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## Intra-individual variability in neurocognitive performance: no influence due to HIV status or self-reported effort

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### Abstract

**Introduction:** HIV-associated neurocognitive disorders (HAND) are estimated to affect approximately 50% of infected individuals at any one time. Dispersion, a type of intra-individual variability in neurocognitive test performance, has been identified as a potential behavioral marker of HAND; however, the specificity of dispersion to HAND and how it is influenced by participant effort when taking neurocognitive tests remains unclear.

**Method:** Data were analyzed from 996 (474 HIV-, 522 HIV+) men enrolled in the Multicenter AIDS Cohort Study (MACS). Dispersion was calculated based on the standard deviation of an individual's test scores within a single assessment. Effort was determined using the Visual Analogue Effort Scale. Predictors of dispersion were determined using stepwise linear regression. Dispersion was compared between the HIV serostatus groups using ANCOVA, considering demographic and psychosocial variables that differed between the groups.

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None of the authors have disclosures regarding possible financial conflicts of interest.

**Results:** Contrary to our hypothesis, dispersion was not influenced by effort. Instead, poorer neurocognitive ability and race were the sole predictors of dispersion. Dispersion did not differ between the serostatus groups.

**Conclusions:** Our results indicate that dispersion is a valid indicator of neurocognitive dysfunction that is not due to suboptimal effort; however, it is not specific to HIV and is therefore of limited utility as a behavioral marker of HIV-related neurocognitive impairment.

### Keywords

Suboptimal effort; HIV-associated neurocognitive disorders; visual analogue scale; NeuroHIV; dispersion

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## Introduction

Intra-individual variability (IIV) is a term used to describe within-person variations in psychometric test performance. IIV includes a longitudinal measure of variability referred to as *inconsistency* (variation on a single task over time) and a measure of variability across tests within a single battery, referred to as *dispersion* (Hilborn, Strauss, Hultsch, & Hunter, 2009; Hultsch, MacDonald, & Dixon, 2002). These measures of IIV have been examined across a range of conditions as a possible psychometric indicator of underlying neuropathology, including general decline in neurocognitive functioning (Hilborn et al., 2009; Rapp, Schnaider-Beeri, Sano, Silverman, & Haroutunian, 2005), multiple sclerosis (Bruce, Bruce, & Arnett, 2010), and other (Nilsson, Thomas, O'Brien, & Gallagher, 2014; Stuss, Murphy, Binns, & Alexander, 2003). Furthermore, both *inconsistency* and *dispersion* increase with age and concomitant neurocognitive dysfunction (e.g., (Burton, Strauss, Hultsch, Moll, & Hunter, 2006; Hilborn et al., 2009; Hultsch et al., 2002; MacDonald, Hultsch, & Dixon, 2003).

Within the context of HIV infection, a small number of studies have examined the relationship between dispersion and HIV-associated neurocognitive impairment. The earliest study examined dispersion among 126 HIV-infected (HIV+) and 40 HIV uninfected (HIV-) adults who were further divided into younger (< 50) and older (≥ 50) groups (Morgan et al., 2011). Log-transformed dispersion was compared among these groups. An age by HIV serostatus interaction was found, such that the older HIV+ group had a higher level of dispersion relative to the older HIV- and younger HIV+ groups. That study laid the foundation for examining dispersion as an indicator of neurocognitive decline in HIV-infected individuals. Linking dispersion to impairments in daily activities, the same group published a follow-up study of 86 HIV+, neurocognitively normal adults in which greater dispersion was a predictor of impairments in basic and instrumental activities of daily living, as well as medication adherence (Morgan, Woods, Grant, & Group, 2012). A later study extended these early findings by examining the longitudinal characteristics of dispersion in 150 HIV+ persons (Thaler et al., 2015). That study focused on determining if baseline dispersion or *changes* in dispersion over a 6-month period predicted antiretroviral (ARV) medication adherence. The results indicated that greater dispersion is associated with poorer ARV adherence at a later time. That is, HIV+ individuals with the greatest increases in dispersion also had the greatest reductions in ARV adherence 6 months later. Most recently,

dispersion was linked to variations in brain volume among 80 HIV+ and 67 HIV-men(Hines et al., 2016), thereby establishing a putative neurophysiological basis for dispersion. Total gray matter volume was inversely correlated with dispersion, with greater dispersion being associated with lower gray matter volume across several cortical areas. However, HIV status was not linked to dispersion-related cortical atrophy. As such, the authors concluded that while dispersion may be a sensitive marker of cortical integrity in older adults, it is not specific to HIV.

While neuropathology may indeed increase dispersion, it is likely that other factors are involved. For example, Hill et al. (2013) examined IIV in 629 individuals with a history of mild traumatic brain injury (TBI) who were evaluated in a private practice setting(Hill, Rohling, Boettcher, & Meyers, 2013). They divided their samples into three groups: loss of consciousness (LOC) < 1 hour, LOC 1 hour to 6 days, and LOC > 6 days. In addition, based on patients' scores on several embedded performance validity tests (PVT), they were categorized by effort (no PVTs failed = valid performance, 1 PVT failure = invalid performance). The authors found that dispersion was influenced separately by TBI severity and objectively measured effort, leading them to conclude the dispersion may be a valid measure of both. The issue of suboptimal effort on neurocognitive testing among HIV cohort participants has not been thoroughly examined. Past studies employed forced-choice memory tests that were in fact intended to detect negative response bias(Janssen, Bertens, Kessels, Kessels, & Koopmans, 2013; Paul et al., 2017). Not surprisingly, when using cutoffs established to detect feigned impairment in compensation-seeking individuals, those studies did not find evidence for suboptimal effort in their HIV+ samples. An arguably more advantageous approach, especially in a population that is not compensation seeking, is to elicit self-reported effort. That is, rather than assessing effort via objective measures, determine an individual' subjective feeling of effort. As we recently reported (Levine, Martin, Sacktor, Munro, & Becker, 2017), in order to determine how effort affects neurocognitive performance and prevalence of HIV-associated neurocognitive disorders (HAND), a visual analogue scale was administered to 995 participants enrolled in the Multicenter AIDS Cohort Study immediately after they completed a battery of neurocognitive tests. Participants rated their effort between 0–100% and provided reasons for suboptimal (<100%) effort when applicable. Just over half of the sample indicated suboptimal effort, with no differences between HIV+ and HIV-groups. The most common reasons provided were “Tired/Fatigued” (42%) and “Distracted/Poor concentration” (36%). Participants with the lowest self-reported effort had significantly higher rates of mild impairment (both symptomatic and asymptomatic) as compared to moderate and high effort individuals.

Our recent findings indicate that suboptimal effort may have a significant influence on the neurocognitive test performance of research participants. Considered alongside the findings of Hill et al. that objectively measured effort has a measurable influence on dispersion, we believe that it is plausible that dispersion is influenced by suboptimal effort, as reported by study participants. Therefore, our hypothesis is that suboptimal effort, as measured by the Visual Analogue Effort Scale (VAES), is a significant predictor of dispersion in both HIV+ and HIV uninfected men. Considering the conflicting results of the aforementioned

dispersion studies in HIV, we take an agnostic stance regarding the question of whether or not HIV+ individuals will have greater dispersion as compared to HIV uninfected controls.

## Methods

### Participants

Data for this study were obtained from 1108 (514 HIV-, 594 HIV+) male participants in the Multicenter AIDS Cohort Study (MACS), with local IRB approval. The inclusion criteria for the MACS included male gender and being at least 18 years of age. Biannual visits included a comprehensive neurocognitive battery and series of questionnaires assessing drug use, medication use, and medical co-morbidities. Due to the low number (1.6% of total sample), individuals classified as “other” were excluded. Chi square analysis revealed higher reported cocaine use in past 6 months among HIV infected group. Considering that cocaine was previously found to affect self-reported effort (Levine et al., 2017), cases reporting any cocaine use were removed, leaving 996 (474 HIV-, 522 HIV+) cases. Group characteristics of the final sample of are displayed in Table 1. CD4+ T-cell count among the HIV+ participants was 693 (SD = 300) and median viral load was 10 (range 10 to 1,525,243), with 90% of cases having a viral load < 120 (not shown).

### Measures

**Visual Analogue Effort Scale (VAES):** The ability to self-assess mental effort related to the execution of a task has been routinely measured in occupational psychology (20) using visual analogue scales such as the Rating Scale of Mental Effort (RSME) (21). The VAES is similar to the RSME and was created for the purpose of evaluating effort in the MACS. The VAES became part of the standard neurocognitive battery protocol in October of 2015. At the conclusion of neurocognitive testing, participants are asked to rate their effort on a horizontal line with numbers ranging from 0 to 100%. A 10cm ruler is then used to determine percent effort. For those who report <100% effort, several reasons for suboptimal effort are provided (e.g., tired/fatigued, unmotivated, distracted), as well as an “other” option for which they then write in the reason. Participants typically complete the form in under 30 seconds.

**Neurocognitive functioning:** Participants complete a battery of neuropsychological tests as part of the standard study protocol (Becker et al., 2014). This battery includes measures of working memory, learning, memory, executive functioning, motor functioning, and processing speed. Z-scores were calculated using normative data derived from the HIV uninfected MACS participants, with demographic corrections for age, education, and ethnicity. The following measures were used to calculate a Mean Z-Score of neurocognitive functioning: Symbol Digit Modalities Test (Smith, 1982), Trail Making Test-Form B (Reitan, 1958), Stroop - Color Naming (Comalli, Wapner, & Werner, 1962), Stroop - Interference, Rey Auditory Verbal Learning Test-Total Learning and Delayed Recall, Rey Osterrieth Complex Figure Immediate Recall, Grooved Pegboard Non-Dominant Hand trial (Kløve, 1963), and the CalCAP Complex Reaction Time 4. In addition to the Lawton Instrumental Activities of Daily Living scale (Lawton & Brody, 1969), these measures are used by the

MACS to derive HAND diagnosis based on 2007 “Frascati” criteria, as previously described (Sacktor et al., 2016).

**IIV-Dispersion:** Dispersion was defined as the standard deviation of the Z-scores of the measures listed above, in accordance with the methods described in (Morgan et al., 2012). Higher dispersion values indicate greater variability.

**Depression:** Depression severity is determined with the Center for Epidemiologic Studies Depression Scale (CES-D) (Radloff, 1977) as part of the standard MACS protocol. Scores on the CES-D are used as a continuous variable, with higher scores indicating more depressive symptoms.

**Race:** For the purposes of this study, individuals were defined as Caucasian, Hispanic, African American, or other (including Asian, Native American, and Native Alaskan). Individuals identifying as Caucasian Hispanic or African American Hispanic were categorized as Hispanic. For the statistical analyses, race was coded as follows: Caucasian = 0, Hispanic = 1, African American = 2.

### Statistical Analyses

In our primary analysis we sought to determine predictors of dispersion using forward stepwise linear regression with dispersion as the dependent variable and the following predictor variables: age, education, race, HIV status, CES-D (depression), VAES score (effort), and mean neurocognitive test Z-score (same tests used to calculate dispersion).

For our secondary analysis, we compared dispersion between HIV+ and HIV uninfected cases, controlling for any factors that differed between the groups using ANCOVA.

### Results

Because of the non-normal distribution of dispersion, it was log-transformed for all analyses. We first examined predictors of dispersion among 996 MACS participants. Contrary to our predictions, effort was not associated with dispersion. The stepwise linear regression model was significant overall [ $F(1, 935) = 18.34, p < .001, R^2 = .038, \text{Adjusted } R^2 = .036$ ], with mean neurocognitive test Z-score (Beta =  $-.040$ ) and race (Beta =  $.014$ ) as significant predictors. That is, poorer neurocognitive functioning and African American race were predictors of increased IIV. Results are shown in Table 2.

We then compared IIV between the serostatus groups. The serostatus groups differed on several variables. The HIV negative group was older, better educated, possessed stronger neurocognitive functioning, were less depressed, had higher rates of alcohol use, and had a higher proportion of Caucasian and lower proportion of African American and Hispanic men (Table 1). These variables were included as covariates in the ANCOVA. To minimize assumption violations for ANCOVA, race was dichotomized (Caucasian vs. Hispanic/African American), as was alcohol use (Monthly or less use vs. weekly or daily use). Error variance in log-transformed dispersion did not differ between the groups (Levene’s Test:  $F = 1.73, p = 1.88$ ). The groups did not differ with regards to dispersion (Table 3).

## Discussion

Dispersion has recently been proposed as a behavioral marker of neurocognitive dysfunction in the context of various neurologic conditions, including neuroHIV. Recently, a large-scale study found that HAND status is determined in large part by the extent of self-reported effort by study participants (Levine et al., 2017). Following the findings of Hill et al. in individuals with mild TBI (Hill et al., 2013), we posited that dispersion in HIV+ study participants may in fact be a consequence of suboptimal effort.

Contrary to our expectation, effort did not explain dispersion. In fact, the strongest predictor of dispersion was overall neurocognitive functioning. That is, stronger neurocognitive ability is associated with less dispersion. Accordingly, our findings appear to validate previous studies whose authors interpreted increased dispersion as an indicator of underlying neurocognitive dysfunction in HIV+ individuals (Morgan et al., 2011; Morgan et al., 2012; Thaler et al., 2015). Race was also a significant predictor of dispersion, with African Americans demonstrating the highest dispersion and Caucasians the least, with Hispanics in the middle. Importantly, in our previous study we found that the higher rate of suboptimal effort among African Americans was explained in large part by their higher rate of cocaine use in our sample. In the current sample, we excluded those cases who reported cocaine use. As such, dispersion, like other psychometric phenomena, may vary as a function of race, age, and other demographic factors, and therefore requires further exploration and characterization.

Another finding is that HIV positive individuals did not demonstrate greater dispersion compared to their HIV negative counterparts. This differs from the findings of one previous study in this population (Morgan et al., 2011), but is congruent with those of the other (Hines et al., 2016). One likely reason is that the latter study drew from the same cohort as the current study. In addition, in the former study, the HIV positive group had significantly higher proportion of females, as well as greater rates of major depression and substance use. As such, we believe that the findings of Morgan et al were due to factors other than HIV. Overall, our results indicate that, while dispersion may be a valid phenomenon indicative of neurocognitive impairment rather than suboptimal effort, it is not specific to HIV. As such, the utility of dispersion as a behavioral marker of neuroHIV is not supported by our results.

There are limitations to our study that should be considered. Firstly, our methods differed somewhat from those of the Morgan et al studies, in that we used a different battery of neurocognitive tests and did not transform some of our variables as they did (e.g., log transforming of dispersion). These minor differences are unlikely to have obscured true differences and associations. Secondly, the MACS cohort is generally healthy when compared to other cohort studies, including perhaps the one examined by Morgan et al and Thaler et al. For this reason, the lack of validation may be due in part to lower variability in neurocognitive functioning among our cohort, or perhaps the greater rate of substance abuse in their cohorts. Thirdly, the validity of the VAES has yet to be established. However, the ability to self-assess mental effort related to the execution of a task has been routinely measured in occupational psychology (Yeo & Neal, 2004) using similar visual analogue scales, such as the Rating of Mental Effort Scale (Zijlstra, 1993). Visual analogue scales



such as the VAES rely on the assumption that self-evaluation of mental effort can be performed intuitively, and that this differs from appraisal of performance. Importantly, evaluation of task difficulty (i.e., appraisal of performance) and appraisal of effort are dissociable, as indicated in a recent neuroimaging study that used the RMSE (Otto, Zijlstra, & Goebel, 2014). In that study, the authors observed activation of the left anterior insular cortex, an area associated with self-awareness, was observed during appraisal of effort but not task difficulty. Still, additional analysis of the VAES in order to establish its validity is needed. A final limitation of the current study is that the MACS is an all-male cohort; therefore, the generalizability of our results to females is unclear.

In summary, our results indicate that dispersion is not influenced by self-reported effort and validate previous findings that dispersion reflects true neurocognitive dysfunction. However, it does not appear to be HIV specific or predict later change in neurocognitive functioning, thus limiting its utility in the context of neuroHIV.

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**Table 1.**

## Sample characteristics

	<b>HIV negative N = 474</b>	<b>HIV positive N = 522</b>	<b>F</b>	<b>P-value</b>
Age in years	57.9 (12.8)	52 (11.6)	59.36	<.001
Education in years	16.1 (2.6)	15 (2.6)	40.58	<.001
Mean Z-Score*	.064 (.72)	-.078 (.78)	8.75	.003
Log IIV	-.102 (.155)	-.092 (.184)	.81	.37
CES-D	9.2 (10.5)	11.3 (11.8)	8.9	.003
Effort (VAES)	92.4 (12.4)	91.1 (13.3)	2.75	.098
	HIV negative N (%)	HIV positive N (%)	Chi- square	P-value
Race			41.54	<.001
Caucasian	351 (74.1%)	285 (54.6%)		
Hispanic	42 (8.9%)	93 (17.8%)		
African American	81 (17.1%)	144 (27.6%)		
Alcohol			12.6	.006
None	172 (36.3%)	243 (46.6%)		
Monthly or less	78 (16.5%)	82 (15.7%)		
Weekly	125 (26.4%)	119 (22.8%)		
Daily	99 (20.9%)	78 (14.9%)		
Cannabis			5.93	.115
None	394 (83.1%)	405 (77.6%)		
Monthly or less	17 (3.6%)	20 (3.8%)		
Weekly	24 (5.1%)	31 (5.9%)		
Daily	39 (8.2%)	66 (12.6%)		

\* Mean Z-Score of neurocognitive tests used to calculate IIV

**Table 2.**

## Results of Regression Analysis

Included Variables	<i>B</i>	Dispersion	
		<i>SE B</i>	<i>t</i>
Mean Neurocognitive Score	-.040	.007	-5.472*
Race	.014	.007	2.116**
Excluded Variables	<i>B</i>	Partial R	<i>t</i>
Age (years)	-.018	-.017	-.522
Education (years)	-.038	-.035	-1.078
HIV Status	-.001	-.001	-.025
CES-D	.031	.032	.963
VAES	.015	.015	.449
Overall Model	R <sup>2</sup>	Adjusted R <sup>2</sup>	F
	.038	.036	18.339*

\*  $p < .001$ \*\*  $p < .05$ 

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**Table 3.**

Results of ANCOVA

	<b>Mean (Standard Deviation) Log Dispersion</b>	<b>Estimated Marginal Mean (Standard Error)</b>	<b>F</b>	<b>p-value</b>
HIV negative	-.1013 (.155)	-.098 (.008)		
HIV positive	-.0916 (.187)	-.095 (.008)	.065	.799

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