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The Impact of Neuropsychological Performance on Everyday Functioning Between Older and Younger Adults With and Without HIV

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Abstract

In this cross-sectional study, a community-based sample of 162 younger and older adults with and without HIV was compared on neuropsychological and everyday functioning measures. In the HIV sample, the relationship between cognition, everyday functioning, and HIV biomarkers was also examined. A battery of cognitive tests were completed along with 2 laboratory measures of everyday functioning and 1 measure of HIV medication adherence. Main effects for age and HIV were found on several neuropsychological measures and on the Timed Instrumental Activities of Daily Living test; those who were older or who had HIV exhibited poorer performance. Although age $\times$ HIV interactions were not observed, older adults with HIV as a group performed worse on 8 out of the 9 neuropsychological and everyday functioning measures. Few of these neuropsychological and everyday measures were related to HIV biomarkers (e.g., CD4+ T-cell count). Implications for nursing practice and research are posited.

Keywords

aging with HIV; cognition; everyday function; Instrumental Activities of Daily Living (IADL);
Observed Tasks of Daily Living (OTDL); neuropsychological function

Although HIV-related dementia has become less prevalent as a result of the neuroprotective effects of antiretroviral therapy (ART), 30% to 60% of people living with HIV (PLWH) will experience some level of neuropsychological decline during their illness (Thames et al., 2011). Concerns remain that as people age with HIV, they may become more susceptible to various forms of neuropsychological and everyday functioning impairment due to a possible

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Conflict of Interest Statement

The authors report no real or perceived vested interests that relate to this article (including relationships with pharmaceutical companies, biomedical device manufacturers, grantors, or other entities whose products or services are related to topics covered in this manuscript) that could be construed as a conflict of interest.

synergistic effect of age and HIV on cognition (Justice et al., 2004). Declines associated with HIV have been shown to be similar to those found in normal aging, with decrements found in many neuropsychological domains such as memory, attention, reasoning, and particularly in speed of processing (Hardy & Vance, 2009; Reger, Welsch, Razani, Martin, & Boone, 2002). Furthermore, these declines have been most evident in individuals with a diagnosis of AIDS (Reger et al., 2002). Such neuropsychological declines have the potential to detrimentally affect everyday functioning such as performance of Instrumental Activities of Daily Living (IADLs).

Everyday Functioning in Aging and HIV

Age is one of the most significant predictors of decline in everyday functioning, which in turn results in declines in autonomy. Neuropsychological functioning is also predictive of impairment in everyday functioning (Ball, Vance, Edwards, & Wadley, 2004). In a sample of 173 older adults without dementia, Owsley, Sloane, McGwin, and Ball (2002) found that speed of processing was an important predictor of IADL performance for activities such as managing finances. Declines in neuropsychological performance appear to impact more complex everyday activities (such as cooking a meal) first and gross everyday activities (such as dressing oneself) later.

Declines in everyday functioning are also observed in many adults with HIV and may be especially prominent among individuals who have developed AIDS, given their increased vulnerability to neuropsychological impairment (Reger et al., 2002). But even adults who are clinically asymptomatic may experience difficulty with performing everyday activities because of emerging subtle neuropsychological problems (Vance, Wadley, Crowe, Raper, & Ball, 2011). For example, in a relatively young ($M_{age} = 39.32$ years) sample of 267 adults with HIV, Heaton and colleagues (2004) found that in comparison with participants without neuropsychological deficits, those with some level of neuropsychological impairment performed worse on measures of IADLs.

In the PLWH clinical population, medication adherence is an extremely important IADL given that a 95% compliance rate with medication is encouraged to achieve optimal viral suppression (viral load < 50 copies/mL; Paterson et al., 2000). In a sample of 148 adults with HIV (25-69 years of age), Ettenhofer and colleagues (2009) examined medication adherence patterns between younger and older groups. Older adults with HIV were found to exhibit better medication adherence in general; however, if the older adults exhibited neuropsychological deficits on measures of executive functioning and psychomotor speed, they were more likely to be classified as poor medication adherers.

Confounding and Covariate Factors

Several confounds of neuropsychological functioning have been observed in individuals aging without HIV, such as education (Stern, 2009), depressive symptomology (Bierman, Comijs, Jonker, & Beekman, 2005), and drug and alcohol use (Rogers & Robbins, 2001; Thomas & Rockwood, 2001). It is not surprising that these confounds would be present among individuals aging with HIV, especially because they have been shown to report higher levels of depressive symptoms and substance use than HIV-uninfected counterparts (Justice et al., 2004). Furthermore, HIV-specific confounds may be related to neuropsychological functioning in HIV-infected individuals that must be considered in future studies, including disease severity (e.g., current CD4+ T-cell count, nadir CD4+ T-cell count, viral load), chronicity (years with HIV; Ettenhofer et al., 2009; Heaton et al., 2004), and ART medication adherence. Although depletion of CD4+ T-cells has been associated with neuropsychological decline, viral load may be a more robust indicator of neuropsychological insults (Marcotte et al., 2003) along with nadir CD4+ T-cell count

(Robertson et al., 2007). Chronicity of HIV has only sporadically been considered as a potential predictor of neuropsychological and everyday functioning (Marcotte et al., 2003). Chronicity implies that the longer someone has been diagnosed with HIV, the more the nervous system is damaged by its effect on the body such as through inflammatory processes (Raper, 2010).

Purpose

The purpose of this study was to further examine the complex relationship between neuropsychological and everyday functioning in older and younger adults with and without HIV. The first aim was to examine neuropsychological and everyday functioning differences in these groups while controlling for potential confounds. We hypothesized that there would be main effects of HIV and age on the neuropsychological and everyday functioning measures. As this was an exploratory study, we were interested in whether or not age by HIV interactions would emerge on these neuropsychological and everyday functioning measures. The second aim was to examine how each neuropsychological measure related to the everyday functioning measures and a medication adherence measure among the HIV-infected sample. We hypothesized that poorer neuropsychological performance (particularly on measures of speed of processing, psychomotor ability, and executive functioning) would be related to poorer performance on the two everyday functioning measures and poorer medication adherence. The final aim was to examine whether, in an era of ART, chronicity and HIV biomarkers (e.g., CD4+ T-cell count) remain related to neuropsychological and everyday functioning. While this was an exploratory study, we hypothesized that HIV chronicity would not be related to neuropsychological and everyday functioning, while disease severity indices (i.e., current CD4+ T-cell count, viral load, nadir CD4+ T-cell count) would be related.

Method

Participants

Three hundred forty-seven adults recruited from the Birmingham, Alabama, metropolitan area were telephone screened for this study. After screening, 78 adults with HIV and 84 adults without HIV remained. Because we were interested in examining differences between younger and older adults, groups were stratified by HIV status and age (i.e., younger HIV-uninfected [22.00-48.84 years of age; $n = 43$; $M_{\text{age}} = 37.78$], younger HIV-infected [20.53-49.16 years of age; $n = 47$; $M_{\text{age}} = 39.87$], older HIV-uninfected [50.05-74.42 years of age; $n = 41$; $M_{\text{age}} = 58.58$], and older HIV-infected [50.45-70.64 years of age; $n = 31$; $M_{\text{age}} = 56.82$]). The demarcation of 50 and older was used to classify the older group; this categorization scheme is commonly used in HIV studies (e.g., Ettenhofer et al., 2009).

Participants with HIV were recruited from a university HIV/AIDS clinic with flyers and brochures. Participants without HIV were recruited from flyers, brochures, university newspaper advertisements, and word-of-mouth. Interested participants called the research center and a telephone-screening interview was conducted to determine eligibility. Because depression and anxiety can impair neuropsychological functioning, participants with HIV had to have been diagnosed for at least 1 year in order to eliminate the potential confounds of reactive anxiety and depression that can often accompany an initial HIV diagnosis; this was also done to establish a minimal amount of time in which HIV could have impacted the nervous system. Additional exclusion criteria for the sample included being homeless, pregnant, blind, deaf, and not being proficient in speaking and reading English. Conditions that interfere with neuropsychological functioning were also used as exclusion criteria because these may obscure the effects of HIV. These criteria included having a developmental disability, undergoing chemotherapy or radiation, past brain injury involving

a loss of consciousness longer than 30 minutes, or having a severe neurological condition (i.e., schizophrenia, bipolar disorder, HIV encephalopathy, dementia, or previous stroke). For the HIV-infected participants, this information was verified with the HIV/AIDS clinic medical charts; those with such conditions were excluded.

Instruments

Demographic and Mental and Physical Health Instruments

Several measures were used to determine whether there were differences between groups that would warrant controlling for any demographic or mental and physical health variables in subsequent analyses. We also gathered information on HIV biomarkers in the HIV-infected sample in order to examine the relationship of these variables to neuropsychological and everyday performance in subsequent analyses.

Demographic questionnaire—This experimenter-generated instrument was administered to all participants in order to acquire demographic information such as gender (0 = *women*; 1 = *men*), race, sexual orientation, household income before taxes, and years of education (i.e., 1 = *grade 1*, 12 = *high school diploma/GED*, 14 = *associate's degree*, 16 = *bachelor's degree*, 18 = *master's degree*, 20 = *doctoral degree*). This was used to examine group differences between HIV-infected and HIV-uninfected younger and older groups on demographics in order to determine potential control for variables for subsequent analyses.

Health questionnaire—This experimenter-generated instrument was completed by all participants to acquire information on various health aspects and was adapted from the health instrument used in the Cardiovascular Health Study (1989). A list of possible medical conditions (e.g., diabetes, hypertension) was presented in order to determine the presence or absence of these conditions over the participant's lifetime. Variables were created for the total number of medical conditions and total number of prescribed medications in order to examine whether there were group differences that may have warranted controlling for these variables. In order to tailor this questionnaire for the HIV-infected participants, questions regarding current CD4+ T-cell count and viral load, prescribed medications, and date of HIV diagnosis were added, and were thus only completed by the HIV-infected participants.

Profile of Mood States—All participants completed this instrument of affective mood state and psychological distress. Participants rated how much (e.g., 0 = *not at all*, 4 = *extremely*) they have experienced 65 different feelings (e.g., friendly, tense, angry) over the previous week. For our study, a total mood disturbance score was used, with higher scores indicative of more negative affect and poorer mood (McNair, Lorr, & Droppelman, 1992). In our study, internal consistency was high (Cronbach's $\alpha = 0.93$). As with the health and demographic questionnaires, this measure was used to determine whether this potential confound should be controlled in subsequent analyses.

Addiction Severity Index—All participants completed this widely used, gold standard measure of alcohol and drug use. Composite scores are created for alcohol and drug use and can be used in analyses as an indicator of alcohol and drug use severity. Higher scores indicate more severity. Interrater reliability is quite high for the alcohol ($r = 0.88$) and drug use ($r = 0.89$) composites (McLellan et al., 1992). This measure was used to determine whether this potential confound should be controlled in subsequent analyses.

CD4+ T-cell count and HIV RNA viral load—Because HIV-infected participants were recruited from the university HIV/AIDS clinic, computerized chart extraction of the last laboratory values of these variables that corresponded closest prior to their entry to the study

were accessed (range: 2 weeks to a few months); clinic values were always used in subsequent analyses instead of self-reported values, unless otherwise stated below. For 75 participants who had both self-reported and corresponding clinic values for their CD4+ T-cell count, there was a high level of agreement ($r = .73, p < .001$). Thus, CD4+ T-cell count values for the three participants whose values were not available from the clinic were imputed using self-reported values because the correlation between self-reported and actual values was high. For 32 participants who had both self-reported and corresponding clinic values for plasma viral load, there was a low level of agreement ($r = .01, p = .92$); thus, only clinic values of plasma viral load were used and, for the four cases who were missing this information, imputation was not deemed appropriate. Nadir CD4+ T-cell count count, the lowest recorded level, was available for 70 participants from the clinic; because the correlation between nadir CD4+ T-cell count and current clinic values for CD4+ T-cell count was high ($r = .67, p < .001$), for the remaining cases, the current CD4+ T-cell count was used to impute this missing value for subsequent analyses.

Neuropsychological Measures

A neuropsychological battery was employed that approximated the basic range of neuropsychological abilities including speed of processing, psychomotor ability, executive functioning, and memory functioning. Extra measures of speed of processing were included to examine this particular ability because several studies have shown that speed of processing may be particularly compromised in adults with HIV (Hardy & Vance, 2009). These neuropsychological measures have been used in HIV and aging research (e.g., Ball et al., 2004; Ettenhofer et al., 2009).

Useful Field of View Test®—This instrument is a computerized measure of speed of processing that utilizes a touch screen response mode. The test includes four increasingly complex subtests. In each subtest, participants attend to central and peripheral (or both) visual stimuli as the presentation time lengths (17-500 milliseconds) of the stimuli become shorter, and thus more difficult. This procedure allows for quantification of speed of processing by using display speed threshold as the score. Using a double-staircase method, scores are generated for each subtest, which reflects the presentation speed in which 75% accuracy has been achieved. These scores were combined to create a total score, with lower scores indicating fewer milliseconds needed to correctly perceive the stimuli, and thus better speed of processing. Test-retest reliability ranges from 0.74 to 0.81 (Edwards et al., 2005).

Complex Reaction Time Test—This instrument is a measure of speed of processing. It is a computerized measure using a mouse response mode. Participants were presented with several road signs (left and right turn arrows, pedestrian, and bicycle) and instructed to react as quickly as possible in a specific way to each sign (either a single click or moving the mouse right or left). There were 2 trials of 12 presentations. The participant's average reaction time in seconds was used as the score for this test, with lower scores indicative of better speed of processing. Test-retest reliability for this measure is 0.56 (Ball & Owsley, 2000).

Letter Comparison—This instrument is a commonly used paper-and-pencil measure of speed of processing. This version of the test consists of 192 pairs of letters with 3 (e.g., NLH, NLZ), 6 (e.g., HCLZXL, HCLZXL), and 9 (e.g., RZRLNLNFL, RZRLNLNFL) segments (64 pairs per set). For each set, participants were instructed to determine whether the pairs of letter sequences were the *same* or *different* by writing either an “S” or “D” beside each pair. In this timed test, participants were given 20 seconds per page (32 pairs per page for a total of 6 pages) to complete as many pairs as possible and were asked to do so as quickly as possible. Total scores were calculated by adding the total number of correct

responses from all pages, with larger scores indicative of better speed of processing (Salthouse, 1991).

Pattern Comparison—This instrument is also a paper-and-pencil measure of speed of processing, except in this version the test consisted of 96 pairs of patterns containing 3, 6, and 9 line segments (32 pairs per set). Again, participants were instructed to determine if the pairs of patterns were the *same* or *different* by writing either an “S” or a “D” beside each pair. Total scores were calculated by summation of the total number of correct responses from all three sections, with larger scores reflective of better speed of processing (Salthouse, 1991). Test-retest for Letter Comparison and Pattern Comparison is 0.65 (Salthouse, 1993).

Finger Tapping Test—This instrument measured psychomotor speed, whereby participants were instructed to tap their index finger as rapidly as possible on a button for 10 seconds. The Finger Tapping Test device automatically records the number of taps per 10 seconds. A total of 10 trials were conducted; 5 on the right hand and 5 on the left, starting with the dominant hand. Averages were calculated for the 5 trials for each hand, and these averages were summed to create a total finger tapping score. Higher scores are indicative of better psychomotor skills. The Finger Tapping Test is highly reliable with test-retest ranging from 0.86 to 0.94 (Lezak, 1995).

Wisconsin Card Sorting Test: Computer version 4—This computerized instrument measures executive functioning and mental flexibility using a mouse response mode. Participants are required to sort the cards on the screen according to different principles (color, form, or number) during the test administration. For this test there are no formal instructions, rather, participants are simply instructed to match the cards and the computer will inform them if they are right or wrong. After matching a response card to a stimulus card, the participant is told whether his/her choice is right or wrong. The participant continues card matching until 10 cards in a row are matched, and the computer then surreptitiously changes the sorting principle for the participant to figure out the principle; six matches are possible. While this computerized version of the Wisconsin Card Sorting Test has 128 possible trials, as in the standard version, when participants consistently perform the trials correctly, the test terminates. Thus, because participants were administered varying number of trials according to their individual performances, percentage of correct responses, rather than total number correct was the preferred value derived for analysis, with higher percentages correct, indicating better executive functioning. This test is highly related to other measures of executive functioning and has modest test-retest reliability after 1 year of .56, a figure that might reflect focal lesions that occurred in the sample of older adults being tested in the study by Greve (2001).

Hopkins Verbal Learning Test—This instrument measures memory and consists of 12 words that are presented via an audiotape, four from each of three semantic categories: animals (e.g., Lion), stones (e.g., Emerald), and shelters (e.g., Cave). There are three learning/free-recall trials in this measure, and the total number of words correctly recalled was used as the score, with higher scores reflective of better memory functioning. Test-retest reliability over 9 months in older adults for this measure was stable at $r = .50$, a figure comparable to those found for other gold standard measures of memory such as the Logical Memory subtest of the Wechsler Memory Scale-Revised and the California Verbal Learning Test (Rasmusson, Bylsma, & Brandt, 1994).

Everyday functioning—Three instruments of everyday functioning were used: two laboratory tasks simulating common instrumental activities of daily living (i.e., a timed/speeded IADL test, a non-timed more complex IADL test), and medication adherence. The

medication adherence measure was only completed by the HIV-infected participants, as this measure included questions related to HIV medication adherence (i.e., ART). These measures are described in detail below.

Timed Instrumental Activities of Daily Living (TIADL)—This instrument is a laboratory measure simulating everyday IADLs. It measures accuracy in performing five tasks and the speed in which they are performed. It is often the case that participants will complete these tasks with no errors, yet some will take much longer to complete the tasks than others. Thus, this task is objectively measuring speed of processing in the context of everyday tasks. The tasks include looking up a number in a telephone book, counting out a specific amount of change, locating ingredients on canned goods, locating items on a shelf, and finding directions on medicine bottles. The time (seconds) needed to complete each task was recorded, and there was a time limit of 2 minutes for each task (3 minutes for the telephone book task). Accuracy in performing each task was also recorded (completed without errors, completed with major or minor errors, or not completed within the time limit). In the case of errors, a time penalty was added to the score. For each task, completion times were transformed to *z* scores, which were then equally weighted to form a total composite score that centered around the mean of zero; thus, scores can include both negative and positive values. Lower scores reflect faster completion times of everyday activities. Test-retest reliability is high at $r = 0.64$ (Owsley et al., 2002).

Observed Tasks of Daily Living (OTDL)—This instrument (Diehl, Willis, & Schaie, 1995) is composed of 28 observational tasks that simulate complex, actual tasks of daily living and have distinct observable elements permitting objective scoring of the participant's performance. The test requires inferential thinking and reasoning in completing medication-related tasks, telephone-related tasks, and financial-related tasks. Participants are given relevant items to each specific task (e.g., medicine bottles for questions regarding locating information from and answering questions about medications) and a card with a question on it for each task. Participants are not timed for these tasks, rather their accuracy is recorded (*yes - completed correctly*, or *no - not completed correctly*) and whether or not a prompt was given. Total scores are created based on accuracy in task completion as well as whether or not prompts are given; higher scores indicate better everyday functioning. The mean kappa across tasks for all 3 domains is 0.93.

Simplified medication adherence questionnaire—HIV-infected participants completed this six-item instrument that measures how consistently they take their HIV medications as prescribed (e.g., Over the past 3 months, how many days have you not taken any medicine at all?). Higher scores indicate less medication adherence. Two participants were not prescribed HIV medications and thus did not complete this measure. This questionnaire has been validated with virological outcomes and overall inter-observer agreement at 88.2% (Knobel et al., 2002)

Procedure

This study was approved by the university's Institutional Review Board for Human Subjects. Upon arrival at the research center, participants were given a description of the study along with an informed consent document by the trained neuropsychological tester in a confidential setting at our research center lobby. Participants were given an opportunity to ask any questions related to the study. After consent was obtained, all measures were administered in a private room at our center during one testing session, which took approximately 2½ hours to complete, with breaks upon request. This battery included demographic, mental and physical health, neuropsychological, and everyday functioning measures. Participants were compensated \$50 for completion of the testing battery.

Experienced neuropsychological test administrators who had demonstrated proficiency in administering the measures used in this study based on their extensive involvement in other center-related research studies were used to administer the tests. These testers were also trained to avoid “drift” (i.e., deviations in how the instruments are administered) during testing sessions.

Data Analysis

The data were analyzed using SPSS 11.5 (SPSS Inc., Chicago, IL). One data point was missing for the following neuropsychological measures: Finger Tapping Test, Complex Reaction Time Test, Useful Field of View Test®, and Wisconsin Card Sorting Test. Based on the remaining neuropsychological scores, linear regression was used to impute the missing values. Groups were created, which were organized by HIV status (infected and uninfected) and age (younger and older), yielding a total of four groups. As mentioned earlier, the demarcation of 50 years of age and older was used to classify the older groups. There were, by design, no significant differences in age between the younger and older groups for the HIV-infected and HIV-uninfected groups ($p > .05$). The demographic and psychosocial differences between groups (Table 1) were compared using ANOVAs and chi-square analyses. Differences between groups in performance on the neuropsychological and everyday functioning measures (Table 2) were examined using ANCOVAs (controlling for education) with alpha set at 0.05. Finally, partial correlations between the neuropsychological and everyday functioning measures and the HIV biomarkers were examined (controlling for education).

Results

Demographics and Medical Characteristics Between Groups

Screening yielded a sample size of 162 participants who met eligibility criteria and who consented to the study. Age ranges for the older and younger HIV-uninfected and HIV-infected groups were similar: Younger HIV-uninfected (22.00-48.84 years of age; $M_{\text{age}} = 37.78$), younger HIV-infected (20.53-49.16 years of age; $M_{\text{age}} = 39.87$); older HIV-uninfected (50.05-74.42 years of age; $M_{\text{age}} = 58.58$), and older HIV-infected (50.45-70.64 years of age; $M_{\text{age}} = 56.82$). ANOVAs and chi-squares were used to examine group differences on each of the demographic and psychosocial variables. There were significantly more men ($\chi^2[N = 162] = 22.55, p < .001$) and homosexuals/bisexuals ($\chi^2[N = 162] = 37.30, p < .001$) in the HIV-infected group. Also, the older participants were more educated than the younger participants ($F[3, 158] = 3.71, p < .05$); however, the HIV-infected participants and older adults had a significantly higher number of comorbidities ($F[3, 158] = 8.84, p < .01$) and prescribed medications ($F[3, 158] = 15.39, p < .01$). No other group differences were detected. Given that it has been demonstrated that gender differences are not evident in the basic neuropsychological domains (Hyde, 2005), subsequent analyses did not control for gender. Similarly, there is no reason to suggest that heterosexuals and homosexuals/bisexuals possess different neuropsychological abilities; thus, subsequent analyses did not control for this. Likewise, because the groups were different by definition based upon age and HIV status, which requires medications that sometimes contribute to comorbidities, it was decided that controlling for these group differences in subsequent analyses would not be logical or ecologically valid given the purpose of the study. Albeit, education level differences between groups were detected and given that education has been implicated with increased cognitive reserve that can impact neuropsychological and everyday functioning (Thames et al., 2011), controlling for education was deemed appropriate.

Characteristics of the HIV-Infected Group on HIV-specific Variables

The HIV-infected participants had been diagnosed on average 12.93 years ($SD = 7.34$, range = 1-26.10). The average current CD4+ T-cell count was 471.30 cells/mm³ ($SD = 274.40$, range = 1-1,140 cells/mm³) and the average nadir CD4+ T-cell count was 236.60 cells/mm³ ($SD = 236.60$, range = 1-1,037 cells/mm³). The normal range for a CD4+ T-cell count is 589-1,505 cells/mm³ (Raper, 2010). Thus, this sample had CD4+ T-cell counts slightly below the normal range. Furthermore, a CD4+ T-cell count below 200 cells/mm³ is indicative of AIDS (Centers for Disease Control and Prevention, 1992). Clearly, with this range and standard deviations, many of the HIV-infected participants had a current CD4+ T-cell count indicative of AIDS ($n = 12$; 15.38%) or at sometime had AIDS as indicated by the nadir CD4+ T-cell count being below 200 cells/mm³ ($n = 30$; 38.46%).

The goal of ART is to promote viral suppression, which is measured by viral load. A viral load of less than 50 copies/mL, also known as being “undetectable” (i.e., some lab values report this at 48 copies/mL), is considered to be an excellent indicator of viral suppression (Kirton, 2001). In our sample, the average viral load was 14,780.82 copies/mL ($SD = 6,7501.02$; range = 48-549,000 copies/mL); 32 (41.03%) of the HIV-infected participants had undetectable viral loads. There were no significant group differences on these biomarkers of HIV between the younger and older HIV-infected participants. The older HIV-infected participants had been diagnosed with HIV significantly longer; on average, older HIV-infected participants had been diagnosed for 16.71 years ($SD = 7.09$) compared to 10.44 years ($SD = 6.44$) in the younger HIV-infected participants. However, this was inextricably related to the group assignments of younger and older.

Group Differences on Neuropsychological and Everyday Functioning

As seen in Table 2, the adjusted (controlling for education) means are presented. From this, using ANCOVAs a number of main effects for age and HIV were detected. For the Useful Field of View Test®, a main effect for age ($F[1, 157] = 13.36$, $p < .001$) and a main effect for HIV ($F[1, 157] = 4.78$, $p = .03$) were observed; those who were older or had HIV performed worse on this visual speed of processing test. For the Complex Reaction Time Test, a main effect for age ($F[1, 157] = 5.19$, $p < .02$) and a main effect for HIV ($F[1, 157] = 7.31$, $p < .01$) were observed; those who were older or had HIV performed worse on this speed of processing test. For Letter Comparison, a main effect for age ($F[1, 157] = 16.70$, $p < .001$) and a main effect for HIV ($F[1, 157] = 7.17$, $p = .01$) were observed; those who were older or had HIV performed worse on this speed of processing test. For Pattern Comparison, a main effect for age ($F[1, 157] = 18.22$, $p < .001$) and a main effect for HIV ($F[1, 157] = 8.03$, $p < .01$) were observed; those who were older or had HIV performed worse on this speed of processing test. For the Finger Tapping Test, a main effect for age ($F[1, 157] = 13.91$, $p < .001$) was observed; those who were older performed worse on this psychomotor test. For the Hopkins Verbal Learning Test, a main effect for age ($F[1, 157] = 6.12$, $p < .05$) was found; those who were older performed worse on this memory test.

For the TIADL test, a main effect of age ($F[1, 157] = 5.08$, $p = .03$) and HIV ($F[1, 157] = 9.58$, $p < .01$) were observed; those who were older or had HIV performed worse on this measure of everyday functioning. An age $\times$ HIV interaction on the TIADL approached significance ($F[1, 157] = 2.854$, $p = .09$) in the expected direction. No other statistically significant differences were observed between the groups. In addition, younger and older HIV-infected participants did not differ in medication adherence.

In additional follow-up analyses, gender, education, sexual orientation, and income were controlled. This did not change the significance of the findings in Table 2 except that an

HIV effect for the Wisconsin Card Sorting Test and for the OTDL was observed. These favored better performance in those without HIV.

Due to the 28 statistical comparisons in Table 2 (i.e., age, HIV, and age $\times$ HIV effects by 9 tests), Benjamini-Hochberg alpha correction was employed, which is less restrictive than the Bonferroni alpha correction. The age effects for Useful Field of View Test®, Letter Comparison, Pattern Comparison, and Finger Tapping Test remained. The HIV main effects for Complex Reaction Time Test, Pattern Comparison, and TIADL also remained.

Association Between Cognition and Everyday Functioning

As seen in Table 3, partial correlations, controlling for education, were examined between the neuropsychological and everyday functioning measures. TIADL was significantly correlated with Useful Field of View Test®, Complex Reaction Time Test, Letter Comparison, Pattern Comparison, and Hopkins Verbal Learning Test; slower speed of processing and poorer memory function were related to poorer functioning on this measure of speed and accuracy of everyday functioning. Similarly, OTDL, a measure of complex everyday functioning, was significantly correlated with Useful Field of View Test®, Complex Reaction Time Test, Letter Comparison, Pattern Comparison, Wisconsin Card Sorting Test, and Hopkins Verbal Learning Test; slower speed of processing and poorer executive and memory functioning were related to poorer functioning on this measure of complex everyday functioning. Incidentally, TIADL and OTDL, both laboratory measures of everyday functioning, were highly correlated ($r = -.45$; $p < .001$), demonstrating excellent construct validity. Medication adherence was not related to TIADL, OTDL, or any of the neuropsychological measures.

Age and HIV Biomarkers on Neuropsychological and Everyday Functioning

As seen in Table 3, partial correlations, controlling for education, were examined between age and HIV biomarkers and neuropsychological and everyday functioning. Age was significantly correlated to chronicity of HIV (which is largely by definition, as individuals who are older have likely had the disease for longer than those who are younger), Useful Field of View Test®, Complex Reaction Time Test, Letter Comparison, Pattern Comparison, and TIADL; being older was related to poorer speed of processing and everyday functioning. Chronicity of HIV was significantly correlated to current CD4+ T-cell count, Useful Field of View Test®, and TIADL; being diagnosed longer with HIV was associated with a lower current CD4+ T-cell count and poorer speed of processing and everyday functioning. Current CD4+ T-cell count was significantly correlated with nadir CD4+ T-cell count and medication adherence; a higher current CD4+ T-cell count was associated with a higher nadir CD4+ T-cell count and better medication adherence. Similarly, a higher nadir CD4+ T-cell count and lower viral load were associated with better medication adherence.

Discussion

The first aim of this study was to investigate whether there were neuropsychological and everyday functioning differences between younger and older adults with and without HIV while controlling for potential confounders; the only potential confounder was education. Specifically, main effects for age and HIV were found on the speed of processing tests (i.e., Useful Field of View Test®, Complex Reaction Time Test, Letter Comparison, and Pattern Comparison) and TIADL; main effects for age only were found on the Finger Tapping Test and Hopkins Verbal Learning Test. Older adults and those with HIV performed more poorly on measures of speed of processing and a timed measure of everyday functioning; older adults performed more poorly on a measure of psychomotor ability and memory. These

main effects were expected; however, no age $\times$ HIV interactions were observed. Yet trends in the data did consistently demonstrate older adults with HIV as a group performed worse on 8 out of the 9 neuropsychological and everyday functioning tests. These findings confirmed those already in the literature (Hardy & Vance, 2009; Ettenhofer et al., 2009).

The second aim of our study was to examine if neuropsychological performance was related to everyday functioning in HIV-infected participants. As seen in Table 3, many of the neuropsychological measures were related to both TIADL and OTDL. These findings are also reflective of the literature, which showed both an age and HIV effect on neuropsychological and everyday functioning. In a sample of 201 younger and older adults with and without HIV, Vance, Eagerton, Harnish, McKie-Bell, and Fazeli (2011) also found that older adults with HIV performed worse on the TIADL test compared to younger adults with HIV and older adults without HIV. Albeit, in both this and the current study, poorer neuropsychological performance was associated with slower speed in performing everyday functioning as measured by the TIADL test.

Surprisingly, neuropsychological functioning was not reflective of medication adherence. As found in the Ettenhofer and colleagues (2009) study, compared to younger adults with HIV, older adults with HIV were more adherent to their medication as measured by the Medication Event Monitoring System (MEMS; a pressure-activated microprocessor embedded in a medication bottle cap that automatically tracks when the bottle is opened). Moreover, they found that those in the older group who exhibited deficits in speed of processing, motor functioning, and executive functioning exhibited poorer medication adherence. Such differences were not observed in our study, perhaps because the sample was largely adherent to their medications, as exhibited by low medication adherence scores. In addition, using a self-reported measure of medication adherence instead of an objective measure may have resulted in socially desirable responses from the participants, which could have obfuscated the findings.

The final aim of the study was to examine whether chronicity and HIV biomarkers were associated with neuropsychological and everyday functioning in the HIV-infected sample. A longer duration of HIV was associated with a lower current CD4+ T-cell count as well as poorer speed of processing and performance on everyday functioning; however, the strength of these associations was not as robust as expected in that more associations were expected between the neuropsychological measures and these HIV biomarkers. These differences are not as obvious as observed in previous years, perhaps due to improvements in treatment. Furthermore, better viral load and CD4+ T-cell counts (current and nadir) were associated with better medication adherence; thus, medication adherence yielded good medical outcomes for HIV management.

Clinical Implications

Given these findings, concerns remain that older adults with HIV may be particularly vulnerable to neuropsychological and everyday functioning declines. Researchers and clinicians should consider screening older adults with HIV for neuropsychological declines that may impair everyday functioning. In addition, further consideration should be given to treating such neuropsychological deficits. For example, Vance and colleagues (2011) posited a number of methods to promote positive successful neuropsychological aging in adults with HIV using “cognitive prescriptions.” Such individualized prescriptions focus on ways to improve or protect neuropsychological functioning. These include specific, measurable behavioral goals to encourage engagement in good sleep hygiene, good nutrition, physical and intellectual exercise, and maintaining good medication adherence.

Given the prevalence of neuropsychological deficits observed in HIV, especially speed of processing, cognitive remediation therapies to improve neuropsychological and everyday functioning should be considered. For example, in a sample of 46 adults with HIV (ages 40 years), Vance, Fazeli, Ross, Wadley, and Ball (in press) used a computerized speed of processing training program to improve the Useful Field of View Test®, a measure of visual speed of processing. After only ten 1-hour training sessions, researchers found that compared to a no-contact control group, those in the training group improved on this measure, which also translated to improvements in the TIADL test. Other cognitive remediation interventions (e.g., memory training) that are commonly used in the gerontological literature may also be effective in individuals with HIV, especially as such adults age with this disease (Ball et al., 2004).

Directions for Future Research

In addition to exploring cognitive interventions and other methods for promoting successful neuropsychological aging in individuals aging with HIV in future research and practice, additional research should continue to examine the neuropsychological and functional differences between individuals with and without HIV. Specifically, older individuals should be included in order to continue exploring whether there is a synergistic effect of HIV and age on neuropsychological functioning. Longitudinal studies should also be employed to more accurately examine the neuropsychological and everyday functional trajectories of this population. Furthermore, as individuals with HIV are increasingly living healthier, longer lives due to ART, studies should examine predictors of successful neuropsychological aging with HIV in the face of well-controlled HIV.

Limitations and Strengths

As mentioned, because this community-based sample was healthy enough to manage a visit to the research center, it reflected a higher functioning group of adults and may not have been reflective of older adults with HIV who were at a greater risk for neuropsychological impairment. Also, given that ART is highly effective, those suffering from subtle neuropsychological declines may not be as easily recognized, which may explain the lack of age $\times$ HIV interactions on the neuropsychological measures observed in other studies. Also, those older adults with HIV may reflect a select sample; those who survive with HIV into later life may be more hardy and resilient. Thus, the lack of age $\times$ HIV interactions observed in this and earlier studies may reflect a survival bias; longitudinal studies will obviously be needed to explore ways to account for such confounds and for changes over time. Additionally, because a self-report measure was used for medication adherence, results could reflect social desirability bias. Including a MEMS cap assessment may have yielded more accurate data for this construct. However, MEMS caps also have limitations, as participants may not consistently open/use the actual pill bottles (i.e., if they have a pill case that they put pills in weekly). Furthermore, participants could also (as a result of social desirability and knowledge of the study's intentions) open the pill bottles and not actually take the medication.

Three primary strengths are observed. First, this study used validated measures of neuropsychological and everyday functioning. Second, this study used actual clinic data on HIV biomarkers. Finally, the demographic differences between the HIV-infected and HIV-uninfected groups were minor, providing reassurances that, in general, the groups were comparable.

Conclusion

By 2015, half of the PLWH in the United States will be ages 50 and older; thus, more research is needed to identify and address neuropsychological deficits in this clinical population. Our study suggests that individuals with HIV are at risk for poorer neuropsychological and everyday functioning than their HIV-uninfected counterparts, and that neuropsychological functioning is related to everyday functioning. However, whether or not there is a pronounced risk for neuropsychological declines in much older HIV-infected adults needs to be explored in future research. Several methodological difficulties when studying the synergistic effects of age $\times$ HIV on neuropsychological and everyday functioning should be considered. These include limited sample size, heterogeneous differences in both the aging and HIV populations, and survival bias. In October 2010, the White House held the first open forum on HIV and Aging and encouraged policy makers and researchers to continue to search for ways to help PLWH age successfully. Aging with HIV is inclusive not only of physical well-being but also of successful neuropsychological aging.

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Clinical Considerations

- Although HIV-related dementia is not nearly as prevalent now due to the neuroprotective effects of ART, 30% to 60% of those with HIV will experience some level of neuropsychological decline at some point during their illness. Older adults with HIV may be particularly at risk for such cognitive declines.
- Researchers and clinicians should consider screening older adults with HIV for neuropsychological declines that may impair everyday functioning, particularly subtle neuropsychological declines that may often be overlooked.
- Given the prevalence of neuropsychological deficits observed in HIV, especially speed of processing, cognitive remediation therapies to improve neuropsychological and everyday functioning should be considered, as well as behavioral interventions to modify lifestyle factors that may be related to cognitive functioning.

Table 1

Demographic and Psychosocial Differences Between Groups (N = 162)

	Younger HIV-infected (n = 47)	Older HIV-Infected (n = 31)	Younger HIV-Uninfected (n = 43)	Older HIV-Uninfected (n = 41)
	<i>M (SD)</i>	<i>M (SD)</i>	<i>M (SD)</i>	<i>M (SD)</i>
Number of Men (%) [†]	35 (74.47)	24 (77.42)	15 (34.88)	18 (43.90)
Number of Heterosexuals (%) [†]	24 (51.06)	15 (48.39)	39 (90.70)	39 (95.12)
Number of Caucasians (%) [*]	30 (63.83)	18 (58.06)	30 (69.77)	25 (60.98)
Income (1 = \$0 - \$10,000; 8 = more than \$70,000) [†]	1.57 (1.23)	2.00 (1.51)	1.65 (1.13)	2.32 (1.81)
Education (years) [†]	12.15 (2.06)	13.71 (2.78)	12.67 (1.43)	12.90 (1.92)
Number of Medical Conditions [†]	2.53 (1.61)	3.48 (2.03)	1.40 (1.72)	2.90 (2.02)
Number of Medications [†]	4.30 (3.23)	5.65 (3.52)	1.19 (2.34)	3.22 (2.77)
Profile of Mood States	37.21 (39.76)	34.07 (40.77)	33.90 (42.03)	28.10 (33.66)
Addiction Severity Index - Alcohol Use	0.17 (0.28)	0.33 (0.88)	0.25 (0.46)	0.23 (0.46)
Addiction Severity Index - Drug Use	0.03 (0.08)	0.03 (0.06)	0.01 (0.04)	0.02 (0.04)
Chronicity of HIV [†]	10.44 (6.46)	16.71 (7.09)	na	na
Current CD4+ T-Cell Count (cells/mm ³)	488.28 (303.81)	445.55 (224.94)	na	na
Nadir CD4+ T-Cell Count (cells/mm ³)	255.32 (236.88)	308.32 (236.42)	na	na
Current Viral Load (copies/mL)	22,490.96 (85,692.21)	2,816.83 (9,804.20)	na	na

Notes. *M* = Mean; na = not applicable; *SD* = standard deviation;

^{*} = All others were African American except one who was an HIV-infected Native American who was older.

[†] *p* < .05

[‡] *p* < .01

Table 2

Education Adjusted Means and Standard Deviations (N = 162) for the Neuropsychological and Everyday Functioning Tests

	Younger HIV-infected (n = 47)	Older HIV-Infected (n = 31)	Younger HIV-Uninfected (n = 43)	Older HIV-Uninfected (n = 41)
	<i>M (SD)</i>	<i>M (SD)</i>	<i>M (SD)</i>	<i>M (SD)</i>
Useful Field of View® ^{A,H}	659.27 (340.23)	856.15 (342.11)	539.93 (335.47)	742.20 (335.51)
Complex Reaction Time Test ^{A,H}	3.65 (1.07)	4.17 (1.07)	3.33 (1.06)	3.59 (1.06)
Letter Comparison ^{A,H}	47.86 (10.50)	40.73 (10.56)	51.71 (10.35)	45.06 (10.35)
Pattern Comparison ^{A,H}	33.87 (7.03)	28.32 (7.07)	36.26 (6.93)	32.18 (6.93)
Finger Tapping Test ^A	104.00 (15.12)	97.33 (15.20)	102.83 (14.92)	91.38 (14.92)
Wisconsin Card Sorting Test (% correct)	0.53 (0.07)	0.47 (0.19)	0.55 (0.18)	0.53 (0.19)
Hopkins Verbal Learning Test ^A	24.55 (6.02)	21.99 (6.05)	25.19 (5.93)	23.00 (5.94)
TIADL ^{A,H}	-0.94 (2.95)	1.77 (2.97)	-0.74 (2.92)	-0.46 (2.92)
OTDL	68.88 (7.05)	66.96 (7.10)	70.13 (6.96)	68.88 (7.05)
Simplified Medication Adherence	3.31 (4.74)	3.02 (4.72)	na	na

Notes. M = mean; SD = Standard Deviation; na = not applicable; OTDL = Observed Tasks of Daily Living; TIADL = Timed Instrumental Activities of Daily Living test.

^A = Significant main effect for age at $p < .05$

^H = Significant main effect for HIV status at $p < .05$; A × H = Significant age × HIV interaction at $p < .05$.

Table 3

Partial Correlations Among HIV Biomarkers, Neuropsychological, and Everyday Functioning (N = 78)

Partial R	Age	Chronicity of HIV	Current CD4+ T-Cell Count	Nadir CD4+ T-Cell Count	Current Viral Load	TIADL	OTDL	Medication Adherence
Age	1.00	.45*	-.14	-.02	-.23	.41*	-.27 [†]	.01
Chronicity of HIV	.45*	1.00	-.26 [†]	-.14	-.08	.31 [†]	-.23	.06
Current CD4+ T-Cell Count	-.14	-.26 [†]	1.00	.69*	-.22	-.06	.07	-.42*
Current Viral Load	-.23	-.08	-.22	-.17	1.00	-.17	.09	.29 [†]
Nadir CD4+ T-Cell Count	-.02	-.14	.69*	1.00	-.17	.08	-.08	-.35 [†]
Useful Field of View®	.38 [†]	.25 [†]	.17	.08	-.16	.52*	-.47*	-.01
Complex Reaction Time	.38 [†]	.14	.07	.13	-.12	.53*	-.42*	-.14
Letter Comparison	-.44*	-.13	.02	-.02	.13	-.55*	.28 [†]	.08
Pattern Comparison	-.49*	-.10	.03	-.05	.11	-.52*	.39*	.10
Finger Tapping Test	-.20	-.08	.05	.09	.09	-.24	.24	-.12
Wisconsin Card Sorting Test	-.24	-.12	.00	-.09	.02	-.10	.36 [†]	.03
Hopkins Verbal Learning Test	-.22	-.09	-.13	-.32	.21	-.40*	.45*	.15
TIADL	.41*		-.06	.08	-.17	1.00	-.45*	-.08
OTDL	-.27	-.13	.07	-.08	.09	-.45*	1.00	.12
Medication Adherence	.01	.06	-.42*	-.35 [†]	.29 [†]	-.08	.12	1.00

Notes. OTDL = Observed Tasks of Daily Living; TIADL = Timed Instrumental Activities of Daily Living;

Partial correlations are controlling for education.

[†] $p < .05$

[‡] $p < .01$

* $p < .001$.