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Is Prospective Memory a Dissociable Cognitive Function in HIV infection?

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Abstract

An emerging literature indicates that HIV infection is associated with deficits in prospective memory (ProM), or the ability to execute a future intention. This literature offers evidence of neurobiological dissociability of ProM from other cognitive abilities and its incremental ecological validity as a predictor of poorer everyday functioning outcomes (e.g., medication non-adherence). The present study evaluated the hypothesis that ProM represents a unique cognitive construct in HIV disease. A confirmatory 4-factor structural equation model was tested on data derived from 162 participants with HIV. The model posited that measures of ProM comprise a unique factor, apart from standard clinical tests of retrospective memory, executive functions, and motor skills. The fit of the model was evaluated using the Bollen-Stine bootstrap method and indicated a 4-factor model with measures of ProM loading on a unique factor fit the data well, and better than a model with a single common factor hypothesized to drive cognitive performance. The results of this study lend further evidence to the dissociability of ProM in HIV infection, are consistent with prior studies in healthy adults, and contribute to a growing literature on the construct validity of ProM in HIV disease.

Keywords

Human Immunodeficiency Virus; AIDS dementia complex; Neuropsychological tests; Cognitive science; Episodic memory

INTRODUCTION

Although the profile of HIV-associated neurocognitive disorders (HAND; Antinori et al., 2007) varies across individuals (Dawes et al., 2008), mild-to-moderate deficits are commonly observed in the domains of episodic memory, executive functions, psychomotor speed, and attention/working memory (Reger et al., 2002). In fact, episodic memory is among the most prevalent and prominent neurocognitive casualties of HIV (Carey et al., 2004). Consistent with the prominent frontal systems effects of HIV, the modal profile of HIV-associated episodic memory impairment involves deficits in initial acquisition (e.g., limited use of higher-level encoding strategies, such as semantic clustering) and strategic retrieval, with relatively spared consolidation (e.g., Delis et al., 1995). Importantly, such deficits have attendant implications for everyday functioning, including poorer vocational outcomes (van Gorp et al., 2007) and medication nonadherence (e.g., Hinkin et al., 2002). However, research focusing on the association between declines in everyday functioning and HIV-associated episodic memory impairments has largely been limited to the construct of retrospective memory (RetM), to the

exclusion of an arguably more ecologically germane facet of episodic memory, *prospective memory* (e.g., Woods et al., 2008).

Prospective memory (ProM) refers to one's ability to "remember to remember," or to execute a future intention in accordance with a time- or event-based cue. Carey and colleagues (2006) articulated a 5-stage component model of ProM that they adapted from prior conceptual work. Specifically, the process begins where an intention is formed and is connected to a time-based (TB) or event-based (EB) cue (e.g., "I have to remember to take my medication...*at 3 o'clock* [TB] or *before I go to bed* [EB]"). An implicit subcomponent to this first stage is the formation of a plan for the execution of the intention. The next stage requires retention or maintenance of the intention over an interval of time during which attentional and other cognitive resources are relegated to on-going activities that preclude rehearsal of the intention. Therefore, strategic monitoring processes may be required under some conditions to detect the occurrence of the appropriate TB or EB cue. In the third stage, a self-initiated retrieval process is triggered by detection of the appropriate cue (e.g., "I told myself to do something before bed today"). The penultimate stage represents the recall (i.e., retrospective memory) of the stored intention. Finally, execution of the intention follows, with an evaluation of the continued applicability of the original intention.

Individuals living with HIV infection endorse more ProM complaints in their daily lives than their seronegative counterparts (Woods et al., 2007). HIV disease is also associated with mild-to-moderate impairment on performance-based measures of both TB and EB ProM (Carey et al., 2006; Martin et al., 2007), specifically in the strategic encoding and self-initiated retrieval of future intentions. HIV-associated ProM impairments are strongly associated with nonadherence to antiretroviral medications, explaining a substantial amount of variance, even after controlling for retrospective learning and memory, and non-cognitive factors such as HIV disease severity, psychiatric comorbidity, psychosocial factors and environmental structure (Contardo et al., 2009; Woods, et al., 2009). Related to this, objective ProM impairment and self-report complaints of ProM were each independently associated with increased risk of dependence in everyday functioning in people with HIV infection and together predicted dependence even after controlling for RetM (Woods et al., 2008).

Although there is emergent evidence for the predictive and incremental ecological validity of ProM in HIV infection, several important issues remain to be explored. For example, the 5-stage model articulated above raises questions about the distinctiveness of the construct. That is, components of the ProM process ostensibly draw upon executive functions and RetM learning and recall. Given this apparent conceptual overlap, can ProM be considered a unique cognitive province? Evidence for the dissociability of ProM arises from several lines of investigation, including neuroimaging and cognitive studies in healthy adults, as well as neuropsychological studies of HIV. Current theoretical models suggest that, while ProM shares some overlapping prefrontal and medial temporal networks with RetM (McDaniel & Einstein, 2007), it nevertheless is singly dissociable perhaps by virtue of its greater reliance on the rostral prefrontal cortex (e.g., Burgess et al., 2003). Although clinical data addressing this conceptual issue are sparse, PET and fMRI neuroimaging studies in healthy adults show that ProM is associated with activation of Brodmann area 10 (Burgess et al., 2003; Haynes et al., 2007; den Ouden et al., 2005; Simons et al., 2006), as well as the right parietal cortex (Burgess et al., 2001; Eschen et al., 2007; den Ouden et al., 2005), and precuneus (Burgess, 2001; Zollig et al., 2007). In one of the few studies to directly compare the neural correlates of ProM and RetM, West and Krompinger (2005) reported that the constructs shared some common, as well as some independent, neural activity patterns as visualized by event-related brain potentials. Specifically, they found that similar processes may underlie ProM and RetM retrieval, whereas neural processes unique to ProM, which support cue detection and post-retrieval processes

(e.g. disengagement from on-going task, post-retrieval monitoring) likely contribute to the realization of delayed intentions.

Despite disagreements regarding the cohesiveness of ProM as a construct in itself (see Cockburn & Smith, 1991 and Ellis, 1996 for opposing viewpoints), evidence for its dissociability is found in psychometric studies within non-clinical samples. Through these studies, ProM has been delineated from RetM, allowing the differential effect of aging on each of these ability areas to be extensively examined (Einstein & McDaniel, 1990; Maylor, 1990; Rendell & Thomson, 1993; for a review, see Henry et al., 2004). Other efforts to establish ProM as a unique construct have centered on its divergent and discriminant validity with other cognitive and personality variables (Einstein & McDaniel, 1996). The few existing factor analytic studies addressing this question tend to offer support for the uniqueness of ProM among other cognitive constructs (Maylor et al., 2002; Salthouse et al., 2004; Uttl et al., 2001). For example, Salthouse et al. (2004) demonstrated the convergent and discriminant validity of the ProM construct in healthy adults using four models with increasingly challenging models. They note that in spite of being allowed to load on every other factor in the model, their measures of ProM retained significant loadings on a unique, separate factor.

Further evidence for the dissociability of ProM and RetM is apparent in the HIV neurocognitive literature. For example, ProM and RetM are found to be moderately correlated, with coefficients in the .40–.50 range (Carey et al., 2006; Martin et al., 2007; Woods et al., 2007), which suggests measures of these abilities are related in HIV-infected individuals, but also exhibit some distinctiveness. Additionally, as mentioned earlier, ProM shows incremental ecological validity over RetM as a predictor of functional outcomes, including self-reported declines in instrumental activities of daily living (Woods et al., 2008) and medication mismanagement (Woods et al., 2009). Furthermore, one study by Woods et al. (2006) indicated that ProM, but not RetM, was associated with select biomarkers of neuropathogenic processes in both blood plasma and cerebrospinal fluid (CSF). In this study, objective ProM impairment was correlated with biomarkers of macrophage activation such as soluble tumor necrosis factor receptor II (sTNFR_{II}) in CSF and monocyte chemoattractant protein-1 (MCP-1) in plasma, and with tau, a biomarker of neuroaxonal injury in CSF, whereas no such correlations were observed for standard clinical tests of RetM (Woods et al., 2006). Most recently in an exploratory factor analysis, component measures of the Memory for Intentions Screening Test (Raskin, 2004) were found to have their highest factor loadings on factors distinct from other factors representing more traditional cognitive abilities measured in HIV (Contardo et al., 2009). Although this latter study represents an important initial attempt at highlighting the distinctiveness of ProM within a larger neurocognitive battery, it suffered from several notable weaknesses that limit the conclusions that can be drawn regarding this important issue. Specifically, the authors took an exploratory approach that included only a single ProM measure and just 2 non-ProM tests in the battery; as might be expected, the subtests for each of these tests loaded on separate factors (i.e., the MIST loaded on 2 factors, whereas Trail Making Test A and B and the Hopkins Verbal Learning Test loaded on 2 separate factors). This raises the very real possibility that the factors on which the subtests loaded represented common method variance because they came from the same instrument, rather than because they represent distinct abilities. In addition, their sample size of 99 participants was quite small for an exploratory factor analysis by most standards (Tabachnick & Fidell, 2001). In addition, the authors reported a factor solution with orthogonal rotation because it was not substantially different from oblique rotation analysis, yet the factor correlations and other important information associated with the latter are not reported. Finally, it is unclear how to interpret their results since they use all 6 scales of the MIST, which are not mutually exclusive and overlap with respect to item content. Taken together, these weaknesses point to the need for further research that uses a confirmatory approach with larger sample sizes and more comprehensive neurocognitive assessments to evaluate the dissociability of ProM in HIV.

In sum, there is a considerable body of evidence indicating that ProM is dissociable from RetM and other cognitive abilities. However, this hypothesis has never been prospectively evaluated within the context of HIV infection using a confirmatory multivariate statistical approach, such as confirmatory factor analysis, which is a more sophisticated and stringent test of theory than exploratory factor analysis. Testing a theory-driven factor model in which two separate objective assessments of ProM load on a unique ProM factor, apart from measures of RetM and other cognitive ability domains, and using a unique combination of neuropsychological tests would lend considerable support to the hypothesis that ProM is a unique construct in HIV disease. The model would only fit the data if measures of ProM shared enough common variance that was also not shared with measures of other cognitive abilities. Therefore, we posit such a model (Model A), in which ProM summary scores from two different prospective memory assessment instruments would load on a factor separate from RetM, executive function and motor factors (see figure 1). We hypothesize that this configuration of the model would represent the best fit to the data, as compared to four competing models: a single common factor model (Model B; see figure 2) because of its designation of ProM, RetM, executive functions and motor functioning as distinct factors; and three additional 3-factor models (Models C, D, and E; see figure 2) in which ProM measures load on a RetM factor, a executive functioning factor, or a motor factor, respectively. These latter three models represent challenges to the assertion that ProM measures are best represented as a unique cognitive construct and do not share enough variance with measures of other ability domains to be represented by them.

METHOD

Participants

One hundred sixty-two participants infected with HIV were recruited to participate in this study from the San Diego metropolitan area via local print media publications and HIV clinical treatment settings. Each participant issued written informed consent prior to enrollment in the study, which was sanctioned by the institute's human research protections program. Individuals with histories of severe psychiatric illness (e.g., schizophrenia), neurological disease (e.g., seizure disorders), substance dependence and a urine toxicology screen positive for illicit drugs (except marijuana) on the day of assessment were excluded. Table 1 displays the demographic and HIV disease characteristics of the study sample, as well as the rates of Major Depressive, Generalized Anxiety, and Substance Use Disorders, which were diagnosed according to the *Diagnostic and Statistical Manual of Mental Disorders* (4th ed., American Psychiatric Association, 1994) criteria using the Composite International Diagnostic Interview (CIDI; version 2.1; World Health Organization, 1998). As shown in Table 1, approximately 32% of the cohort met diagnostic criteria for an HIV-associated neurocognitive disorder (HAND; Antinori et al., 2007) based on a comprehensive medical, psychiatric, and neuropsychological examination, a prevalence rate that is consistent with current epidemiological estimates of HAND in largely healthy populations of HIV-infected individuals (e.g., Heaton et al., 2009).

Materials and Procedure

Prospective Memory Assessment—All participants completed the Memory for Intentions Screening Test (MIST; Raskin, 2004) and the Abbreviated Assessment of Intentional Memory (AAIM; Iudicello et al., 2007; Raskin & Buckheit, 2001; Woods et al., in press). The order of administration of the MIST and AAIM was randomized for each participant. The MIST is a 30-minute, eight-trial ProM task that includes four time-based (e.g., "In 15 minutes, tell me that it is time to take a break") and four event-based (e.g., "When I show you a postcard, self-address it") trials. The MIST yields several ProM performance scores (e.g. summary score, recognition total, distractor total), but for the purposes of this investigation, only the summary scores were used. Similarly, the AAIM is a 30-minute ProM

task that also includes four time-based (e.g., “In 15 minutes, move the pen”) and four event-based (e.g., “When I show you a picture of a cow, snap your fingers”) trials, of which summary scores were also entered into the analysis. As such, two separate objective measures of ProM performance were included in this study (i.e., MIST and AAIM summary scores). The principal difference between the MIST and AAIM is the semantic relatedness of the cue and response (see examples above). For both ProM tests, word search puzzles were provided as an ongoing distractor task to prevent active rehearsal of the prescribed intentions.

Basic Neuropsychological Assessment—Other neuropsychological measures were selected *a priori* for inclusion in the analysis from a larger test battery based on their sensitivity to HAND and/or conceptual similarity to the component processes of our conceptual model of ProM. In particular, measures were selected which would best represent hypotheses challenging the uniqueness of ProM within the domains of RetM, executive functions, and motor skills. See Table 2 for a comprehensive list of the neurocognitive tests by domain, along with the specific raw score from each test that was used in the current analyses. Note that, we elected to use the delayed recall indices from our RetM tests, rather than the corresponding measures of learning. This decision was based on several factors, including absence of an appropriate ProM score or measure that would be analogous to the learning trials of RetM measures in this study (i.e., CVLT-II Total Trials 1–5 and Logical Memory I). Moreover, considering the conceptual model described above, measures of delayed recall, which are among the most commonly impaired tasks in HIV disease (e.g., Heaton et al., 2009), arguably provide the most rigorous test of the dissociability of ProM from RetM. Finally, the measures of immediate and delayed recall given in this study were correlated at the $r > .80$ ($ps < .0001$) level, suggesting a strong degree of collinearity.

Data Analyses

Given that our aim was to establish the distinctiveness of the ProM construct—particularly with respect to RetM and executive functions—the selected tests were configured such that they loaded on the factor with which they shared the most conceptual similarity. Therefore, we articulated a confirmatory model to test for fit to the data (Model A; see Figure 1) in which measures of delayed recall of verbally presented information loaded on a RetM factor, measures of planning, set shifting, working memory and verbal fluency loaded on an executive functions factor, and measures of fine motor dexterity loaded on a motor factor, leaving measures of ProM to load on a unique ProM factor. Additional models were analyzed (see Figure 2) that were designed to evaluate competing hypotheses about the uniqueness and dissociability of ProM. Model B evaluates the hypothesis that a single general factor underlying all of the measured neurocognitive abilities best explains the data. Models C, D, and E evaluate the hypotheses that ProM measures are better represented by other measured abilities. The preceding models were evaluated for fit using confirmatory factor analysis (CFA) via *Amos Graphics 16.0* (Arbuckle, 1997) structural equation modeling (SEM) program, which can use a variety of procedures to derive parameter estimates and evaluate model-data fit. Although the inputs for the analyses were raw data, Amos derives and analyzes the variance-covariance matrix of the data to calculate parameter estimates. For the purposes of univariate interpretation, we have included the correlation matrix of these data, which is displayed in Table 3. The frequency of missing data was very low with only 15 data points missing out of a total 2430 (0.6%). Because missing data are problematic in confirmatory factor analyses, these 15 missing data points were imputed using a regression-based data imputation algorithm available in the Amos Graphics software.

RESULTS

Jackson et al. (2009) articulated recommendations for reporting practices in CFAs and the results reported here are consistent with these guidelines. Each of the models articulated above was evaluated for fit to the data (see Figures 1 and 2). Prior to evaluating the fit of the models, the distributional properties of the data were examined, particularly for joint multivariate normality. Consistent with prior studies of ProM, the data in many cases were non-normal with respect to individual variables and departed considerably from acceptable thresholds of joint multivariate normality. Table 4 displays an assessment of normality for each measured variable included in the model, as well as a value for multivariate normality. Critical ratios (c.r.) greater than 2.0 and less than -2.0 for skew and kurtosis, indicate significant degrees of non-normality. A number of individual measured variables have c.r. values outside this bound for skew, kurtosis or both. C.r. values for multivariate normality less than 2.0 also suggest adequate multivariate normality, c.r. values greater than 2.0 but less than 10.0 indicate moderate multivariate non-normality, and c.r. values greater than 10.0 indicate significant non-normality. Given a multivariate c.r. value of 22.880 observed in this sample, we concluded that the data were significantly joint multivariate non-normal. This precluded the use of Maximum Likelihood estimation procedures as the data violated the assumption of joint multivariate normality.

Consequently, the Bollen-Stine bootstrap method was used to assess model-data fit (Bollen & Stine, 1992). In the case of each model, 2000 bootstrap samples with replacement were generated and model chi-squares were calculated for each bootstrap sample by the program. The significance test for fit evaluates the null hypothesis that the hypothesized model is correct. In the case of Model A, the Bollen-Stine *p*-value, which is based on the proportion of bootstrap samples for which the model fit worse than the study sample, indicated the model would not be rejected ($p = .51$). In other words, the model significantly fit the data and the mean chi-square fit for the 2000 samples was 26.8, with a standard error of .184 for a model with 29 degrees of freedom. By contrast, the Bollen-Stine *p*-value for the general factor Model B, with 35 degrees of freedom, was $p < .0001$, which indicates rather unequivocally that the model should be rejected. The Bollen-Stine *p*-values for the remaining models (C, D, and E) also fell within the rejection region ($p < .05$). Their *p*-values, the mean Chi-square fits, and other measures of model-data fit are displayed in Table 5. Note that hypothesized Model A's fit diagnostics are superior to all others. It is notable that Model A fits the data very well, both in an absolute sense and, as can be seen from the (lowest) Akaike Information Criterion (AIC) value, better than the other models.

Given that we achieved acceptable fit of our hypothesized model to the data, parameter estimates were also derived and are displayed in Figure 3. Amos Graphics provides standardizes estimates of factor loadings and the proportion of variance accounted for in each measured variable, by its respective factor. Finally, parameter estimates of inter-factor correlations are also presented, which show that the correlation between the ProM factor and the RetM factor is $r = .55$. This is similar to the level observed in univariate associations mentioned earlier and lends additional support to the idea that ProM functions have some degree of convergence with RetM and executive functions, but also show a considerable amount of uniqueness or dissociability.

DISCUSSION

The aim of the present research was to examine the construct validity of ProM in HIV infection, and to specifically evaluate the hypothesis that ProM is dissociable from conceptually related constructs, such as RetM and executive functions. Multivariate approaches to addressing this issue are relatively rare in the ProM literature, particularly in clinical groups for whom the

construct may be most ecologically relevant. In brief, results from a confirmatory 4-factor structural equation model in our HIV sample revealed that measures of ProM loaded on a unique factor, apart from tests of RetM, executive functions, and motor skills. The fit of the model was very good in absolute terms and was superior to a competing model, thereby lending additional evidence to the dissociability of ProM in persons living with HIV infection.

Model A (Figure 1) represented our *a priori* hypothesis that ProM is a cognitive construct that has a considerable conceptual distinctiveness from other cognitive constructs and could be psychometrically set apart. Considerable support for this assertion could be marshaled if well-operationalized objective measures of ProM shared more variance among one another than among measures of other ability domains. Model B represented at least one model challenging this assertion. Specifically, Model B assessed whether the data were not better represented by a general factor, thought to drive performance across all measures. Given that this latter model failed to adequately fit the data, it lends credence to the idea that the performance of subjects in one cognitive domain did not necessarily predict performance in another domain. The remaining models tested the hypothesis that ProM is best characterized by other domains of cognitive functioning, the results of which do not support these conclusions. Rather, the results suggest that there is considerable independence and dissociability in the various domains of cognitive functioning measured and that ProM stands on its own as a unique and independent cognitive domain, insufficiently measured by others. Additionally, examination of the structural coefficients yielded findings in resonance with previous studies. Specifically, as indicated in Figure 2, ProM and RetM factors show moderate correlations with one another ($r = 0.55$), which is very similar to univariate associations reported in separate samples, which fell in the 0.40 to 0.50 range (Carey et al., 2006; Martin et al., 2007). Parameter estimates also suggest that the ProM factor accounts for more than 50% of the variance in both objective measures of ProM performance.

Our results resonate with a growing body of literature in healthy adults and HIV by suggesting that, although aspects of ProM overlap with RetM, ProM nevertheless is dissociable from RetM at the neural, cognitive, and behavioral levels. Others (Einstein & McDaniel, 2007; West & Krompinger, 2005) have noted that ProM and RetM display overlapping as well as unique patterns of neural systems activation during strategic retrieval processes. This is commensurate with the finding that ProM, but not RetM, correlates with HIV biomarkers of neuronal injury and macrophage activation (Woods et al., 2006). Prior correlational studies show that not only does ProM correlate with RetM, but it also explains variance in self-report declines in instrumental activities of daily living above and beyond these factors (Woods et al., 2008). Behavioral research on medication adherence similarly shows objectively-measured ProM to be an independent predictor of antiretroviral nonadherence in models in which RetM was included as a covariate (Woods et al., 2009).

Although the results of this study generally offer rather strong support for the dissociability of ProM, weaknesses evident in this study remain to be addressed and caution against overgeneralization. The sample in this study consisted of mostly men, a majority of whom were Caucasian. This warrants cross-validation with more diverse HIV samples (e.g., older adults, women, and ethnic minorities) and with other clinical samples (e.g., Parkinson's disease) to confirm our findings, particularly before assertions can be made that ProM should be a routine part of clinical neuropsychological assessment. Also, this study was limited by a sample size that was rather smaller than oftentimes used in CFAs; nevertheless, the bootstrapping technique deployed in this study tends to allow for some degree of latitude in sample size recommendations. Limitations notwithstanding, we feel that the results of this study contribute a notable advancement in the reification of the ProM construct as a dissociable cognitive ability among people living with HIV.

Future efforts to examine the dissociability of ProM could further enhance the literature in a number of important areas. For example, there is a clear need to establish differential patterns of neural activation for ProM tasks and tasks representing other cognitive domains, such as RetM and executive functions. Future neuroimaging endeavors that offer the spatial and temporal resolution needed to evaluate these activation patterns would add to our understanding of the uniqueness of ProM as a cognitive domain at least partially sub-served by its own neural networks. Another limitation of this study was inconsistency in the structure and format of the RetM and ProM measures. Specifically, the RetM tasks did not include recall for actions, and instead require recall of verbal responses, while both of the ProM measures require 50% verbal responses and 50% action responses. Obviously, a better test of the cognitive dissociability of these would require equal proportions of each for ProM and RetM (as well as comparability in other psychometric properties, including difficulty); however memory for actions may actually tap into separate domains of praxis and consequently share little variance with measures of delayed verbal recall. Although the motor domain was not expected to challenge the dissociability of ProM to the same extent as the RetM and executive functions domains, it was included for its sensitivity to HAND (Carey et al., 2004), and while other domains such as processing speed have also been demonstrated to be sensitive to HAND, the study battery included only one measure of cognitive speed, which is insufficient for a CFA. Also, structural examinations of longitudinal data that include ProM could be useful in evaluating the robustness of ProM measurement and structural relations over time. This latter would be useful in exploring whether ProM measurement converges with measurement of other cognitive domains upon retest with the same battery, or whether it remains a distinct cognitive construct. Future investigations of any type will require well-operationalized measures of the ProM construct and well-designed methods for such testing hypotheses.

Assuming satisfaction of these preconditions, we believe that it is very likely that ProM will remain robust to challenges to its cognitive sovereignty and ultimately prove to be a useful clinical tool. Measures of ProM annex a substantial amount of unique variance in the neurocognitive performance of people with HIV, demonstrate evidence for the predictive and incremental ecological validity in HIV infection, and show significant associations with prognostically salient behavioral data, such as medication management. The development of demographically adjusted normative standards for measures of ProM, such as the MIST, is critical to enable these tasks to be deployed as a routine part of neuroAIDS clinical assessments and research protocols. Results of this study lend further support for the construct validity of ProM in HIV, supplement the extant literature on its clinical utility in cognitive assessments of people living with HIV, and ultimately highlight the potential importance of its clinical measurement, despite the additional time burden.

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MODEL A

Figure 1.
Structural Equation Model A

Figure 2.
Structural Equation Models B, C, D, and E

Figure 3.
Structural Equation Model A with Parameter Estimates

Table 1

Participants' demographic, psychiatric, and HIV disease and treatment characteristics

Participant Characteristics	(n = 162)
Demographic Characteristics	
Age (years) [†]	45.5 (8.8)
Education (years) [†]	13.5 (2.7)
Estimated Verbal IQ ^{a,†}	103.6 (12.4)
Sex (% men)	87.0
Ethnicity (% Caucasian)	61.1
HIV Disease Characteristics	
Estimated duration of infection (years) ^b	15.1 (7.2, 20.2)
Current CD4 count ^b	524.0 (328.0, 777.0)
Nadir CD4 count ^b	170.5 (39.5, 302.0)
HIV RNA log ₁₀ ^b	1.7 (1.7, 2.3)
Proportion with AIDS (%)	60.5
Proportion on HAART (%)	79.6
HIV-associated neurocognitive disorders (% impaired)	32.1
Asymptomatic Neurocognitive Impairment (%)	24.1
Mild Cognitive-Motor Disorder (%)	6.9
HIV Associated Dementia (%)	1.2
Psychiatric Characteristics	
Lifetime Major Depressive Disorder (%)	53.1
Lifetime Generalized Anxiety Disorder (%)	6.9
Lifetime substance dependence ^c (%)	53.1
Profile of Mood States (total mood disturbance)	55.6 (34.6)

Note.

[†] Sample means (standard deviations);

^a Verbal IQ ($M = 100$; $SD = 15$) was derived from the Wechsler Test of Adult Reading (WTAR);

^b Median (interquartile range);

^c Reflects any prior substance dependence diagnosis.

Table 2**Neuropsychological Test Battery by Domain**

Test Name	Domain
WMS-III Logical Memory II (LM II)	Retrospective
CVLT-II Long Delayed Free Recall (CVLT LDFR)	Memory
Trail Making Test-B total time (TMT-B)	
Tower of London total moves (TOL)	Attention & Executive
Digit Span (DSp)	Functions
Verbal fluency (letter C)	
Grooved Pegboard Test, Dominant Hand (GP-D)	Motor
Grooved Pegboard Test, Non-dominant Hand (GP-ND)	Coordination
MIST, Summary Score	Prospective
AAIM, Summary Score	Memory

Note: Only raw scores from above tests were entered into analysis. WMS-III = Wechsler Memory Scale (3rd ed.); CVLT-II = California Verbal Learning Test (2nd ed.); MIST = Memory for Intentions Screening Test; AAIM = Abbreviated Assessment of Intentional Memory.

Table 3
Correlation Matrix and Sample Means, Standard Deviations and Ranges of Measured Variables

	[1]	[2]	[3]	[4]	[5]	[6]	[7]	[8]	[9]	[10]	Mean (SD)	Range
LM II [1]	1.00										24.14 (9.3)	0–45
CVLT LDFR [2]	.62 ^c	1.00									9.95 (3.9)	0–16
TMT-B [3]	-.36 ^c	-.31 ^c	1.00								71.16 (39.4)	28–301
TOL [4]	-.25 ^b	-.24 ^b	.46 ^c	1.00							28.45 (20.0)	0–96
DSP [5]	.33 ^c	.27 ^b	-.51 ^c	-.39 ^c	1.00						17.02 (3.9)	7–28
VF-Ltr [6]	.26 ^b	.30 ^c	-.35 ^c	-.19 ^b	.36 ^c	1.00					14.53 (4.4)	4–25
MIST-Sum [7]	.33 ^c	.36 ^c	-.31 ^c	-.20 ^b	.25 ^b	.20 ^a	1.00				38.15 (7.5)	15–48
AAIM-Sum [8]	.34 ^c	.25 ^b	-.30 ^c	-.12	.20 ^b	.09	.54 ^c	1.00			32.51 (7.4)	6–48
GP-D [9]	-.17 ^a	-.25 ^b	.37 ^c	.22 ^b	-.20 ^a	-.27 ^b	-.12	-.16 ^a	1.00		69.95 (15.0)	46–139
GP-ND [10]	-.15	-.23 ^b	.33 ^c	.17 ^a	-.24 ^b	-.30 ^c	-.12	-.19 ^a	.69 ^c	1.00	76.23 (19.8)	53–230
	[1]	[2]	[3]	[4]	[5]	[6]	[7]	[8]	[9]	[10]		

Note: LM II = WMS-III Logical Memory II; CVLT LDFR = CVLT-II Long Delayed Free Recall; TMT-B = Trail Making Test-B total time; TOL = Tower of London total moves; DSP = Digit Span; VF-Ltr = Verbal Fluency-Letter C; MIST-Sum = MIST-Summary Score; AAIM-Sum = AAIM Summary Score; GP-D = Grooved Pegboard Test (Dominant Hand); GP-ND = Grooved Pegboard Test (Non-dominant Hand);

^a
 $p < .05$;

^b
 $p < .01$;

^c
 $p < .001$

Table 4

Assessment of Univariate and Multivariate Normality

<u>Variable</u>	<u>Skew</u>	<u>c.r.</u>	<u>Kurtosis</u>	<u>c.r.</u>
LM II [1]	-.302	-1.568	-.417	-1.085
CVLT LDFR [2]	-.233	-1.208	-.852	-2.215
TMT-B [3]	2.603	13.524	9.230	23.980
TOL [4]	.760	3.948	.024	.062
DSp [5]	.230	1.194	-.035	-.092
VF-Ltr [6]	.251	1.306	-.095	-.246
MIST-Sum [7]	-.887	-4.611	.387	1.004
AAIM-Sum [8]	-.569	-.2954	.455	1.182
GP-D [9]	2.244	11.659	7.117	18.491
GP-ND [10]	3.705	19.253	22.498	58.452
Multivariate			55.698	22.880

Note: LM II = WMS-III Logical Memory II; CVLT LDFR = CVLT-II Long Delayed Free Recall; TMT-B = Trail Making Test-B total time; TOL = Tower of London total moves; DSp = Digit Span; VF-Ltr = Verbal Fluency-Letter C; MIST-Sum = MIST-Summary Score; AAIM-Sum = AAIM Sumamry Score; GP-D = Grooved Pegboard Test (Dominant Hand); GP-ND = Grooved Pegboard Test (Non-dominant Hand);

^a
 $p < .05$;

^b
 $p < .01$;

^c
 $p < .001$

Table 5

Indices of Model Fit

Model	Bollen Stine <i>p</i> -value	IFI	TLI	AIC	Mean X ² (S.E.)	Model <i>df</i>
Model A	.508	1.02	1.04	77.63	26.80 (.18)	29
Model B	<.0001	.45	.24	150.64	36.27 (.25)	35
Model C	.030	.87	.80	95.83	29.87 (.20)	32
Model D	.017	.84	.75	100.85	34.48 (.21)	32
Model E	.005	.78	.65	109.56	31.43 (.21)	32

Note: IFI = Incremental Fit index; TLI = Tucker-Lewis Index; AIC = Akaike Information Criterion; Mean X is mean Chi-square over 2000 bootstrapped samples; (S.E.) = Standard Error of Mean X²