusion criteria for the current study were: (a) ability to provide informed consent; (b) positive HIV serostatus, determined by enzyme-linked immunosorbent assays and confirmed by a western blot test; and (c) the absence of HAND, as determined by a global clinical rating below the cutoff for neurocognitive impairment (i.e., <5) on a comprehensive neuropsychological battery (ratings provided by trained neuropsychologists; *see* Woods et al., 2004). Potential participants were excluded if they: (a) reported histories of major neuromedical (e.g., seizure disorders, closed head injuries with loss of consciousness >15 min, stroke, and central nervous system neoplasms or opportunistic infections) or psychiatric conditions (e.g., psychotic disorders); (b) had an estimated verbal IQ score of <70 on the Wechsler Test of Adult Reading (WTAR; Psychological Corporation, 2001); (c) were not prescribed any medications (non-antiretroviral medications, or ARVs, were allowed, but 87% of the sample was prescribed some form of ARV therapy); (d) met criteria for a substance use disorder within 6 months of evaluation as determined by the Composite International Diagnostic Interview (CIDI version 2.1; World Health Organization, 1998); or (e) provided a positive urine toxicology screen for illicit drugs (other than cannabis) on day of evaluation. Table 1 displays the demographic, psychiatric, and HIV disease characteristics of the study sample.

Materials and Procedure

After providing written informed consent, all participants completed comprehensive neuropsychological, psychiatric, and medical research evaluations. For the current study, we derived a measure of dispersion from the standardized and normed clinical tests administered as part of the neurocognitive battery. 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). The tests (and specific variables) included the California Verbal Learning Test-2nd edition (CVLT-II; Total Learning Trials 1–5; Delis, Kramer, Kaplan, & Ober, 2000), Logical Memory (LM) subtest of the Wechsler Memory Scales–3rd edition (LMI Unit Score; Psychological Corporation, 1997), Boston Qualitative Scoring System for the Rey–Osterreith Complex Figure Test (Immediate Presence and Accuracy Summary; Stern et al., 1999), Tower of London–Drexel (Total Move Score; Culbertson & Zillmer, 2001), Trail Making Test (Parts A and B; Reitan & Wolfson, 1993), Digit Span subtest of the Wechsler Adult Intelligence Scale-3rd edition (Total Score; Psychological Corporation, 1997), Animal (Benton, Hamsher, & Sivan, 1983; Gladsjo et al., 1999) and Action (Woods, Scott, Dawson, et al., 2005) Fluency,

Table 1. Demographic and psychiatric characteristics of the study participants

Variable	Sample ($N = 82$)	Range
Demographic characteristics		
Age (years)	45.1 (7.8)	27–70
Education (years)	13.4 (2.7)	7–20
Sex (% male)	90.2	—
Ethnicity (% Caucasian)	64.6	—
Cognitive characteristics		
Estimated verbal IQ[a]	104.8 (10.7)	82–126
Dispersion	9.0 (2.3)	5.1–14.0
Mean *T*-score	53.3 (4.7)	42.4–63.9
HDS Total	15.2 (1.4)	9–16
Functional characteristics		
BERMA Medication Management Efficiency	76.9 (15.1)	39–99
ADL-dependent (%)	31.7	—
Unemployed (%)[b]	58	
Psychiatric characteristics		
Lifetime Major Depressive Disorder (%)	46.3	—
Lifetime Generalized Anxiety Disorder (%)	4.8	—
Lifetime Substance Use Disorders (%)	71.9	—
POMS Total Mood Disturbance	53.5 (37)	0–159
HIV disease characteristics		
HIV Infection Duration (years)[c]	13.5 (7.4)	0.7–25.9
Current CD4 (cells/ml)[c]	528.5 (260)	0–1138
Nadir CD4 (cells/ml)[c]	176.4 (151.6)	0–725
Plasma HIV RNA ($\log_{10}$)[c]	2.3 (1.24)	1.7–5.9
CSF HIV RNA ($\log_{10}$)[c]	1.92 (0.6)	1.7–3.9
AIDS (%)	67.1	—
cART (%)	84.2	—
Hepatitis C Co-infection (%)	11.3	—

Notes: BERMA = Beliefs Related to Medication Adherence; Higher raw scores = better self-reported medication adherence; POMS = Profile of Mood States; Dispersion = intra-individual standard deviation score;
Mean *T*-score = average of *T*-scores included in dispersion variable;
HDS Total = HIV Dementia Scale Total raw score;
ADL-dependent = dependence in activities of daily living as defined by decline in two or more functional abilities (current functioning rated lower than highest functioning) on the modified Lawton & Brody (1969) scale; cART = combined antiretroviral therapy; CSF = Cerebrospinal fluid.
[a]Standard Verbal IQ Estimate based on the Wechsler Test of Adult Reading (WTAR).
[b]Employment status was available for 66 of the 82 total participants.
[c]Data represent median (interquartile range).

Memory for Intentions Screening Test (Raskin, 2004; Woods, Moran, et al., 2008), Boston Naming Test (Total Score; Goodglass, Kaplan, & Barresi, 2001), and Grooved Pegboard Test (Total Time; Kløve, 1963). Although no specific symptom validity tests were included in the battery, no participant evidenced suboptimal effort as measured by the Reliable Digit Span index (Mathias, Greve, Bianchi, Houston, & Crouch, 2002).

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 investigating dispersion (e.g., Christensen et al., 1999; Hilborn et al., 2009). As in the case of these prior studies, standard summary measures from tests that evaluate several different cognitive domains were selected for inclusion in the dispersion variable. When multiple summary measures were available for a given test, measures were selected based on their demonstrated sensitivity in HIV infection (e.g., Carey et al., 2004) because those measures could be expected to yield meaningful variability in performance due to HIV infection (e.g., "spotty"-deficit profile). For example, from the CVLT-II, the Total Learning measure (i.e., Trials 1–5) was selected because of the previously demonstrated sensitivity of a total verbal list-learning measure to HIV-associated learning deficit (e.g., Woods, Scott, Sires, et al., 2005). The number of measures used for the calculation of the dispersion variable in the current study was similar to prior studies (e.g., Christensen et al., 1999; Hilborn et al., 2009; Morgan et al., 2011), and equal weight was given to each measure (i.e., the tests represented different cognitive abilities but were not grouped according to the domain, *per se*). Raw scores from each of the selected measures of interest were converted into demographically adjusted *T*-scores and an intra-individual standard

deviation (ISD) was computed across these selected *T*-scores for each participant. Each individual's ISD, therefore, indicated the degree of variability in performance across the selected measures such that higher dispersion scores signify greater variability across measures in the battery. Although some studies have used corrected measures of IIV that adjust for the level of performance (e.g., mean-adjusted indices such as the coefficient of variation), recent evidence suggests that such correction may complicate interpretation of results (e.g., Schmiedek, Lovden, & Lindenberger, 2009). Of note, a mean *T*-score (i.e., average of the *T*-scores that comprise that dispersion variable such that higher values indicate better global neurocognitive performance) was included in the statistical models, and the use of the coefficient of variation (ISD divided by mean *T*-score instead of the simpler ISD-based dispersion measure) did not change the results described below.

Everyday Functioning Questionnaires

Activities of daily living. All participants completed a modified version of the Lawton and Brody (1969) ADL scale, which consists of participant self-ratings for performance of numerous daily tasks (e.g., managing finances, grocery shopping, housekeeping, medication adherence, and employment). The modification allowed participants to rate both their current level of functioning and their highest level of functioning for each item, and the primary dependent variables of interest was the summed total of domains on which declines were reported in current versus past functioning (*see* Woods et al., 2006; Woods, Iudicello, et al., 2008). Consistent with prior research (e.g., Vigil et al., 2008), two separate subscales were generated to reflect IADL (e.g., medication management, finances) and BADL (e.g., grooming, house maintenance). A functional cupoint was based on previous work (e.g., Woods et al., 2006) and the Frascati criteria for HAND research diagnosis (Antinori et al., 2007) whereby a decline in two or more areas of self-rated functional performance was defined as "dependent" status (i.e., rating current level of functioning lower than best prior level of functioning for two or more items).

Beliefs related to medication adherence. The belief related to medication adherence (BERMA) survey was used to evaluate each participant's self-reported medication management (McDonald-Miszcak, Maris, Fitzgibbon, & Ritchie, 2004). The "Medication Management Efficiency" subscale of the BERMA contains 20 items (e.g., "I am less efficient at adhering to my medication regimen than I used to be") that participants rate on a five-point Likert scale ranging from 1 ("strongly disagree") to 5 ("strongly agree"). Higher values reflect better medication adherence. The construct validity of the BERMA is supported by prior research showing that it is associated with non-adherence in HIV as measured by the medication event monitoring system (Woods et al., 2009).

Psychiatric and Neuromedical Assessments

The CIDI was used to determine psychiatric diagnoses, including Major Depressive, Generalized Anxiety, and Substance Use Disorders. Participants also completed the Profile of Mood States (POMS) questionnaire as a measure of current affective distress (McNair, Lorr, & Droppleman, 1981). Finally, participants also received a full neuromedical evaluation, which included a thorough review of medications, medical history and current symptoms, a complete physical and neurological evaluation, Centers for Disease Control staging, and a blood draw. Standard flow cytometry methods were used to count CD4+ lymphocytes in blood samples. Plasma HIV RNA levels were quantified using reverse transcription polymerase chain reaction (RT-PCR) (Amplicor, Roche Diagnostics, Indianapolis, IN).

Results

A series of multiple linear regressions were conducted to predict IADL, BADL, and BERMA from dispersion, which was the primary variable of interest. In order to determine the unique predictive value of dispersion in this regard, we also included previously demonstrated predictors of functional status in HIV infection, including a traditional summary of neurocognitive performance (i.e., mean *T*-score), psychiatric distress (i.e., POMS total mood disturbance), demographic factors (i.e., age), historical disease status (i.e., AIDS status), and an index of current disease status (i.e., plasma HIV RNA) in each of the models. The details of each of these three models are displayed in Table 2. Furthermore, each model was run a second time with a dichotomous variable indicating the clinical cutpoint for "independence" versus "dependence" to determine whether dispersion was related to this established threshold for functional decline (e.g., *see* Woods et al., 2006; Woods, Iudicello, et al., 2008). Although heuristics vary for determining an appropriate number of predictors for a given sample size in regression analyses, our selection of six predictors for 82 participants falls within liberal guidelines (VanVoorhis & Morgan, 2007). Furthermore, a reduced model with four predictors (i.e., excluding AIDS status and plasma viral load) is consistent with more stringent guidelines (i.e., $N > 50 + 8\,m$, where m is the number of predictors; Green, 1991) and yielded a similar pattern of results.

Table 2. Predictors of everyday functioning in the study sample ($N = 82$)

Variable	Model	β	p-value
IADL			
Adjusted R^2	0.28		
F	6.13		<.0001
Dispersion		0.24	.018
Mean T-score		−0.15	.123
Age		−0.06	.549
POMS Total		0.45	<.0001
AIDS		0.07	.473
Plasma HIV RNA		0.10	.298
BADL			
Adjusted R^2	0.15		
F	3.26		.007
Dispersion		0.11	.299
Mean T-score		−0.19	.079
Age		0.00	.986
POMS Total		0.35	.002
AIDS		−0.09	.421
Plasma HIV RNA		0.67	.669
BERMA			
Adjusted R^2	0.39		
F	9.70		<.0001
Dispersion		−0.22	.015
Mean T-score		0.24	.011
Age		−0.21	.031
POMS Total		−0.48	<.0001
AIDS		−0.15	.110
Plasma HIV RNA		−0.23	.018

Notes: IADL = instrumental activities of daily living; BADL = Basic Activities of Daily Living; BERMA = Beliefs Related to Medication Adherence; POMS = Profile of Mood States; Mean T-score = average of T-scores included in dispersion variable.

The IADL model explained 28% of the variance in IADL ($p < .0001$). Within this model, dispersion was a unique predictor (i.e., higher levels of dispersion predicted a higher total number of areas of functional decline; $p = .018$), as was POMS total ($p < .05$). Results did not change when IADLs were examined as a dichotomous outcome (i.e., dependence = declines in two or more domains) in a logistic regression—$\chi^2(6) = 23.2$, $p = .0007$. Dispersion was a significant predictor of IADL dependence—$\chi^2(1) = 9.7$, $p = .002$—such that each unit increase in dispersion was associated with a 1.6 times increased risk of dependence (95% *CI*: 1.2–2.4). The BADL model explained 15% of the variance in BADLs ($p < .001$), but was primarily explained by POMS total (i.e., higher POMS total mood disturbance score predicted a higher total number of areas of functional decline; $p < .05$). In contrast, dispersion was not significant and there was only a trend-level effect of mean ($p < .10$). Interestingly, when BADLs were analyzed in a logistic regression as a dichotomous variable (see above), the overall model was significant—$\chi^2(6) = 24.5$, $p = .0004$—but dispersion—$\chi^2(1) = 9.1$, $p = .003$—and mean—$\chi^2(1) = 6.9$, $p = .009$—were the only significant predictors, whereas POMS total was associated at a trend level ($p < .10$). For each unit increase in dispersion risk for BADL dependence increased by 1.6 times (95% *CI*: 1.2–2.3). The BERMA model explained 39% of the variance in the BERMA Medication Management Efficiency subscale ($p < .0001$). With the exception of AIDS status, all of the predictors were uniquely associated with the BERMA, including dispersion (i.e., higher levels of dispersion predicted lower BERMA scores or worse self-reported adherence; ps $< .05$).

A set of follow-up correlational analyses was conducted to investigate the associations between standard HIV disease biomarkers and both mean neuropsychological T-score and the dispersion index. The selected biomarkers and the respective sample sizes for each due to the availability of biomarker data were as follows: duration of HIV infection (years; $n = 79$), nadir CD4 count ($n = 82$), current CD4 count ($n = 81$), plasma viral load ($n = 81$), and cerebrospinal fluid viral load ($n = 57$; fewer participants agreed to undergo lumbar puncture than blood draw). Given that these measures are not normally distributed, non-parametric Spearman's ρ was used to evaluate the associations. The mean neuropsychological T-score was not significantly correlated with any of the HIV disease biomarkers (all ps $> .10$). A significant negative association was observed between nadir CD4 count and dispersion ($\rho = -0.23$, $p = .04$), such that lower nadir CD4 was associated with higher levels of dispersion. A trend-level association was observed between dispersion and current CD4 count ($\rho = -0.22$, $p = .05$). No significant relationships were observed between dispersion and the other selected biomarkers (ps $> .10$).

Discussion

Although prior evidence has shown a strong association between neurocognitive impairment in the context of HIV infection (i.e., HAND) and functional disability, the sensitivity of HAND is relatively weak in this regard. As many as half of functionally impaired individuals demonstrate "normal" cognitive performance on comprehensive, well-validated batteries. As such, some of these individuals classified as "neurocognitively normal" based on the traditional assessment methods may actually be experiencing cognitive alterations that are not typically measured, which may increase risk for functional difficulties in daily life. Consistent with this hypothesis, increased levels of neurocognitive dispersion, which measures within-person variability in performance across tasks representing multiple neurocognitive domains, were significantly related to poorer performance on BADL and IADL, as well as medication management among HIV-seropositive individuals without a HAND diagnosis. This suggests that HIV-seropositive individuals who demonstrate high levels of dispersion on neuropsychological testing may have similar problems with regulating their cognitive resources for successful performance of functional activities in their daily lives, thereby increasing their risk of disability.

Specifically, results from the present study revealed that dispersion was a significant predictor of several levels of functional status, including clinical dependence in BADL and IADL. Notably, when ADL outcomes were examined as continuous variables to assess the relationship of dispersion to the full range of severity in functional decline, results were similar for IADL functioning but dispersion was not a significant predictor of the continuous variable representing BADL. This discrepancy may be a statistical artifact due to a positively skewed distribution (coefficient of skewness = 3.67), or it may be the case that for BADL, which by definition are more basic, straightforward, and universal in nature, it is more informative that an individual has crossed the clinical threshold for dependence in those activities rather than the degree to which they are dependent (which would be reflected in the continuous BADL variable). It is also possible that dispersion had a greater impact on the more complex IADL functioning, but each unit increase in dispersion resulted in a similarly increased risk for BADL and IADL dependence; that is, significant odds ratios of approximately 1.6 were observed for each functional outcome. Furthermore, higher neurocognitive dispersion scores were also associated with poorer self-reported medication management in the present study. Of note, the average score on the BERMA in the present sample approximated that which was recently reported among a group of HIV-seropositive individuals with objective evidence of non-adherence (i.e., medication event monitoring system; Woods et al., 2009). The association between dispersion and medication non-adherence extends previous investigations of IIV in HIV infection, in which increased IIV was observed among HIV-seropositive individuals and was significantly associated with poorer medication adherence (Ettenhofer et al., 2009; Levine et al., 2008). These studies evaluated reaction time inconsistency as a marker of IIV and reported that it had unique, incremental validity relative to reaction time latency. Similarly, in the present study, dispersion significantly accounted for unique variance in the functional outcomes even with the mean level of performance and other previously demonstrated predictors of functioning, including age, affective distress, and markers of the past and current disease severity, included in the model.

The current study findings suggest that a shift toward conceptualizing risk for functional impairment across the full range of cognitive performance may be warranted. Accordingly, in the case of IIV, markers such as dispersion could be used to supplement the traditional means of summarizing neurocognitive impairment such as the standard mean level of performance or a GDS in which impaired performances are weighted. In terms of clinical utility, the link between HAND and functional impairment is well-established, but it may be beneficial to examine an index of IIV such as dispersion among individuals who are not impaired given its unique association with functional outcomes controlling for the level of performance. In the clinic setting, this would represent a second level of triage whereby the first indicator of risk is demonstrated HAND, and for those whose performance is within normal limits on the standard measures, the clinician would evaluate the variability of individual's performance was across tasks. Dispersion across the standard measures could be calculated for any battery, an opportunity for detecting and intervening (e.g., with compensatory strategies) in functional problems that might be been missed without this second level of triage. Importantly, in the current study, dispersion was examined as a continuous predictor of functional status and thus does not provide information for interpreting a dispersion score in isolation or for informing clinical cutpoints for dispersion. In fact, it is understood that some degree of variability is expected in everyone's performance, even among healthy individuals (i.e., those without HIV infection) who are not impaired (e.g., Schretlen et al., 2003), and it would be expected that greater dispersion would lead to difficulty with performing everyday activities among healthy individuals. Therefore, future work delineating ranges of IIV observed in individuals with no functional difficulties (i.e., normative standard) compared with those who do experience dysfunction in daily activities would be clinically useful. Nevertheless, evidence suggesting that HIV infection may be elevating dispersion, thereby elevating risk for daily functioning impairment, is the significant correlation observed between nadir CD4 count and the dispersion index. Lower nadir CD4 count was significantly associated with higher dispersion, whereas no relationship was observed between the average neuropsychological performance and any biomarkers of HIV infection. Interestingly, low nadir CD4 is a risk factor for developing HAND (e.g., Heaton et al.,

2010), and therefore, its negative association with dispersion among individuals without HAND supports the notion that dispersion may be a sensitive and early marker of cognitive alteration, possibly due to loss of neural integrity (e.g., MacDonald, Li, & Backman, 2009).

The association between high levels of dispersion and declines in everyday functioning may reflect problems effectively harnessing and directing cognitive resources to manage a range of complex day-to-day activities, perhaps expressed as variable performance within and across ADLs. Numerous important daily functions, particularly higher level or complex activities, are time-intensive or involve multiple steps for successful completion, such that variability in performance may lead to poorer outcomes. For example, vocational functioning requires the regulation of cognitive resources for completion of specific tasks across a full shift or workday, and increased variability could result in poorer work performance across a spectrum of job types, from factory work requiring consistency in small details to more advanced positions with less structure that require self-initiation and regulation of a variety of skills (e.g., professional medical and legal positions). Although not directly tested in the present study, increased dispersion may also present as difficulty with functional multitasking, which requires an individual to organize, prioritize, and impose structure on his or her actions when numerous competing demands are required. Notably, deficient functional multitasking has shown incremental validity beyond HAND in predicting IADL dependence in HIV infection (Scott et al., 2010).

Regarding cognitive mechanisms of dispersion, increased performance variability may result from reduced efficiency in sustaining cognitive control processes that coordinate behavior in relation to internal goals and environmental demands (*see* Badre, 2008; for a review). As such, disruption of this top-down process subserving ongoing maintenance of goal-directed behavior could manifest as increased IIV. In other words, although the construct of IIV likely falls under the vast umbrella of executive functions, we propose that its temporal features involving sustained cognitive control of multiple aspects of neurocognitive performance represent a unique and separable cognitive mechanism. Cognitive dyscontrol has been linked to increased IIV in populations with frontal systems dysregulation, including frontal lesions (e.g., Stuss, Murphy, & Binns, 1998) and aging (Hultsch et al., 2002). Moreover, higher levels of IIV have been demonstrated for cognitively demanding tasks that heavily recruit executive functions, such as an inhibition task (Bellgrove et al., 2004), 1-back task (West et al., 2002), and working memory and set-shifting tasks (Strauss, et al., 2007). A functional magnetic resonance imaging (fMRI) study also showed that individuals with high levels of IIV demonstrated greater activation in frontal regions during an inhibition task, suggesting a greater demand for cognitive control to maintain task performance (Bellgrove et al., 2004). Regarding our current findings, the preferential effect of HIV disease on prefrontal systems could result in cognitive dyscontrol, which may then impact dispersion of performance across test scores even among individuals whose global performance on traditional neuropsychological tests is within normal limits. As such, our findings regarding the association of dispersion and functional impairment suggest that dispersion may be capturing important cognitive alterations due to HIV infection that are not reflected in HAND diagnostic criteria.

The present study has several limitations worth noting, which may inform future directions for additional work. Our functional outcomes were self-report measures, which may be biased by factors such as depression (Heaton et al., 2004). However, an index of current affective distress was included in our models, which reduces the likelihood that our results were severely confounded. Use of other report and/or performance-based measures in future studies may help to elucidate the relationship between dispersion and daily functioning because some individuals may have mild problems for which they lack awareness but nevertheless may be subtly impacting their functional performance (i.e., there might be an even stronger relationship between dispersion and objective functional measures). Furthermore, part of our rationale for examining increased IIV as a risk for functional impairment across the full range of neurocognitive performance among HIV-seropositive individuals, including those who perform within the "normal" range on traditional measures, was based on the conjecture that higher levels of IIV may precede and forewarn of future cognitive and functional decline. However, the cross-sectional nature of the study did not allow for direct examination of this theory. It is important to note that, although dispersion was a significant predictor of medication non-adherence, it is possible that poor adherence to an ARV regimen may have preceded the emergence of increased dispersion (Ettenhofer et al., 2009), which could not be tested in the current cross-sectional study. The lack of longitudinal data also limited our ability to evaluate the proposed cognitive dyscontrol mechanism of dispersion, as did our lack of an external criterion of executive functions. Specifically, evidence of different patterns of performance across domains between two testing sessions for functionally impaired participants and/or demonstrations of significant associations between dispersion and measures of executive functions (i.e., demonstration of construct validity with care to avoid criterion contamination) would support inefficiency of sustained cognitive control as the proposed mechanism underlying dispersion. As with most studies addressing complex clinical questions, there were unmeasured variables in our study that may have confounded our results. For example, we did not thoroughly evaluate the history of learning disabilities and, therefore, could not include this history as a formal exclusion criterion. However, the potential effects of this confound were reduced by exclusion of individuals with estimated premorbid IQ scores of <70 (based on WTAR), and we are not aware of evidence

linking learning disability and intra-individual neurocognitive variability beyond the increased variability often observed in impaired performance, particularly in the context of HIV infection.

In addressing the above-described limitations and extending our findings, several suggestions for future directions can be offered. Future studies may seek to evaluate whether dispersion relates to other important functional outcomes in HIV infection, including automobile driving, computer use (e.g., Internet navigation), and additional, ostensibly more objective, indices of medication adherence, such as medication event monitoring systems. Since performance-based functional tasks are purportedly more ecologically valid indicators of functional status as they are reliant on performance in the laboratory rather than self-report, future work may examine the association between IIV markers and scores from performance-based tasks. Furthermore, the cognitive mechanisms of IIV as it relates to functional status could be evaluated in a prospective study in which measures of executive functions are administered but not included in the calculation of the dispersion score, such as the Delis–Kaplan Executive Functions System (Delis, Kaplan, & Kramer, 2001), to prevent criterion contamination. Additionally, neural correlates of IIV observed among individuals with otherwise intact neurocognitive performance may be explored, in part to evaluate whether IIV may be an early signal regarding loss of neural, and therefore cognitive, integrity that is not yet detected by traditional neuropsychological summary scores and cutpoints.

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Conflict of interest

None declared.

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