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Authors

Anderson, Ariana E
Jones, Jacob D
Thaler, Nicholas S
et al.

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Intra-individual variability in neuropsychological performance predicts cognitive decline and death in HIV

Ariana E. Anderson[*,1,2], **Jacob D. Jones**[1], **Nicholas S. Thaler**[1], **Taylor P. Kuhn**[1], **Elyse J. Singer**[4], and **Charles H. Hinkin**[1,3]

[(1)]Department of Psychiatry and Biobehavioral Sciences, UCLA Geffen School of Medicine, Los Angeles, CA.

[(2)]Department of Statistics, University of California Los Angeles, Los Angeles, CA.

[(3)]Psychology Service,VA Greater Los Angeles Healthcare System, Los Angeles, CA.

[(4)]Department of Neurology, University of California Los Angeles, Los Angeles, CA

Abstract

Objectives: HIV-Associated Neurocognitive Disorder (HAND) occurs in a significant percentage of HIV-infected (HIV+) adults. Increased intra-individual variability (IIV) in cognitive function may be an early marker of emerging neurocognitive disorder, which suggests that IIV may be a sensitive measure of neurologic compromise in HIV. In the current study, we hypothesize that increased IIV may predict impending morbidity, including future cognitive decline and death.

Methods: In 708 HIV+ participants followed longitudinally for up to 14 years, we assessed the role of dispersion in forecasting death and cognitive decline. Incident neurocognitive impairment was predicted in a mixed-effects ordinal logistic regression model using age, gender, baseline mean cognitive functioning, CD4+, time followed, years of education, and dispersion at the previous visit. Death before the next visit was predicted in a binomial mixed-effects regression model using age, gender, baseline mean cognitive functioning, CD4+, time followed, years of education, and dispersion.

Results: Point-in-time dispersion and change in dispersion between visits predict future cognitive decline and death in HIV + individuals. Individuals with greater dispersion at a visit or who had larger changes in dispersion between visits were more likely to demonstrate greater neurocognitive impairment at the subsequent visit. Greater IIV was also associated with an increased risk of death prior to the subsequent visit, even after controlling for HAND severity and global cognitive functioning.

Conclusions: We conclude that the IIV in cognitive functioning may be more predictive of future disease consequence than mean level of cognitive functioning.

[*]Ariana E. Anderson, Ph.D., Semel Institute at UCLA, 760 Westwood Plaza, Suite 28-224, Los Angeles, CA 90095, (310) 254-5680, ArianaAnderson@mednet.ucla.edu.

Introduction

Cognitive impairment is prevalent among HIV-infected individuals (Heaton et al., 2010). Although advances in HIV treatment have led to a reduction in HIV-associated morbidity and mortality, over time deficits in cognitive function can still emerge, which are in turn associated with difficulties in basic and independent activities of daily living. Historically, HIV was thought to primarily impact subcortical regions and give rise to what has been termed a subcortical dementia. However, based on heterogeneous findings from both neuropsychological and neuroimaging it is now recognized that that there may not be a "prototypical pattern" of cognitive impairment in HIV, as impairments can present across various brain regions and cognitive domains (Woods et al., 2004). Since cognitive impairments can present in some domains while sparing others, there has been increased interest in examining the spread/variability of neurocognitive scores as a measure of neurologic compromise.

The normal aging literature has laid much of the groundwork regarding intra-individual variability (IIV) in cognitive functioning. Traditionally, IIV has been measured by either examining variability across multiple trials within a single task (most commonly reaction time), termed inconsistency, or by measuring variability across multiple tests scores within a single or multiple testing occasions, termed dispersion (Stuss, Murphy, Binns, & Alexander, 2003). Studies of healthy aging report that dispersion captures "spotty" profiles that emerge in the earlier stages of cognitive impairment and reflect a variable pattern of scores, in which some domains start to drop while others remain relatively preserved (Ardila, 2007). Elevated dispersion levels predict declines in functional abilities and earlier mortality rates and do not appear tied to a single, prototypical pattern of impairment but rather represent variability among a range of domains (MacDonald, Hultsch, & Dixon, 2008).

Dispersion and other forms of IIV have also been explored in HIV. Dispersion may be particularly salient as HIV also does not necessarily produce a single pattern of neurocognitive decline (Woods, Moore, Weber, & Grant, 2009). A cross-sectional study previously identified neuroanatomical correlates of dispersion in both healthy and HIV+ individuals, demonstrating that cortical gray matter volume, particularly in the frontal lobes, was inversely associated with dispersion (Hines et al., 2016). This is consistent with prior literature tying elevated dispersion to gray matter lesions in adults who have suffered a traumatic brain injury (Stuss et al., 2003) and provides support for the contention that increased dispersion is a marker of CNS dysfunction rather than just random fluctuation. Others have suggested that increased dispersion can emerge secondary to deficits in executive control (Bellgrove, Hester, & Garavan, 2004) resulting in a reduced ability to maintain the top-down attentional focus required for consistency in cognitive function. Increased IIV has been associated with worse medication adherence, more pronounced immunocompromised, and alterations in white matter integrity (Ettenhofer et al., 2010; Thaler et al., 2015). Moreover, increased IIV had a stronger relationship with adverse outcomes than did mean-level global cognitive performance. Dispersion has also been linked to advancing age among HIV+ individuals, such that greater dispersion was evident in older HIV+ individuals relative to both younger HIV+ individuals and older HIV- controls (Morgan, Woods, & Grant, 2012).

Despite these promising findings, methodological and interpretive concerns regarding extant studies of IIV in HIV are apparent. Dispersion, at a cross-sectional level, simply reflects within-subtest variability of performance, which is always expected to occur to some degree in any neuropsychological assessment. Schretlen and colleagues (Schretlen, Munro, Anthony, & Pearlson, 2003; Schretlen, Testa, Winicki, Pearlson, & Gordon, 2008) have convincingly demonstrated how healthy controls exhibit significant levels of dispersion reflective of the normal variability in cognitive functioning and neuropsychological testing. Therefore, cross-sectional studies of dispersion are confounded by natural, and normal, within-subject variability. Longitudinal investigations of dispersion may prove more fruitful, for if a reliable pattern of increasing dispersion linked to incipient declines in neurological status can be detected, IIV may serve as a harbinger of emerging cognitive deterioration. To date, the majority of studies on dispersion have been cross-sectional in nature. Recent studies support the utility of longitudinal investigations of even brief duration, showing that increases in dispersion, but not change in mean-level cognitive functioning. IIV changes predicted subsequent decline in medication adherence and decreased white matter integrity over time among HIV+ adults (Jones et al., 2017; (Thaler et al., 2015). However, longitudinal studies have yet to examine if dispersion is predictive of other important outcomes such as the risk of transitioning into more severe stages of HIV Associated Neurocognitive Disorder (HAND), or if dispersion increases the risk of impending death.

The current study expands upon the HIV dispersion literature by examining whether total dispersion at a prior visit as well as increases in dispersion over time predict downstream cognitive and functional impairments, defined by HAND staging (Antinori et al., 2007), and predict future risk of death. This study is the first to formally test this hypothesis using a large cohort of HIV+ adults who were followed for up to 14 years and who were assessed multiple times (as many as 24 times) on visits roughly 8 months apart. Based on work to date, we anticipate that individuals who experience greater point-in-time dispersion as well as increases in dispersion relative to previous levels will be more likely to be subsequently diagnosed with a more severe HIV-associated neurocognitive disorder during future assessments. Additionally, we hypothesized that increased dispersion would also be predictive of an increased risk of death.

Methods

Study Design.

The study design was a retrospective analysis of 708 HIV+ participants enrolled in the National NeuroAIDS Tissue Consortium (NNTC) study. The NNTC study design has been previously described in detail (Morgello et al., 2001). In brief, the NNTC is a longitudinal study of HIV+ adults with advanced disease, who agree to donate their tissues to research after death. The cohorts are recruited through one of four sites: a) the National Neurological AIDS Bank located in Los Angeles, CA, b) the Texas Repository for AIDS Research located in Galveston, TV, c) the Manhattan HIV Brain Bank located in New York, NY, and d) the California NeuroAIDS Tissue Network located in San Diego, CA. Institutional review board (IRB) approval was obtained at all respective sites. Participants provided written consent at the four study sites prior to participation study activities. The NNTC database consisted of

2,720 HIV+ participants. We included HIV+ participants with at least 3 visits (including baseline) recorded where participants underwent neurocognitive testing, resulting in a sample size of 708 with number of visits ranging from 3 to 24 after excluding observations for missing data. Median time between visits was 233 days, with 50% of visits occurring between 185 and 388 days as shown in Supplemental Figure 1.

Neuropsychological Measures.

All participants underwent neuropsychological testing, which has previously been described (Morgello et al., 2001; Woods et al., 2004). The current study utilized 15 variables drawn from the following neuropsychological measures: subtests from the Wechsler Adult Intelligence Scale-III (Symbol Search, Digit Symbol Coding, Letter-Number Sequencing), the Trail Making Test parts A & B, Trial 1 from the Paced Auditory Serial Additional Test, the total learning (sum of trials 1–3) and delayed free recall trials of the Hopkins Verbal Learning Test-Revised and the Brief Visuospatial Memory Test, Grooved Pegboard (dominant and non-dominant hand), letter fluency (FAS) and animal fluency from the Controlled Oral Word Association Test, and Boston Naming Test.

Baseline mean cognitive functioning was computed using the mean of the 15 cognitive scores at the first assessment. Neurocognitive dispersion was calculated using the coefficient of variation (within person standard deviation divided by the within person mean) of the 15 neuropsychological test t-scores (Hilborn, Strauss, Hultsch, & Hunter, 2009; Morgan et al., 2012; Thaler et al., 2015).

Using Frascati criteria, HAND severity was classified as follows: no neurocognitive impairment, asymptomatic neurocognitive impairment (ANI), mild neurocognitive disorder (MND), and HIV-associated dementia (HAD; (Antinori et al., 2007). Functional impairment was assessed using the Lawton & Brody Activities of Daily Living measure (Lawton & Brody, 1969). ANI was defined if there was evidence of cognitive impairment (1 SD below the mean on 2 domains or more domains) but no evidence of functional impairment. MND was defied as evidence of cognitive impairment (<1 SD, but >2 SD, across 2 cognitive domains) and functional impairment. A diagnosis of HAD required impairment in cognitive functioning at least 2.0 SD below the mean across two or more domains with marked interference in daily functioning.

Models:

The role of total dispersion in predicting future cognitive decline was assessed in Model 1 (i.e. do individuals with more dispersion have a greater risk for transitioning to a more severe HAND stage). HAND stage was modeled by the log of the CD4 count (at each visit), age, gender, years of education, time the patient had been enrolled in the study, baseline mean cognitive functioning, and the dispersion at the previous visit (lagged dispersion). The dependent variable, HAND stage, was treated as a ranked/ordinal variable (i.e. no cognitive impairment < ANI <MND < HAD), therefore we used an ordinal mixture model fit by REML in the R package *ordinal* (Christensen, 2010). We decided, a priori, to model current CD4 as opposed to nadir CD4. This decision was due to the fact that the current study focuses on longitudinal changes in cognitive functioning. Therefore, current CD4 would be a

more proximal measure of disease severity, which could potentially change throughout the course of the study; as opposed to nadir CD4 that would have been treated as a static variable and could conceivably have been measured decades prior to study activities. Because subjects were seen multiple times, Subject ID was included as a random effect to account for repeated measures. All parameter estimates were converted to odds ratios, and 95% confidence intervals for the odds ratios were computed.

The predictive power of the subject's change in dispersion between the previous and current visit was assessed in Model 2 (i.e. do individuals who show increases in dispersion over time have a greater risk for transitioning to a more severe HAND stage). HAND stage was modeled by the log of the CD4+ count, age, gender, years of education, time followed in days, baseline mean cognitive functioning, and the difference in dispersion between the previous and current visit, using an ordinal mixture model fit. Subject ID was included as a random effect to account for repeated measures. All parameter estimates were converted to odds ratios, and 95% confidence intervals for the odds ratios were computed.

The power of total dispersion to predict death before the next visit was assessed in Model 3 (i.e. do individuals with greater dispersion or increases in dispersion have a higher risk of death). In order to assess stability of the model to censoring, since all subjects were not necessarily followed until death, we conducted two models: one within all available subjects, and a second utilizing only the 305 subjects who died. Death occurring after a given visit was modeled using the log of the CD4+ count, age, gender, years of education, time followed in days, baseline cognitive functioning, and the last available dispersion score prior to death, using a mixed-effects binomial logistic regression fit in R using the package lme4 (Bates, Mächler, Bolker, & Walker, 2014). Subject ID was included as a random effect to account for repeated measures. All parameter estimates were converted to odds ratios, and 95% confidence intervals for the odds ratios were computed.

Finally, predictive factors of dispersion were assessed in Model 4. Dispersion at baseline was modeled using CD4+, Age, Education, Gender, and baseline mean cognitive functioning using a general linear model.

Results

Participants at baseline were between 21 – 81 years old (mean = 43.9 years; standard deviation (SD) = 8.84), 78.5% male, with 12.6 years of education on average (SD = 2.82). Ethnic composition of the sample was 41.3% White, Non-Hispanic Caucasian, 31.2% African American, 24.0% Hispanic, 3.7% Other, and. At baseline, 33.1% of the subjects were rated as neurocognitively normal, 20.1% met criteria for ANI, 30.9% met criteria for MND, and 16% met criteria for HAD. Approximately 57% of the subjects experienced cognitive decline (defined as transition into a more severe HAND staging) during the study. Approximately 63 % of participants died during the course of study. Disease severity and neurocognitive characteristics are shown in Table 1.

Dispersion and Cognitive Decline.

Model 1, which examined whether individuals with higher levels of dispersion have a greater risk for future transitioning to a more severe HAND stage, found dispersion to be a risk factor for worsening cognitive impairment (Figure 1). Specifically, greater dispersion of neurocognitive scores at the previous visit ($p<0.001$), and older age ($p<0.001$) were significantly predictive of transitioning to a more severe HAND stage. Higher levels of education were protective against cognitive decline ($p<0.05$), along with male gender ($p<0.001$) and higher baseline mean cognitive functioning ($p<0.001$). Subjects who remained in the study longer showed less cognitive decline (attrition bias) ($p<0.001$).

In Model 2, increased change in dispersion between the previous and current visit predicted transitioning to a more severe HAND stage ($p<0.001$). Other significant predictors were length of time followed ($p<0.001$) and older age ($p<0.001$). Protective factors for HAND stage included male gender ($p<0.001$), higher baseline mean cognitive functioning ($p<0.001$), and higher levels of education ($p<0.01$).

Dispersion and Mortality Risk.

In Model 3, dispersion at the last available visit was significantly predictive of death ($p<0.01$). Additional risk factors for death included greater time followed in the study ($p<0.001$) and older age ($p<0.001$) estimated within all subjects (Figure 3). Equivalent findings were reached when modeling death only within those subjects who died during the study, suggesting that the findings are not due to censoring.

Predictors of Dispersion.

In Model 4, higher dispersion was strongly associated with increased age ($p<0.05$). In contrast, lower levels of dispersion were associated with better baseline mean cognitive functioning ($p<0.001$) and greater educational attainment ($p<0.01$) (Table 2, Figure 4).

Discussion

This is the first large scale longitudinal study of extended duration to show that IIV, independent of mean cognitive functioning, may serve as a risk indicator for future cognitive decline and death among HIV+ individuals. Individuals with greater IIV were more likely to experience greater neurocognitive impairment at the next visit. Similarly, individuals who experienced increased IIV (scores became more dispersed) were at greater risk for progression of HAND. Individuals with greater IIV also had an increased risk of dying before their next visit.

The finding that IIV was related to progression of HAND and death is generally consistent with previous literature of HIV+ individuals. Among HIV+ individuals, measures of IIV have been linked to immunosuppression, decreased cortical volume, decreased white matter integrity, older age, and poorer medication adherence (Ettenhofer et al., 2010; Hines et al., 2016; Morgan et al., 2012; Thaler et al., 2015). Additionally, these studies have generally found that IIV, relative to mean-level cognitive functioning, is independently, and perhaps more strongly, related to markers of neurologic compromise. This finding also furthers the

literature suggesting that current cognitive compromise can predict future cognitive decline in HIV. Specifically, a study from the CHARTER group found that asymptomatic neurocognitive impairment (ANI) predicted future cognitive decline and conversion to HAND (Grant et al., 2014). Our findings extend that work, suggesting that IIV may allow us to predict conversion to HAND even *before* patients meet criteria for ANI. This integrated finding drives home the clinical utility of IIV as a predictive indicator of future cognitive performance and compromise.

To date, the majority of such studies have been cross-sectional in nature, and weakened by confounds inherent to a cross-sectional approach (Ettenhofer et al., 2010; Hines et al., 2016; Morgan et al., 2012). For one, a certain amount of variability in neuropsychological testing is normal (Schretlen et al., 2003). Therefore, cross-sectional studies are limited in the ability to determine if cognitive variability is long-standing (and represents a person's natural strengths and weaknesses) or if variability is a deviation from a person's premorbid functioning (and may be an early sign of neurologic compromise). The current study expands upon the previous literature by not only showing that people with more variability/dispersion at a single point in time are more likely to transition into more severe HAND staging; but we also showed a within-person effect, such that as a person's neurocognitive performance becomes more dispersed over time, their risk for transitioning into more severe HAND stages increases. This finding is consistent with longitudinal aging studies, which have shown that increases in neuropsychological dispersion scores over time were associated with increased risk for downstream mild cognitive impairment and dementia (Vaughan et al., 2013).

Although investigating possible underlying mechanisms was outside the scope of the current study, past studies have suggested that markers of IIV may be particularly sensitive to frontal-subcortical cognitive systems. Given that HIV may exercise a particular affinity for similar frontal-subcortical systems, disruption of these frontal-subcortical systems may mediate the relationship between HAND severity, mortality and IIV. Indeed, brain MRI studies in HIV+ individuals have shown that greater IIV was related to thinner frontal cortices and less intact white matter tracts underlying frontal-posterior cortical connections (Hines et al., 2015; Jones et al., 2017). Studies of IIV in the healthy aging population have also focused on the role of frontal-subcortical networks. Increased IIV has been linked to both gray and white matter structures within the frontal lobes as well as specific cortical regions important for cognitive functioning (e.g. anterior cingulate and orbital frontal cortex (MacDonald et al., 2008). These structural MRI findings are corroborated by function neuroimaging studies. For example, higher IIV was associated with increased BOLD activity in bilateral frontal regions, which the authors suggested indicated a greater executive control demand in order to successfully complete the task (Bellgrove, Hester & Garavan, 2004). Further, the strength of the relationship between task-positive (e.g. attention network) and task-negative (e.g. default mode network) brain networks has been shown to predict IIV, both when the brain is at rest and when it is engaged in cognitive performance (Kelly, Uddin, Biswal, Castellanos, & Milham, 2008). This finding that network connectivity is associated with IIV was bolstered by a more recent study which, using graph theory, showed that modularity, or the organization of the network, predicted IIV across testing sessions (Stevens, Tappon, Garg, & Fair, 2012). This burgeoning literature is beginning to

demonstrate that behavioral IIV may be a proxy for neural processes, potentially IIV of neural integrity (e.g. increased variability of brain function during a cognitive task required due to reductions in the efficiency, strength or health of that brain region/network).

There are several limitations to this study. The calculation of dispersion was based on neuropsychological T-scores that were computed from separate normative samples. Therefore, some tests were normed adjusting for age and others adjusted for age and other demographic factors such as education and gender. This is a limitation shared by most of the extant IIV studies in the HIV literature (Morgan et al., 2012; Thaler et al., 2015). This study had a predominantly male sample (78.5%), so these results may not accurately reflect the relationship between dispersion and cognitive decline/death in a female population. Other factors such as depression may impact cognitive ability; these analyses were then replicated in 449 subjects for whom the Becks Depression Inventory (BDI) was available - after holding constant the level of depression, dispersion still predicted cognitive decline. Moreover, other medical comorbidities may have influenced dispersion in addition to the primary HIV process. We investigated this by creating a medical comorbidity burden score which tallied the incidence of associated diagnoses: hypertension, diabetes, hyperlipidemia, hepatitis, end stage liver disease, renal disease, cardiac disease, chronic obstructive pulmonary disease, cerebrovascular disease, and non-AIDS cancer. Using this variable to predict dispersion demonstrated a non-significant effect, likely due to its moderate correlation with age ($r = 0.30$). The comorbidities risk was only weakly correlated with dispersion ($r = 0.05$), as shown in Supplementary Figure 2. Future studies may benefit from further parsing out possible confounding effects of neuropsychiatric conditions, substance use disorders and/or medical comorbidities. The models predicting death were validated twice: in the entire cohort, and only within patients who died during the study, to avoid any bias from censoring. Death was also modeled using HAND staging and current cognitive functioning as predictors, instead of baseline mean cognitive functioning, with equivalent findings.

Conclusions

Overall, this study provides evidence that dispersion of neurocognitive functioning may be a sensitive marker for identifying individuals at risk for cognitive decline and death. IIV may potentially be a valuable measure in a neuropsychological assessment. Neuropsychologists typically focus on mean-level performance of cognitive tests, however this study suggests that variability of performance may be an important clinical marker and a harbinger of future mortality and cognitive decline.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Increased Variability in Cognitive Function Over Time Predicts Future Cognitive Decline and 1

Death in HIV: NEUROCOGNITIVE DISPERSION, DECLINE, AND DEATH IN HIV

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Public Significance:

Adults with HIV may develop a form of dementia known as HIV-Associated Neurocognitive Disorder (HAND). In 708 patients, we demonstrate that variability in cognitive functioning precedes and increases the risk of future cognitive decline and death in individuals with HIV.

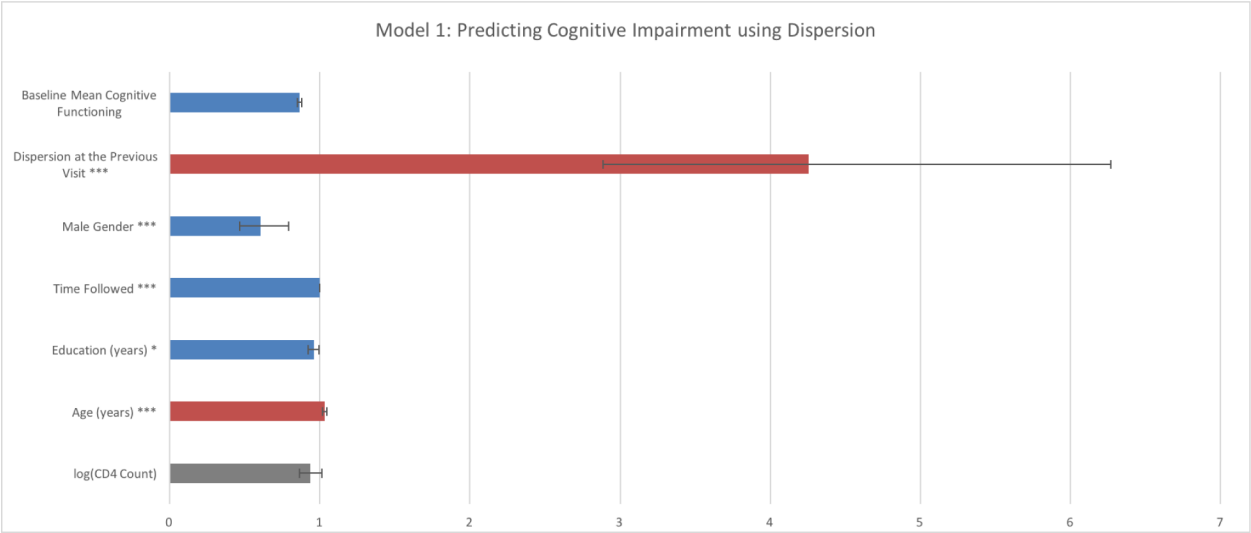

Figure 1:

Dispersion of neurocognitive assessments increased the chance of future cognitive decline ($p<0.001$), as did age ($p<0.001$). Education was protective against cognitive decline ($p<0.05$), along with male gender ($p<0.001$), baseline mean cognitive functioning ($p<0.001$), and time followed ($p<0.001$). Level of impairment was predicted using an ordinal mixed-effects regression model, holding constant for CD4, age, education, gender, time followed, the dispersion at the previous visit, and baseline mean cognitive functioning. Red bars indicate statistically significant risk factors measured in odds ratios, while blue indicate protective factors. Error bars denote 95% confidence intervals of estimates. Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1. logLik=−3546.88, AIC=7115.76.

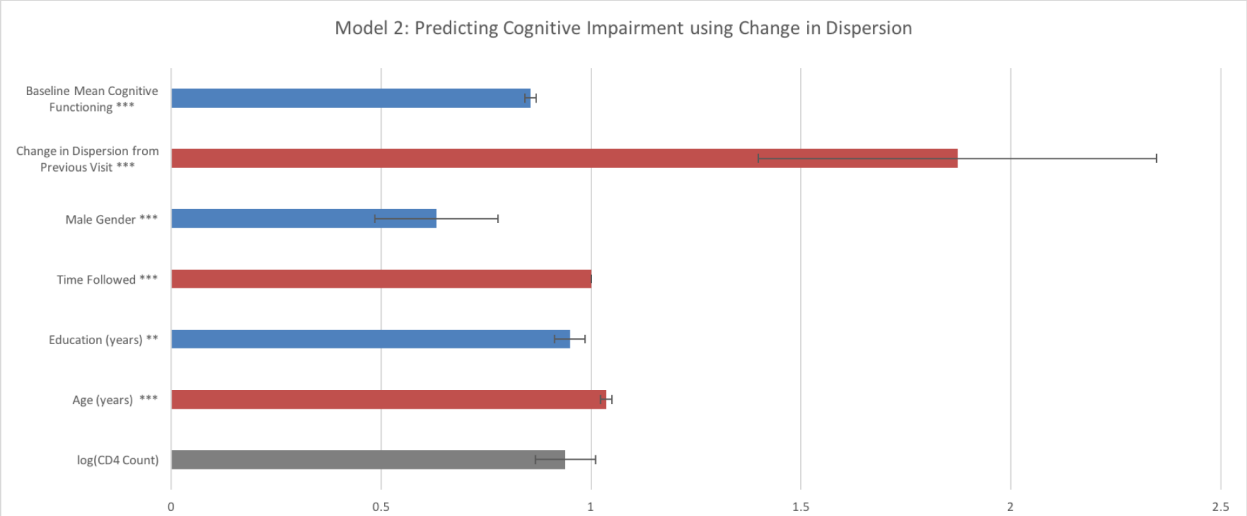

Figure 2:

Increased change in Dispersion between the previous and current visit was significantly predictive o f cognitive decline ($p<0.001$), along with time followed ($p<0.001$), and age ($p<0.001$). Protective factors for cognitive decline included male gender ($p<0.001$), baseline mean cognitive functioning ($p<0.001$), and education ($p<0.01$). Level o f impairment was predicted using an ordinal mixed-effects regression model, holding constant for CD4, age, education, gender, total time followed, change in the dispersion at the previous visit, and baseline mean cognitive functioning. Red bars indicate statistically significant risk factors measured in odds ratios, while blue indicate protective factors. Error bars denote 95% confidence intervals o f estimates. Signif. codes: 0 ‘***’ 0.001 0.01 0.05 0.1 ‘ ’ 1. logLik= −3548.69, AIC=7119.37

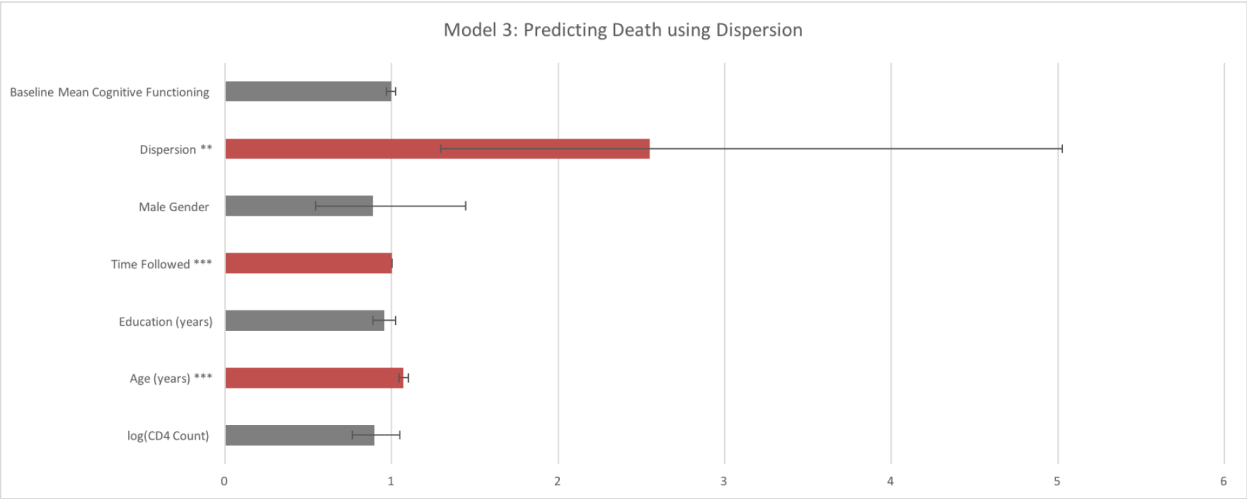

Figure 3:

Dispersion from the most recent visit was significantly predictive of death after that visit (p<o.o1). Additional risk factors for death included time followed (p<o.oo1) and age (p<o.oo1). Death within each subject was predicted using a mixed-effects binomial logistic regression model, holding constant for CD4, age, education, gender, total time followed, dispersion, and baseline mean cognitive functioning. Red bars indicate statistically significant risk factors measured in odds ratios. Error bars denote 95% confidence intervals o f estimates. Signif. codes: 0 '***' 0.001 0.01 0.05 0.1 ' ' 1 . AIC = 2021.5; BIC=2077.5; logLik=−1001.7.

Table 1:

Baseline HIV Disease Severity and Neurocognitive Characteristics. ANI = asymptomatic neurocognitive impairment; MND = minor neurocognitive disorder; HAD = HIV-Associated Dementia

Variable	Mean	Standard Deviation
Cognitive Functioning	44.1	7.17
Dispersion	0.639	0.243
Log CD4	4.81	1.23
No Neurocognitive Impairment (total)	177	-
ANI (total)	79	-
MND (total)	107	-
HAD (total)	23	-
Log Viral Load	2.22	0.744

Table 2:

In Model 4, dispersion at baseline was increased for older patients ($p<0.05$), and decreased for greater education ($p<0.01$) and higher baseline mean cognitive functioning ($p<0.001$). Signif. codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1. Multiple R-squared: 0.1156, Adjusted R-squared: 0.1121. F-statistic: 33.36 on 5 and 1276 DF, p-value: < 2.2e-16

Variable	Estimate	Std. Error	t value	Pr(>|t|)
(Intercept)	1.11	0.06	20.07	***
Male Gender	0.02	0.02	1.07	
Baseline Mean Cognitive Functioning	−0.01	0.00	−12.55	***
log(CD_4)	0.01	0.00	0.06	
Age (years)	0.01	0.00	2.54	*
Education (Years)	−0.01	0.00	−3.06	**