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The Semantic Relatedness of Cue-Intention Pairings Influences Event-Based Prospective Memory Failures in Older Adults with HIV Infection

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Abstract

HIV infection and aging are each independently associated with prospective memory (ProM) impairment, which increases the risk of poor functional outcomes, including medication adherence. The incidence and prevalence of HIV infection among older adults has increased in recent years, thereby raising questions about the *combined* effects of these risk factors on ProM. In the present study, 118 participants were classified into four groups on the basis of HIV serostatus and age (i.e., ≤ 40 years and ≥ 50 years). Results showed significant additive effects of HIV and aging on event-based ProM, with the greatest deficits evident in the older HIV+ group, even after controlling for other demographic factors and potential medical, and psychiatric confounds. Event-based ProM impairment was particularly apparent in the older HIV+ group on trials for which the retrieval cue and intention were not semantically related. Worse performance on the semantically unrelated cue-intention trials was associated with executive dysfunction, older age, and histories of immunocompromise in the older HIV+ cohort. These data suggest that older HIV-infected adults are significantly less proficient at engaging the strategic encoding and retrieval processes required to a execute a future intention when the cue is unrelated to the intended action, perhaps secondary to greater neuropathological burden in the prefrontostriatal systems critical to optimal ProM functioning.

Keywords

Human immunodeficiency virus; Episodic memory; aging; AIDS dementia complex; multi-process theory

The incidence and prevalence of HIV infection among older adults has risen sharply in the last decade (Centers for Disease Control and Prevention, 2007). In the United States, persons age 50 years and older represent nearly one-quarter of the HIV epidemic and approximately one-third of the reported AIDS cases (CDC, 2007). As compared to their younger counterparts, older HIV-infected adults are greater risk for rapid disease progression (e.g., Goetz et al., 2001) and death (Perez & Moore, 2003). Older adults with HIV are also more likely to experience HIV-associated central nervous system (CNS) complications, including increased neuropathological burden (e.g., beta-amyloid deposition; Green et al., 2005), smaller frontal grey matter volumes (i.e., Jernigan et al., 2005), and spectroscopic evidence of neural injury in the frontal white matter and basal ganglia (e.g., Ernst & Chang, 2004). Older HIV-infected

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adults are also at heightened risk for HIV-associated neurocognitive disorders (e.g., HIV-associated dementia; Valcour et al., 2004), even after disease severity, treatment factors, psychiatric confounds, and other demographic variables are considered.

Early research findings suggest that older adults with HIV are most susceptible to impairment in executive functions, attention, information processing speed, and episodic memory (e.g., Cherner et al., 2004; Sacktor et al., 2007). To our knowledge, however, no studies have examined the combined effects of HIV infection and aging on prospective memory (ProM). ProM is an aspect of episodic memory that refers to the diverse set of cognitive abilities involved in successfully executing a future intention, or more simply: "remembering to remember." Highlighting the clinical relevance of this construct, everyday examples of ProM include remembering to return a telephone call, take prescribed medications on schedule, and pay the monthly household bills. Although conceptual models of ProM vary across the literature (see Kleigel, McDaniel & Einstein, 2008 for a review), some of the essential component processes involved in this complex cognitive ability include: 1) forming an intention; 2) pairing that intention with an appropriate cue for subsequent retrieval; 3) maintaining the intention-cue pairing over time (during which time both strategic and automatic monitoring may occur; McDaniel & Einstein, 2000); 4) disengaging from an ongoing task to detect and recognize the cue (which may be based on the passing of time or the occurrence of a specific event); 5) search and retrieval from retrospective memory for the appropriate intention; and 6) accurate execution and confirmation of the intention. At the level of neural systems, ProM is heavily dependent on the prefronto-striato-thalamo-cortical circuits, particularly Brodmann's area 10 (e.g., Burgess et al., 2001; 2003; Simons et al., 2006) and the medial temporal lobes (Martin et al., 2007b; McDaniel & Einstein, 2007), regions that have both been implicated in the neuropathophysiology of HIV in older adults (Khanlou et al., in press).

Research on ProM first gained prominence in the aging literature (Einstein & McDaniel, 1990). Healthy older adults reliably demonstrate moderate impairment on laboratory tests of time- and event-based ProM as compared to younger individuals (e.g., Henry et al., 2004). The relationship between ProM deficits and aging appears to be moderated by several factors, particularly the level of controlled/strategic (cf. automatic) processing demands of the task. For example, older adults perform comparably (and occasionally superior) to younger persons on semi-naturalistic tasks (e.g., daily telephone calls to the experimenter) or event-based ProM measures in which spontaneous (i.e., automatic) monitoring demands predominate (Henry et al., 2004). In contrast, age effects are quite large for time-based tasks, which place more demands on self-initiated executive processes (e.g., internally monitoring the passage of time; McDaniel & Einstein, 2007), but also for event-based tasks that impose heavy strategic demands (e.g., non-focal tasks that require the allocation of sufficient attentional resources for monitoring; Henry et al., 2004), emphasizing the vulnerability of strategic processing abilities to age-related frontal systems changes (Craik, 1986). Importantly, impaired ProM in older adults is associated with poorer medication adherence (e.g., Vedhara et al., 2004) and may be a harbinger of incident dementia (e.g., Duchek et al., 2006).

ProM impairment is also prevalent in HIV disease. Individuals living with HIV endorse more frequent ProM failures in their daily lives (Woods et al., 2007) and demonstrate mild-to-moderate deficits on semi-naturalistic (Carey et al., 2006) and laboratory measures of ProM (Martin et al., 2007a), which are broadly characterized by deficient encoding and retrieval of future intentions (i.e., elevated omission errors but normal recognition) (Carey et al., 2006). Furthermore, deficits in ProM, but not retrospective memory, are associated with host biomarkers of HIV-associated neuropathogenesis (e.g., tau, a marker of neuronal injury), suggesting the potential dissociability of the neural mechanisms underlying these episodic memory deficits (Woods et al., 2006). Perhaps of greatest clinical relevance are emergent

findings that HIV-associated ProM impairment is a unique predictor of medication nonadherence (Woods et al., 2008a; 2009) and general declines in the independent performance of instrumental activities of daily living (Woods et al., 2008b).

Although both HIV infection and aging are each associated with impaired ProM, no studies have yet evaluated the combined effects of these increasingly comorbid CNS risk factors. The present study was therefore undertaken to clarify the effects of aging on HIV-associated prospective memory impairment. Considering that both conditions converge neuropathologically on the structure (e.g., reduced synaptodendritic complexity) and function (e.g., executive deficits) of prefrontal systems, it was expected that their comorbidity would therefore exert greater adverse effects on ProM than either condition alone. Drawing from McDaniel and Einstein's (2000) influential multi-process theory of ProM, we were specifically interested in evaluating the possibility that older HIV infected adults may be particularly susceptible to ProM impairment under conditions of increased strategic encoding and retrieval demands (i.e., when the cue (i.e., target) is not semantically related to the intended action). Multi-process theory posits that parameters of the ProM cues, including the degree of semantic relatedness between the cue and intention, can place varying demands on ongoing cognitive resources and thereby affect performance. Semantically unrelated cue-intention pairings (e.g., remembering to buy stamps when at the grocery store) are posited to draw more heavily on strategic encoding and retrieval processes (e.g., McDaniel et al., 1998). In contrast, semantically linked cue-intention pairings (e.g., remembering to buy stamps when mailing a letter at the post office) are thought to rely on automatic-associative memory. Therefore, considering prior literature suggesting that both HIV and aging are independently associated with larger deficits in the strategic aspects of ProM, we hypothesized that their comorbidity would exacerbate event-based ProM impairment in conditions in which the strategic task demands are amplified by semantically unrelated cue-intention pairs.

Method

Participants

One hundred and eighteen individuals were drawn from a larger NIMH-funded R01 cohort (N = 221) based on their HIV serostatus (HIV- and HIV+) and age (i.e., younger ≤ 40 years and older ≥ 50 years). Note that, this age-based classification scheme produced cohorts of “older” adults that are somewhat younger than is traditionally used in cognitive aging studies, but this approach is nevertheless commensurate with NIMH neuroAIDS research guidelines (Stoff et al., 2004). HIV serostatus was determined by enzyme linked immunosorbent assays and confirmed by a Western Blot test. The application of the age and HIV study inclusion criteria yielded 20 Younger HIV- participants (Y-), 35 Younger HIV+ participants (Y+), 15 Older HIV-participants (O-), and 48 Older HIV+ participants (O+). Individuals with severe psychiatric illnesses (e.g., psychotic disorders, mood disorders with psychotic features), neurological disease (e.g., seizure disorders, closed head injuries with loss of consciousness greater than 15 minutes, stroke, anoxia, non-HIV-associated dementias, and CNS opportunistic infections), medical conditions (e.g., advanced liver disease or other organ systems failures) that might impact cognition (NB. all medical exclusionary determinations were made in consultation with a board-certified neurologist and/or infectious disease physician), substance abuse or dependence within six months of evaluation or a positive urine toxicology screen for illicit drugs (other than marijuana), and/or estimated IQ scores < 70 (as determined by the Wechsler Test of Adult Reading [WTAR; Psychological Corporation, 2001] were excluded.

The participants' demographic, psychiatric, and HIV disease and treatment characteristics are displayed in Tables 1 and 2. Although the Younger and Older HIV+ groups were comparable to their seronegative counterparts in age, they obtained fewer years of education and included a smaller proportion of women (*p*s < 0.05). Lifetime major depressive disorder was more

prevalent in the older HIV+ individuals as compared to the younger seronegative group ($p < .05$). The Younger HIV+ group also endorsed significantly greater levels of current affective distress relative to other three groups ($p < 0.05$). With regard to HIV disease and treatment status, the Older HIV+ group had a longer duration of infection, lower nadir CD4 lymphocyte counts, and a higher prevalence of AIDS diagnoses ($ps < 0.05$), but did not differ from the Younger HIV+ sample in viral load, current CD4 count, or treatment characteristics (all $ps > 0.10$).

Materials and Procedure

The study was approved by the University's human research protections program and all participants provided written, informed consent. Participants received the Memory for Intentions Screening Test (MIST; Raskin, 2004; Woods et al., 2008c) and the Abbreviated Assessment of Intentional Memory (AAIM; Raskin & Buckheit, 2001; Iudicello et al., 2007) in a randomized order. The MIST and AAIM are each 30-min laboratory measures of ProM that include four time-based and four event-based trials that are administered along with a standardized ongoing word search task. Prior studies support the inter-rater and split-half reliability of the MIST (Woods et al., 2008c), as well as its construct validity in HIV infection (e.g., Carey et al., 2006). Little is known about the psychometric properties of the AAIM, but a recent investigation by Iudicello et al. (2007) supported the convergent and divergent validity of this novel task in healthy adults, including its relationship with older age and impairment on standardized measures of executive functions, RetM, and ProM.

For the present study, our conceptual framework (McDaniel & Einstein, 2000) dictated that we focus exclusively on the event-based scales of these tasks, which differ only in the semantic relatedness of the cue-intention pairings (cf. cue timing, modality of response). The MIST utilizes semantically-related (S-R) cue-intention pairings (e.g., “When I hand you a postcard, self-address it”), whereas the AAIM uses semantically unrelated (S-UR) cue-intention pairs (e.g., “When I show you a picture of a cow, snap your fingers”). The administration and scoring of the MIST (S-R) and AAIM (S-UR) event-based scales are identical, with each yielding scores that range from 0 to 8. We also coded the following error types that were exclusive to the event-based scales of the MIST (S-R) and AAIM (S-UR): 1) No Response (i.e., omissions); Task Substitutions (e.g., substitution of an action for a verbal response [or *vice versa*], repetitions, or intrusions); 3) Loss of Content (e.g., recognition of a ProM cue, but forgetting all or part of the prescribed intention); and 4) Loss of Time (i.e., performing a correct intention at the wrong time). Finally, we extracted the event-based items (range = 0–4) from the 3-choice recognition post-tests that are administered after completion of the S-R and S-UR trials.

Standard Neuropsychological Assessment—Participants were also administered standardized neuropsychological battery that included tests of retrospective learning and memory, executive functions, and attention/working memory. Raw scores were converted to population-based z-scores derived from the entire sample, then averaged across the tests in that domain to create a mean domain z-score. The *retrospective learning* and *memory* domains were comprised of the immediate and long delayed trials of the California Verbal Learning Test – Second edition (CVLT-II; Delis et al., 2000), Rey-Osterreith Complex Figure (Stern et al., 1999), and Wechsler Memory Scale – Third Edition (WMS-III; The Psychological Corporation, 1997). Measures of *executive functions* included Trailmaking Test, Part B (total time; Reitan & Wolfson, 1985) and the Tower of London-Drexel version (Culbertson & Zillmer, 2001) total move score. Tests in the *attention/working memory* domain included digits backward from the Wechsler Adult Intelligence Scale – Third Edition (The Psychological Corporation, 1997) and total errors from the self-ordered pointing test (Morgan et al., in press; Shimamura et al., 1994).

Psychiatric and Medical Assessment—Each participant underwent a structured psychiatric assessment using the Composite International Diagnostic Interview (CIDI version 2.1; World Health Organization, 1998) to generate lifetime diagnoses of Major Depressive Disorder (MDD), Generalized Anxiety Disorder (GAD), and Substance Use Disorders per *Diagnostic and Statistical Manual of Mental Disorders* (4th ed.; American Psychiatric Association, 1994) criteria. The Profile of Mood States (POMS; McNair, Lorr, & Droppleman, 1992) was administered to assess overall acute (i.e., the week prior to evaluation) affective distress. Finally, all participants received a neuromedical evaluation, which included a comprehensive review of medications, medical history and current symptoms, a complete physical and neurological evaluation, CDC staging, lumbar puncture, and blood draw.

Data Analysis

Considering the non-normal distributions of the AAIM and MIST variables (Kolmogrov-Smirnov *p*s < 0.01) and the hypothesized additive effects of HIV and aging, the primary analyses were conducted using a series of Jonckheere-Terpstra tests for ordered monotonic trends. The Jonckheere-Terpstra tests evaluated the hypotheses that the level of ProM performance decreases in an orderly fashion from groups expected to be high on the primary criterion (i.e., Younger HIV-) to samples low on the criterion (i.e., Older HIV+). This approach is arguably more powerful than other nonparametric tests for independent samples because of its use of *a priori* ordered alternatives. For this study, we employed a three-level Jonckheere-Terpstra approach, which predicted that Younger HIV+ individuals would perform comparably to Older HIV- persons (van Gorp et al., 1989). All Jonckheeree-Terpstra tests were followed-up by confirmatory Monte Carlo estimates for the Exact Test. Pair-wise analyses were conducted using Wilcoxon Rank-Sum tests and were confined to comparisons involving only the HIV+ older sample in an effort to minimize Type I error risk. Finally, to evaluate the possible effects of confounding variables on the hypothesized ProM effect, a series of follow-up linear regressions were performed in which the four-level aging and HIV grouping variable was used as a predictor of ProM, alongside the demographic, psychiatric, and medical variables upon which omnibus group differences were observed (see Tables 1 and 2). The critical alpha level was set at .05 for all analyses.

Results

Table 3 shows the hypothesized additive effects of HIV and aging on ProM, such that across both the S-R and S-UR scales, the best ProM performance was observed in the Younger HIV- individuals and the worst performance in the Older HIV+ group (*p*s ≤ 0.001). A follow-up linear regression analysis further demonstrated the Aging/HIV group effect on the S-UR ($p = 0.009$) and S-R ($p = 0.002$) scales as compared to the other three groups, even when education, sex, hepatitis C, hypertension, lifetime Major Depressive Disorder, and the POMS total mood disturbance were included in the statistical model (S-UR adjusted $R^2 = 0.09$, $p = 0.029$; S-R adjusted $R^2 = 0.08$, $p = 0.047$). A series of post-hoc analyses confirmed that the inclusion of substance abuse and/or dependence in the above-described model, including individual substances (e.g., methamphetamine), did not change the significance of the Aging/HIV group effect (*ps* < .01).

On the S-UR scale, planned post-hoc tests showed that the Older HIV+ group performed significantly below the Younger HIV- ($p = 0.002$, Cohen's $d = 0.85$), Younger HIV+ ($p = 0.02$, Cohen's $d = 0.52$), and Older HIV- ($p = 0.006$, Cohen's $d = 0.79$) groups. The Older HIV+ group was impaired on the S-UR task relative to the Younger HIV+ sample ($p = .005$), even when HIV disease severity indicators upon which the groups differed (i.e., estimated duration of infection, nadir CD4 count, and AIDS status) were included as predictors in a simultaneous multiple regression (adjusted $R^2 = 0.12$, $p = .01$). On the S-R task, the Older HIV+ group also

performed significantly below the Younger HIV+ ($p = 0.02$, Cohen's $d = 0.50$) and Younger HIV- ($p < 0.0001$, Cohen's $d = 1.0$) samples. However, the Older HIV+ group did not differ significantly from the Older HIV- comparison subjects on the S-R task ($p > 0.10$, Cohen's $d = 0.13$), suggesting the absence of an HIV effect in the older cohort when the cue-intention pairing was semantically-related.

A review of Table 3 revealed possible ceiling effects on the S-R scale, which may have decreased our ability to detect an HIV effect in the older adults on this task. Post-hoc analyses revealed that 51% of the entire sample was at ceiling (i.e., raw score = 8) on the S-R scale, whereas only 6% of participants were at ceiling (i.e., raw score = 8) on the S-UR scale. Yet it was the younger study groups who evidenced the most prominent ceiling effects on the S-R (Younger HIV+ 60%; Younger HIV- = 95%), which were much less prevalent within the older cohorts (Older HIV- = 27%; Older HIV+ = 33%). As such, ceiling effects would be most likely to mask the effects of HIV on the S-R task in our younger groups; however, post-hoc analyses nevertheless revealed a significant difference between the Younger HIV+ and Younger HIV- samples on the S-R scale ($p < .01$, Cohen's $d = 1.01$). By contrast, and as noted above, there was no significant S-R difference between the Older HIV+ and Older HIV- groups ($p > .10$, Cohen's $d = 0.13$), who had less than half the prevalence of ceiling effects observed in the younger cohorts.

Next, a simultaneous multiple regression was conducted to evaluate the relative contributions of age (as a continuous variable) and HIV disease (i.e., estimated duration of infection, nadir CD4 count, current CD4 count, plasma HIV RNA) and treatment (i.e., HAART status) characteristics as predictors of the S-UR scale in the Older HIV+ sample ($N = 48$). The overall model was significant (adjusted $R^2 = 0.28$, $p = .009$), with age ($p = .01$) and nadir CD4 count ($p = .01$) emerging as independent predictors of S-UR performance (all other ps > .10).

Considering the salience of the HIV-aging effect on the S-UR scale (relative to the S-R scale), we then conducted a series of Jonckheeree-Terpstra tests on the ongoing task, error types, and post-test recognition task that accompany this scale (see Table 3). Although omnibus additive effects were observed on several measures, including no response and loss of content errors, recognition, and distractor items (ps < .05), pairwise comparisons did not show any specific evidence of an HIV effect in the older cohorts. For example, while overall group differences were observed for the ongoing task ($p < 0.01$), the Older HIV+ group was slower than Y+ ($p < 0.0001$, $d = 1.09$), Y- ($p < 0.0001$, $d = 1.28$), but not O- ($p > 0.10$, $d = 0.13$). Similar omnibus differences were apparent on the post-test recognition test, which pair-wise comparisons revealed was driven by differences between the Older HIV+ and Younger HIV-groups ($p = 0.004$, $d = 0.72$). There were no differences between the Older HIV+ and Younger HIV+ ($p > 0.10$, $d = 0.13$) or Older HIV- samples ($p > 0.10$, $d = 0.13$).

Finally, correlational analyses between the ProM tasks and our standard clinical battery of tests were conducted within the Older HIV+ group alone to clarify the cognitive correlates of event-based ProM in this cohort (see Table 4). Results indicate that the S-UR scale correlated with executive functions ($p = 0.03$), but not with working memory or RetM learning or delayed memory (ps > 0.10). In contrast, the S-R scale was most strongly correlated with RetM learning ($p = 0.04$), but also with executive functions at a trend level ($p = 0.09$). The S-R scale was not correlated with delayed or working memory (ps > 0.10) in this sample.

Discussion

Although both HIV infection and aging are independently associated with impairment in ProM, no prior studies have examined the hypothesis that the convergent frontotemporal neuropathophysiologies of these conditions confer additive adverse effects on prospective

memory (ProM) functioning. Results from the present study largely supported this hypothesis. Specifically, significant additive effects of aging and HIV were observed on standardized laboratory measures of event-based ProM; that is, a stair-step effect was evident such that younger seronegative individuals obtained the best ProM scores, whereas older HIV-infected adults generally demonstrated the worst performance. The effects of aging and HIV on ProM were not better explained by other demographic (e.g., education and sex), psychiatric (e.g., affective distress and substance use), or medical (e.g., hepatitis C infection and cardiovascular disease) factors. These findings converge with prior data showing that older adults with HIV infection are at greater risk for HIV-associated neurocognitive disorders (Valcour et al., 2004), particularly deficits in episodic memory and executive functions (e.g., Sacktor et al., 2007). Given the critical role of prefrontal systems (e.g., BA 10) in ProM (e.g., Simons et al., 2006), these data also align with studies showing that older HIV+ adults are especially susceptible to neural injury in the fronto-striato-thalamo-cortical loops (e.g., Ernst & Chang, 2004; Jernigan et al., 2005).

Of particular note, was the apparent discrepancy in the effects of aging and HIV on semantically-related and –unrelated cue-intention pairings. Older HIV+ adults were impaired relative to their Older HIV- counterparts on event-based ProM when the retrieval cue and intention were not semantically related (Cohen's d = .79), but not when the these factors were related (Cohen's d = .13). Interpreted within the context of McDaniel and Einstein's (2000) multi-process theory, these data suggest that older HIV-infected adults are significantly less efficient at engaging the strategic encoding and retrieval processes required to a execute a future intention when the cue is unrelated to the intended action. In contrast, their performance was comparable to their older seronegative counterparts when the cue-intention pairings were semantically related, which is a function that is purportedly driven by automatic processes. Thus, the stronger effects observed on semantically-unrelated ProM may be secondary to the combined neural burden of HIV and aging in prefrontal systems involved in higher-level cognitive control processes (e.g., Khanlou et al., in press).

Consistent with this premise, the semantically-unrelated (S-UR) event-based ProM impairment was exclusively associated with executive dysfunction (i.e., a composite measure of divided attention and planning) in the older HIV-infected group. These data are commensurate with studies from the cognitive psychology literature showing that low association cue-target pairings are also more susceptible to interference from divided attention (McDaniel et al., 2004) and manipulating the importance of the ongoing task (Loft & Yeo, 2007) in healthy adults. Furthermore, a lower degree of semantic relatedness of cue-intention pairings at encoding and retrieval has been associated with lower task accuracy (e.g., Marsh et al., 2003; McDaniel et al., 1998) and slower reaction times (Loft & Yeo, 2007). By contrast, the semantically linked cue-intention pairings of the S-R scale were most strongly related to RetM learning in our older HIV sample. At first glance, these data support the hypothesis that S-R pairings may be more “automatic” and driven by medial temporal networks; however, one cannot rule out the additional contribution of frontal systems (e.g., dorsolateral prefrontal cortex), which are known to play an important role in “working with” episodic memory (Moscovitch, 1992), including event-based ProM (McDaniel & Einstein, 2007). In fact, the RetM profile of HIV-associated deficits in RetM is characterized by impairment in the strategic aspects of encoding and retrieval (e.g., Delis et al., 1995) and has been linked to dysfunction in both frontal and temporal systems (e.g., Maki et al., 2009). A limitation of this study is the observational nature of our data, which do not allow us to directly speak to the role of prefrontal and/or medial temporal systems in the expression of HIV-associated ProM impairment in older adults. Future studies that use biomarkers of HIV neuropathogenesis (e.g., tau), multimodal neuroimaging techniques, and antemortem-postmortem approaches are needed to shed light on the hypothesized neural mechanisms.

While these results of this study implicate broad dysfunction in strategic encoding and retrieval in the older HIV-infected cohort, they do not allow us to draw more specific inferences regarding the relative role(s) of encoding, monitoring, and retrieval processes. Despite evidence of an omnibus additive effect on several measures, we were surprised to discover no clear deficits in the component process measures embedded within the S-UR scale in the Older HIV+ group, including the ongoing task, error types, and the post-test recognition test. It is possible that the absence of findings reflects variability in the cognitive mechanisms of failure across individuals and/or the psychometric limitations of the variables themselves (e.g., floor effects and a restricted range of scores). There are nevertheless several interesting hypotheses regarding the possible cognitive architecture of the omnibus effect of HIV and aging on semantically unrelated event-based cues that deserve further study. For example, it is conceivable that this finding reflects a primary encoding deficit (i.e., impairment at the intention formation stage), which might be evaluated further by studies that employ targeted encoding manipulations (e.g., training in higher-level strategic encoding strategies) to improve performance when the cue and intention are not semantically linked.

Although these data are preliminary and did not include demographically-adjusted normative standards (which have not yet been published for these tasks), they nevertheless suggest that older HIV-infected adults are impaired on aspects of event-based ProM above and beyond the effects of HIV and aging alone. Not only was the HIV effect on S-UR ProM evident in the older study groups, but also the Older HIV+ group was impaired on this task relative to their younger HIV+ counterparts, even when we included HIV disease severity in our statistical modeling. An important direction for future research will be to examine the independent (and perhaps dissociable) effects of HIV and aging on various aspects of ProM, which was not prudent within the confines of the current study design and small sample sizes (e.g., $N = 15$ in the Older HIV- sample). Nevertheless, preliminary findings from our study hint at the possibility that both age and HIV may play important roles in the expression of ProM deficits, even within the subpopulation of older HIV-infected adults. Specifically, post-hoc analyses showed that older age and lower nadir CD4 counts were significant, independent predictors of S-UR ProM deficits within the Older HIV+ cohort. These data are consistent with prior studies showing that older HIV-infected adults with more severe HIV disease (e.g., Cherner et al., 2004), including those with histories of immunocompromise (e.g., Valcour et al., 2006), are at higher risk for developing neurocognitive impairment. Conclusions regarding the relative contributions of age, HIV disease severity, and common psychiatric (e.g., substance use disorders) and medical (e.g., cardiovascular disease) to HIV-associated ProM impairment await future, large-scale cohort studies.

Interpretation and generalization of this study's findings are limited by several factors. Most notably, the seronegative study cells were relatively small and the samples were mismatched on important demographic (e.g., education, sex), psychiatric (e.g., substance use), and medical (e.g., HCV infection) factors; however, these discrepancies also generally reflect the current epidemiology of HIV infection and did not alter the primary study findings when included in the statistical modeling. Nevertheless, the fact that our HIV+ sample was relatively well educated, largely Caucasian, and included very few patients who were currently immunocompromised may restrict the generalizability of our findings. Also of note, although our study exclusionary criteria were rigorous, it was not feasible to exclude or systematically document all possible psychiatric (e.g., Bipolar Disorder, Attention-Deficit/Hyperactivity Disorder, learning disabilities, etc.) and medical conditions (e.g., cardiovascular disease) that might have cognitive effects and therefore may have biased the results. Moreover, the use of a urine toxicology screening and a self-report diagnostic interview does not exclude the possibility that a small subset of participants may have recently used illicit substances, including stimulants such as methamphetamine, which are known to adversely impact episodic memory and executive functions (e.g., Scott et al., 2007). However, post-hoc analyses showed

that inclusion of a history of substance use disorders, including stimulants, in the statistical models did not alter our primary findings.

Another limitation of this study is the ceiling effects observed on the S-R scale, which arguably increased our risk of Type II error in the comparisons between the Older HIV+ and HIV- samples. Such ceiling effects are commonly encountered in event-based ProM research and reflect the difficulties inherent in constructing a laboratory-based ProM task that is representative of the construct, psychometrically sound (e.g., possesses an adequate range and distribution of scores and is reliable), and not overly burdensome in its administration time and procedures (see Woods et al., 2008c). Nevertheless, two factors argue against the confounding role of ceiling effects on the results of the present study. First, the S-R ceiling effects were over twice as prevalent in the younger study groups (72.7% vs. 32.5%) in whom a strong HIV effect was detected (Cohen's $d = 1.01$). Second, the prevalence of S-R ceiling effects was highly comparable between the older HIV- (27%) and HIV+ (33%) groups, who did not differ on this task (Cohen's $d = .13$). Accordingly, it is unlikely that the ceiling effects evident on the S-R scale were the primary factor driving the small and non-significant effect of HIV serostatus in the older study participants.

As previously highlighted, research on the cognitive mechanisms of ProM in this cohort is of considerable public health importance with the growing incidence and prevalence of older adults living with HIV. The clinical relevance of such investigations is underscored by data showing that older HIV-infected adults are not only at greater risk for more rapid HIV disease progression and exacerbated CNS complications, but are also for declines in the independent performance of instrumental activities of daily living, particularly in the context of neurocognitive impairment. Older age is an independent risk factor for poorer vocational functioning and unemployment in HIV disease (Henninger et al., 2007). Moreover, a recent study demonstrated that cognitive impairment was the sole predictor of medication nonadherence in older adults (Barclay et al., 2007). Although older age is sometimes associated with better antiretroviral compliance (Wutoh et al., 2001), older adults with HIV-associated cognitive impairment are at substantially increased risk for nonadherence (Hinkin et al., 2004), which is important because antiretroviral therapies show evidence of neuroprotective effects in older adults (Larussa et al., 2006). Examinations of the cognitive mechanisms by which ProM deficits emerge and persist in older HIV+ adults may drive future investigations into possible avenues of intervention to ameliorate such everyday functioning declines.

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Table 1

Demographics and psychiatric characteristics of the study samples.

	Younger HIV- (n=20)	Older HIV- (n=15)	Younger HIV+ (n=35)	Older HIV+ (n=48)	*p*	Pairwise Comparisons
Demographic Characteristics						
Age (years)	32.1 (6.0)	56.1 (6.7)	34.8 (4.9)	55.5 (6.4)	<.001	Y- = Y+ < O- = O+
Education (years)	16.0 (2.3)	15.1 (2.3)	13.2 (3.0)	13.5 (2.9)	.001	Y- > Y+, O+; O- > Y+
Sex (% female)	65.0%	33.3%	14.3%	20.8%	<.001	Y- > Y+
Ethnicity (% Caucasian)	50.0%	60.0%	42.9%	64.6%	.239	-----
Psychiatric Characteristics						
Major Depression[a]	25.0%	33.3%	40.0%	56.3%	.080	O+ > Y-
Generalized Anxiety[a]	0.0%	6.7%	5.7%	8.5%	.610	-----
Substance Dependence[a]	30.0%	33.3%	60.0%	47.9%	.120	----
POMS Total	37.1 (18.4)	46.4 (29.0)	61.1 (37.5)	49.6 (25.7)	.032	Y+ > Y-
Cognitive Characteristics						
WTAR verbal IQ	109.6 (8.7)	106.1 (10.7)	101.7 (13.2)	102.5 (14.1)	.114	----
HIV Dementia Scale	50.5 (8.5)	47.3 (15.0)	49.3 (10.5)	48.5 (17.3)	.919	----
Global Cognitive Imp.	15.0%	20.0%	37.1%	31.3%	.263	----

Note: POMS = Profile of Mood States. WTAR = Wechsler Test of Adult Reading. Imp. = impairment, as determined by clinical ratings of performance on a standardized, traditional battery of neurocognitive tasks (see Woods et al., 2008).

[a]Denotes a lifetime diagnosis. Y- = Younger HIV seronegative; O- = Older HIV seronegative; Y+ = Younger HIV seropositive; O+ = Older HIV seropositive.

Table 2

HIV disease and medical characteristics of the study samples.

	Younger HIV− (n = 20)	Older HIV- (n = 15)	Younger HIV+ (n = 35)	Older HIV+ (n = 48)	*p*	Pairwise Comparisons
Hepatitis C	5.3%	0%	8.6%	28.6%	.009	O+ > O-, Y+
Hypertension	0%	26.7%	8.6%	10.4%	.077	O- > Y-
Hypercholesterolemia	0%	0%	2.9%	6.3%	.483	-----
Diabetes mellitus	0%	13.3%	2.9%	6.3%	.298	-----
HIV Disease Characteristics						
HIV Duration (years)	-	-	9.4 (6.4)	15.5 (7.0)	<.001	Y+ < O+
AIDS (%)	-	-	37.1%	68.8%	.004	Y+ < O+
HAART (%)	-	-	71.4%	75%	.730	----
ARV adherence [a,b] (%)	-	-	100 (100, 100)	100 (100, 100)	.920	----
Nadir CD4 [a] (cells/μl)	-	-	248 (133, 324)	102 (29, 282)	.014	Y+ > O+
Current CD4 [a] (cells/μl)	-	-	547 (303, 879)	512 (253, 693)	.385	----
Plasma HIV RNA [a] (log_{10})	-	-	1.7 (1.7, 3.8)	1.7 (1.7, 1.8)	.144	-----
CSF HIV RNA [a,c] (log_{10})	-	-	1.7 (1.7, 1.8)	1.7 (1.7, 1.7)	.507	-----

Note:

[a] Data represent medians with interquartile ranges in parentheses.

[b] Based on the AIDS Clinical Trials Group (ACTG) self-report adherence questionnaire.

[c] O+ *n* = 18 and Y+ *n* = 14. Y- = Younger HIV seronegative; O- = Older HIV seronegative; Y+ = Younger HIV seropositive; O+ = Older HIV seropositive

Table 3

Event-based prospective memory performance in the four study samples.

ProM Task	Younger HIV− (*n* = 20)	Older HIV- (*n* = 15)	Younger HIV+ (*n* = 35)	Older HIV+ (*n* = 48)	*p*	Pairwise comparisons [a]
Semantically-Related	8 (8, 8)	7 (6, 8)	8 (7, 8)	7 (6, 8)	.001 [b]	O+<Y+, Y-
Semantically-Unrelated	6.5 (6, 7)	6 (6, 7)	6 (5, 7)	6 (4.3, 6)	<.001 [b]	O+<O-,Y+, Y-
No response	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	.015	----
Task substitutions	0 (0, 1)	1 (0, 2)	1 (0, 1)	1 (0, 2)	.074	----
Loss of content	0 (0, 1)	0 (0, 1)	0 (0, 1)	1 (0, 1)	.030	----
Loss of time	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)	.269	----
Recognition post-test [c]	4 (4, 4)	4 (3, 4)	4 (3, 4)	4 (3, 4)	.010	O+<Y-
Distractor items	27 (18, 33)	16 (14, 23)	26 (19, 32)	18 (15, 20)	<.001	O+<Y+, Y-

[a] Pairwise comparisons were restricted to the Older HIV+ group.

[b] p-values reflect Jonckheere-Terpstra tests for ordered monotonic trends.

[c] Event-based trials only. ProM = prospective memory S-UR = Semantically-Unrelated. S-R = Semantically-Related. Y- = Younger HIV seronegative; O- = Older HIV seronegative; Y+ = Younger HIV seropositive; O+ = Older HIV seropositive.

Table 4

Correlations between semantically-related and un-related event-based prospective memory tasks and other cognitive domains in the Older HIV+ group (*N* = 48).

Cognitive Domain	1	2	3	4	5	6
1. S-UR ProM	---					
2. S-R ProM	0.50**	---				
3. Executive Functions	-0.32*	-0.25	---			
4. RetM Learning	0.14	0.30*	-0.47**	---		
5. RetM Delayed Recall	-0.17	-0.11	-0.01	0.04	---	
6. RetM Working Memory	-0.11	-0.03	-0.02	0.03	-0.08	---

Note: S-UR = Semantically-Unrelated. S-R = Semantically-Related. ProM = prospective memory. RetM = retrospective memory.

* $p<.05$

** $p<.01$