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Aging and Neurocognitive Functioning in HIV-Infected Women: A Review of the Literature Involving the Women's Interagency HIV Study

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Abstract

HIV-infected women may be particularly vulnerable to certain types of neurocognitive impairments which may be exacerbated by aging and other predictors. Within the context of cognitive reserve, this article examines issues surrounding women as they age with HIV. For this, a review of 12 recent studies (2013–2016) using data from the Women's Interagency HIV Study (WIHS), the largest cohort study comparing HIV-infected and demographically-matched uninfected women, is presented that specifically examine neurocognition. In general, HIV-infected women are more vulnerable to developing neurocognitive impairments than uninfected women; other factors that may contribute to these neurocognitive impairments include recent illicit drug use, reading level (educational quality/cognitive reserve), stress, PTSD, insulin resistance, liver fibrosis, and age. Surprisingly, when examined in some analyses, age X HIV interactions were not observed to impact neurocognitive performance, findings largely consistent in the literature; however, longitudinal analyses of these data have yet to be performed which may yield future insights of how cognitive reserve may be compromised over time. Yet, with insulin resistance,

liver fibrosis, stress, and other known predictors of poorer neurocognition also occurring more with advanced age, in time the synergistic effect of age and HIV may be more robust and observable as this population ages.

Keywords

Aging; HIV; AIDS; cognition; neurocognition; cognitive reserve women; women with HIV; HIV-infected women; MRI; memory; verbal memory; verbal learning; verbal fluency; executive function; fine motor skills; attention; WIHS; Women's Interagency HIV Study; liver fibrosis; insulin resistance; diabetes mellitus; stress; PTSD; anthropometric; neuroimaging

Since combination antiretroviral therapy (cART) blocks the replication cycle of HIV, many infected adults adherent to cART have suppressed viral loads, improved immune function, and better overall health. As a consequence, they are living longer, are aging with this disease, and are expected to have lifespans tantamount to those uninfected with HIV.^{1,2} By 2020 over 75% of those with HIV in the United States will be 50 and older.³ With 52% to 59% of HIV-infected adults already experiencing some degree of HIV-Associated Neurocognitive Disorder (HAND) ranging from Asymptomatic Neurocognitive Impairment (ANI) to HIV-Associated Dementia (HAD),^{4,5} those aging with this disease appear to be more vulnerable to developing HAND. In fact, one study found that older adults with HIV experience two to three times the risk of living with HAD compared to younger adults with HIV.⁶ Albeit, there remains debate as to whether cognitive aging in this population is accentuated (i.e., made worse than normal) or accelerated (i.e., occurs at an earlier time in the lifespan).⁷ Yet, this disproportionate expression in neurocognitive impairment reflects a detrimental impact in cognitive reserve in this population as they age, as well as a host of other factors that are related to cognitive reserve including sex, drug use, education, trauma, stress, comorbidities, and so forth.⁸

Cognitive reserve refers to how well the brain can absorb physiological insults (e.g., reduced brain perfusion, white matter hyperintensities, transient ischemic attacks, neuroinflammation, oxidative stress, drug abuse) and yet engage in optimal neurocognitive operations. Cognitive reserve normally increases during the course of one's life, especially in childhood and young adulthood when the brain is developing and maturing, in which one learns and thus builds stronger and more sophisticated connections between neurons. This neuronal growth and strengthening occurs in challenging educational attainment, occupation/employment opportunities, and social and intellectual engagement. Cognitive reserve may be supported by healthy behaviors such as physical exercise or good nutrition that simply promotes general health which benefits brain health.^{8,9} On the contrary, cognitive reserve may be unsupported by unhealthy behaviors such as drug use, stress, and a sedentary lifestyle.¹⁰⁻¹³ Several studies have shown that in normal older adults,¹⁴ as well as HIV-infected adults,¹⁰ active engagement facilitates increased cognitive reserve and successful cognitive aging.

Cognitive aging may be further improved by a recent clinical change of how HIV is treated clinically. Since 2013, the medical treatment for HIV has progressively emerged to current recommendations to offer cART to all HIV-infected adults, arguing that the detrimental

impact of viral replication on the body is immediately addressed before irreparable damage to the immune system occurs.¹⁵ This is a profound change in that everyone, regardless of disease stage, is now considered for treatment with these medications. Since HIV can cross the blood brain barrier and compromise the central nervous system, earlier initiation of cART may also produce neuroprotective effects that preserves cognitive reserve over the lifespan.⁸

Recent changes in timing of cART initiation could influence extenuating factors in how HIV impacts cognitive reserve and neurocognitive functioning, particularly among women.⁸ In some studies,^{16–19} these changes may be particularly influential as differential patterns and risk factors for neurocognitive functioning have been observed between HIV-infected men and women, yet such neurocognitive differences have not universally been found.²⁰ For example, compared to HIV-infected men, HIV-infected women may be more vulnerable for developing verbal learning and verbal memory deficits.¹⁸ Also, compared to a gender-matched HIV-negative sample, women have been shown to experience poorer performance on procedural learning tasks while HIV-positive men did not.¹⁶

Furthermore, for uninfected women, menopausal stage and/or menopausal symptoms may affect neurocognitive functioning.²¹ For HIV-infected women, such debut of menopausal stage may occur earlier (i.e., accelerated aging) and menopausal symptoms such as psychological symptoms, sleep problems, and vasomotor symptoms may be more severe (i.e., accentuated aging) compared to uninfected women;^{22–25} yet, in one cross-sectional study, the severity of menopausal symptoms in each of the five categories (mood, sleep, vasomotor, somatic, vaginal) was similar in HIV-infected women and uninfected women overall and as a function of menopausal stage. In adjusted analyses, HIV-infected women remained at increased odds on persistent night sweats only.²⁶

In addition, women are more vulnerable to neurocognitive impairments due to more exposure to trauma, physical and sexual abuse, lower education and income, barriers to health care utilization, and depression, all of which can directly or indirectly compromise physiological health as well as brain health.^{13,27} This point is particularly germane as women, worldwide, comprise most of those infected with HIV.²⁸ Unfortunately, most studies that examine HIV-related neurocognitive impairment primary have focused on men or on small samples of women, which prevents the ability to reliably extrapolate what the cognitive aging profile in HIV-infected women may be.

The purpose of this article is to provide an updated review current HIV-related neurocognitive literature (published from 2013 to 2016) that reflects recent medical standards of HIV treatment as it pertains particularly to women with HIV, especially as they age. To accomplish this goal, the source material for extrapolating the neurocognitive profile of HIV-infected women as they age comes from the Women's Interagency HIV Study (WIHS), which is the largest cohort study of HIV-infected women. These most recent neurocognitive and brain imaging studies from this large, comprehensive dataset are summarized (Table 1) and then synthesized as they relate to cognitive reserve and cognitive aging.

Overview of the WIHS's Neurocognitive Protocol

WIHS is the largest cohort study following HIV-infected women which also has a demographically-matched sample of uninfected women. These women are followed longitudinally and are administered a variety of psychosocial and physiological measures (e.g., CD4 cell count, viral load, liver function tests) every 6 months, with four visits occurring over a 2-year period. WIHS has been on-going since October 1994 and has a rich database supported by a coordinating center (Johns Hopkins University) with several current/past sites (Brooklyn, NY; Bronx/Manhattan, NY; Chicago, IL; Los Angeles, CA; San Francisco/Bay Area, CA; Washington, DC) and newly added southern sites (Atlanta, GA; Chapel Hill, NC; Birmingham, AL; Jackson, MS; Miami, FL).^{29,30}

All of the current WIHS neurocognitive protocols published in 2013–2016 share the following strengths and limitations. First, all are cross-sectional and use the data from the original sites; although WIHS has incorporated an additional follow-up wave of neurocognitive data, these longitudinal data are only recently becoming available for analysis. Second, with such a large generalizable urban sample, all of these analyses are statistically able to incorporate a rich array of covariates which are available to control for potential confounds. These covariates vary slightly between the various articles and even within the individual articles themselves depending on the aims within each secondary analysis. In some studies, some of these variables are controlled, while in others, normed-based regression scores are used to handle these covariates. Although not comprehensive, the typical covariates include: age; study site; annual household income; Center for Epidemiological Studies Depression Scale (CES-D cutoff = 16); hepatitis C status; antidepressant use; smoking status (recent, former, never); marijuana, cocaine, and/or heroin use (recent, former, never); recent heavy alcohol use; and, prior exposure to neurocognitive tests. Third, although age was not a primary focus in most of these studies, the sample itself represents mostly middle-aged women in their 40's with a large age range across the lifespan. Fourth, all of the sites conformed to a three-step certification process to train testers to administer the neurocognitive battery without “drift” in the protocol, thus ensuring quality data collection. Fourth, the neurocognitive test battery was selected by a panel of experts that would allow a HAND diagnosis to be calculated using the Antinori et al. research nosology³¹ as well as comparisons to be made with the Multicenter AIDS Cohort Study (MACS) which focuses specifically on HIV-infected men;^{30,31} however, at the moment, none of the WIHS studies have incorporated the HAND diagnosis yet.

From October 2004 to September 2006 as part of the WIHS core assessment (visits 21–24), participants were administered the Trails Making Test and the Symbol Digit Modalities Test. Between October 2006 and September 2008, the Comalli-Kaplan Stroop Test was also administered (visits 25–28). The Hopkins Verbal Learning Test was administered between April 2007 – 2008. Then in 2009, the full standardized, neurocognitive battery was incorporated in the assessment visits which measure seven cognitive domains: 1) Fine Motor Skills (Grooved Pegboard Test); 2) Psychomotor Speed (Symbol Digit Modalities Test); 3) Attention (Stroop Test, trials 1 & 2; Trails Making Test Part A; Letter-Number Sequence (LNS) Test, control/attention condition); 4) Executive Function composed of working/verbal memory, behavioral inhibition, and mental flexibility (Stroop Test, Trial 3 of the color-word

interference condition; Trails Making Test Part B; LNS Test, working memory condition); 5) Verbal Learning (Hopkins Verbal Learning Test – Revised (HVLTR), single trial learning and total words recalled across the three trials); 6) Verbal Memory (HVLTR delayed recall & percent retention); and 7) Verbal Fluency (Letter Fluency Task & Category Fluency Task).^{13,27,30} Finally, these neurocognitive scores are examined either raw (unadjusted) or adjusted (e.g., multivariable models,^{32–34} propensity score methods²⁷). In addition, in some of the studies, the cognitive domains were averaged by deriving *t*-scores within the individual tests within the cognitive domain; however, this varies by analysis within each article. Since these *t*-scores are derived internally, the WIHS avoids bias associated with external norming, a factor that is particularly important for this cohort that is rich with diversity in race and lifestyle behaviors and is made up entirely of women.

The sample characteristics for these cross-sectional analyses are for data collected 2009 to 2011. Of the 1,908 women in WIHS, 84% completed the neurocognitive battery.³⁰ Approximately 60% of the women are African American, 30% have significant depressive symptomatology (CES-D cutoff = 16), and the average educational level is around 12 years (high school graduate).³⁰ The average age of the sample was 46.15 years (range: 25 to 87), and 45% has an annual household income = \$12,000/year. With missing data and using listwise deletion, for most of the WIHS neurocognitive articles presented here, approximately 1,000 HIV-infected and 500 uninfected women are available for most analyses. Of the HIV-infected women, approximately 37% had suboptimal cART adherence, 47% had detectable HIV RNA in their plasma, and 87% had a CD4+ T-cell count > 200 cells/mcL, which is above the AIDS criteria.³⁵ The frequency of viral suppression falls between that reported by the CHARTER (CNS HIV Antiretroviral Therapy Effects Research) and MACS cohorts and requires separate sensitivity analyses to understand the impact of HIV on cognition among suppressed participants, a population increasingly pertinent to clinical care.

WHIS Neurocognitive and Brain Imaging Studies

The WIHS neurocognitive articles published in the past three years focus on predictors on neurocognitive functioning and/or brain imaging differences between and among HIV-infected and uninfected women. Study details for these have been briefly summarized above and more specifically in Table 1. Few of these studies specifically examined age as a predictor or interaction with HIV; yet, given that the average sample age is in the mid 40's with a wide range in age, the results provide a context in which to consider cognitive aging in this clinical population.

Neurocognitive Comparisons of Women with and without HIV

The focus on predictors of neurocognition in the WIHS range from perceived stress to liver fibrosis. Instead of presenting the articles in chronological order in which they were published, they have been grouped by category: Psychosocial Predictors, and Biological Predictors.

Psychosocial Predictors—In one of WIHS's overarching analyses of cognition, Maki and colleagues³⁰ examined the relationship and magnitude between neurocognition and HIV

status across several predictors. In general, compared to uninfected women, HIV-infected women as a group performed worse on measures of attention, psychomotor speed, verbal learning, delayed (memory) recall, and recognition. Overall, the greatest HIV impairment was in verbal memory (Cohen $d = -.20$). Also, it was found that the effect size for HIV on neurocognition was very small, ranging from .05 to .09 SD units. In comparison, the effect size on neurocognition was larger for age, race/ethnicity, annual household income, years of education, reading level (e.g., Wide Range Achievement Test-3, an indicator of education quality), and in some cases, depressive symptomatology. In fact, reading level yielded the strongest effect sizes for predicting neurocognition in attention as well as verbal learning and verbal memory, ranging from 0.15 to 0.35 SD units. Furthermore, HIV status and reading level produced a significant interaction on measures of executive and psychomotor function; this finding suggests infected women with poorer reading level are more susceptible to developing neurocognitive impairments.

Stress is a unique psychosocial predictor of neurocognition in which HIV-infected women may be particularly vulnerable. In this next WIHS article, Rubin and colleagues¹³ examined the association between stress, as measured by the Perceived Stress Scale. As expected, HIV serostatus was associated with poorer performance on verbal learning, verbal memory, and attention; however, for both HIV-infected and uninfected women, higher stress was associated with poorer verbal learning, verbal memory, attention, speed of information processing, and executive functioning. Notably, there was an interaction between HIV and stress indicating that in the context of HIV, women experiencing more stress exhibited poorer verbal memory compared to women experiencing less stress. Furthermore, this pattern was exacerbated among HIV+ women with viral loads >10,000 copies/ml. Similarly, in HIV-infected men, Pukay-Martin and colleagues³⁶ found that acute stressful life events was also associated with worse executive functioning, attention, and processing speed, but not memory.

In a related analysis, Rubin and colleagues²⁷ investigated the role of post-traumatic stress disorder (PTSD) on neurocognitive functioning. This examination is of particular importance because compared to uninfected women in the United States: 1) childhood sexual abuse in HIV-infected women is twice as great,^{37,38} and 2) HIV-infected women are three times more likely to experience PTSD.³⁹⁻⁴¹ In this analysis, HIV status had little interaction with PTSD status; in fact, women with PTSD performed worse on measures of verbal memory, verbal learning, and psychomotor speed. However, the association of PTSD on neurocognitive functioning varied depending on the exposure to sexual abuse and/or violence. Specifically, the exposure to violence or sexual abuse was associated with a greater number of cognitive domains and an overall worse neurocognitive profile. The only significant interaction between HIV and PTSD revealed that uninfected women with PTSD performed worse on a measure of fine motor skills compared to HIV-infected women with PTSD. This study is in contrast to a study examining the relationship between HIV-infected men with PTSD, which found that PTSD was only associated with memory;⁴² however, both studies used a different neurocognitive battery and a different measure of PTSD.

Another psychosocial factor that can impact neurocognitive functioning is drug use. Meyer and colleagues¹² examined the role in which HIV interacts with drug use to impact

neurocognition. Drug use was categorized in three decreasing frequencies: recent drug use, former drug use, and non-use. These researchers found that recent drug use and HIV infection each contributed to poorer verbal learning and verbal memory; however, the interactions between HIV serostatus and recent drug use, compared to non-use, was associated with poorer verbal learning and memory; specifically, the combination of HIV and recent drug use exacerbate neurocognitive impairment in these domains. Yet, there was no HIV X recent drug use on measures of executive functioning and information speed of processing. Given that women have a greater tendency to use cocaine currently or over the lifespan than men,⁴³ and that cocaine use may accelerate HIV progression,⁴⁴ these finds are particularly compelling as the interaction between HIV progression and recent drug use may compromise the neurocircuitry that supports these neurocognitive abilities. This study used WIHS visit 25 data that only included the Stroop and HVLRT-R; thus, more work is needed to see if this replicates and whether the effects are specific to learning and memory since this was not examined.

Biological Predictors—Several biological predictors have been examined in WIHS including menopause staging, anthropological measures, insulin resistance, and liver fibrosis. Unique to women, menopausal stage/symptoms may debut earlier/more severely in HIV-infected women.^{22–25} Studies in uninfected women suggest that menopausal stage, and/or menopausal symptoms such as vasomotor, sleep, and mood symptomatology, can affect neurocognitive functioning.²¹ In addition, studies involving animals and humans show that estrogen influences the prefrontal cortex and hippocampus, which are brain regions important for verbal learning and memory.^{45,46} To examine this potential relationship, Rubin and colleagues⁴⁷ examined the staging of menopause (early perimenopause, late perimenopause, & postmenopause) and accompanying menopausal symptoms on neurocognition. Overall, HIV infection, but not menopausal stage, was related to poorer attention, memory, and executive functioning. However, menopausal symptoms were inversely associated with neurocognitive functioning. Whereas anxiety symptoms were also associated with poorer verbal learning and memory, depressive symptoms were related to these two cognitive abilities as well as poorer attention and executive functioning. Additionally, greater vasomotor symptoms were related to poorer attention. Furthermore, the association between anxiety symptoms and verbal learning was moderated by HIV status such that elevated anxiety was associated with worse verbal learning in HIV-infected women only. It was surprising that menopausal staging was not observed to differentially affect cognition in these women; however, other studies in uninfected, more educated Caucasian women (e.g., SWAN) detected such changes longitudinally.²¹ Likewise, this sample of HIV-infected women was comprised of more African Americans, were less educated and less economically stable, engaged in more drug use, and experienced a higher prevalence of depression than studies with uninfected women showing such menopausal effects of cognition.²¹

In another WIHS study, Gustafson and colleagues⁴⁸ examined the association of anthropometric measures (i.e., waist-to-hip ratio, waist circumference, and body mass index) on neurocognition in middle-aged women; this study used WIHS visit 21 – 24 data that only included the Trails Making Test and the Stroop Test, so the full comprehensive battery was

not examined. These researchers found that among HIV-infected women, using BMI between 20 – 24.9 kg/m² as a reference group, a BMI of <18.5 kg/m² was associated with poorer executive functioning and speed of information processing. Meanwhile, among HIV-infected women, a BMI 30.0 kg/m² was associated with better executive functioning. Yet, for HIV-infected women, a BMI 30.0 kg/m² was associated with poorer speed of information processing. Furthermore, a waist circumference greater than 88 cm was associated with better executive functioning while those with a waist circumference in the middle category (80 – 87.9 cm) performed best on attention. Similarly, a greater waist-to-hip ratio was associated with speed of information processing. Although the results are somewhat mixed, in general higher anthropometric values are associated with better neurocognition in HIV-infected women, which is rather contradictory compared to studies examining uninfected women, a finding that may, in part, be due to body habitus changes associated with antiretroviral exposure that could complicate the link of BMI to cardiovascular and brain health outcomes.⁴⁹ This may also reflect a restoration of health linked to higher BMIs, a testament to the efficacy of these HIV medications that also may be neuroprotective as suggested in the CHARTER study.^{50,51} This point is particularly relevant as over 80% of this sample of women with HIV were taking cART.

Although cART has been shown to improve neurocognition in HIV-infected adults,⁵⁰ these medications may contribute to metabolic disorders, such as diabetes mellitus and insulin resistance, which diminishes neurocognitive function.⁵¹ In a sample of 658 HIV-infected and uninfected women without diabetes, Valcour and colleagues³² examined the relationship between insulin resistance, measured by the homeostasis model assessment (HOMA) and neurocognition. Elevated HOMA (greater insulin resistance) predicted poorer attention and verbal fluency. Furthermore, an HIV X HOMA interaction was observed; specifically, in HIV-infected women, elevated HOMA predicted poorer attention. In a separate analysis including WIHS participants with diabetes mellitus, this metabolic disorder predicted poorer function in attention and psychomotor speed. These findings confirm previous research on diabetes mellitus and insulin resistance on neurocognition.³⁴

Since HIV also impairs gut epithelium, it has been suggested that Minimal Hepatic Encephalopathy may also contribute to poorer neurocognition, particularly among participants with both HIV and HCV. To examine this, Valcour and colleagues³³ examined the associated between cognitive correlates and liver fibrosis, using the aspartate aminotransferase to platelet ratio index (APRI) and Fibroscan, in HIV-infected and uninfected women with and without Hepatitis C. Using APRI, moderate/severe liver fibrosis was associated with poorer fine motor skills, psychomotor speed, verbal learning, verbal memory, verbal fluency, and executive functioning. Using FibroScan, severe liver fibrosis was associated with poorer verbal fluency, attention, and executive functioning. This study showed that independent of HIV and hepatitis C, liver fibrosis has a unique contribution to neurocognitive impairment; however, authors caution that a common pathway to both cognitive outcomes and liver fibrosis is chronic inflammation. Thus, both cognitive outcomes and fibrosis may be a result of inflammation rather than causative of each other.

Brain Imaging Studies

Four brain imaging studies have been conducted in WIHS within the past 3 years. Given the nature and cost of neuroimaging studies, the sample sizes are expectedly small (Table 1).

In this first study, Liu and colleagues⁵² used advanced fMRI techniques to examine if neural specificity, an index of neuronal dysfunction, is observed in HIV-infected women before structural changes in the brain or neurocognitive impairments are detectable. In examining the fusiform face area in the temporal lobe, 15 HIV-infected and 13 uninfected women were administered a face discrimination test outside the scanner as well as an in-scanner face discrimination task. Both groups of women performed comparably on the behavioral neurocognitive face discrimination test outside the scanner. Neural specificity was defined as “an earlier recovery from adaptation” and a narrow versus a broadened neural activation in the fusiform face area during the in-scanner face discrimination task. Neural specificity was decreased in HIV-infected women. This decreased neural specificity suggests that before behavioral neurocognitive changes or structural changes in the brain emerge, neuronal dysfunction is occurring in HIV-infected women.

In this second study, Meyer and colleagues¹¹ examined the effect of crack cocaine use on verbal memory and prefrontal cortical dysfunction in 30 HIV-infected women. A memory task-based fMRI paradigm was used to examine brain activation/dysfunction while participants engaged an in-scanner verbal memory task that paralleled the HVLRT-R so that semantic clustering could be studied. Those currently using crack cocaine performed poorer on verbal memory, specifically semantic clustering. During the encoding task, left anterior cingulate cortex activation was higher in those who never used crack cocaine compared to those who were current and former users. During the recognition task, bilateral dorsolateral prefrontal cortex and left dorsal medial prefrontal cortex activation was higher in those who never used crack cocaine compared to those who were current and former users. Furthermore, poorer performance on the recognition task correlated with lower activation in the left dorsolateral prefrontal cortex. Thus, dysfunction in the prefrontal cortex and the anterior cingulate cortex may account for poorer verbal memory and verbal learning associated with crack cocaine use.

In this next study, Rubin and colleagues⁵³ examined the effect of stress on verbal memory and brain volume in 38 HIV-infected women. The Perceived Stress Scale (PSS-10) was used to categorize participants between lower stress (lowest two tertiles < 18) and higher stress levels (highest tertile = 18) and structural MRI was used to examine brain volume. HIV-infected women with higher stress levels performed worse on measures of verbal memory and strategic retrieval and showed smaller volumes in the prefrontal cortex, and specifically in the superior, medial, and inferior frontal gyrus and the parahippocampal gyrus (bilaterally). In addition, poorer verbal learning and memory were associated with smaller brain volumes in the superior, medial, and inferior frontal gyrus (right hemisphere).

Finally, in a similar study, Rubin and colleagues⁵⁴ examined the effect stress had on verbal memory and prefrontal cortical dysfunction in 36 HIV-infected women. As in the study before, the Perceived Stress Scale (PSS-10) was used to categorize participants between lower stress (lowest two tertiles < 18) and higher stress levels (highest tertile = 18). A

memory task-based fMRI paradigm was used to examine brain activation/dysfunction while participants. HIV-infected women with higher stress levels performed worse on measures of verbal memory including strategic retrieval. During the verbal recognition task, women with higher stress levels displayed greater deactivation in the posterior cingulate cortex and the medial prefrontal lobe. Similar findings were observed when examining PTSD symptoms but not depressive symptoms.

Discussion

Collectively, these recent WIHS neurocognitive studies tell a unique story about HIV-infected women. First, compared to uninfected women, HIV-infected women in general perform worse neurocognitively, especially on measures of verbal learning and verbal memory; and this finding is consistent across studies even when either controlling for a number of covariates or examining for particular predictors. In contrast, HIV-infected men are observed to experience worse neurocognitive functioning in executive functioning and learning.^{55,56}

Second, the effect of HIV on neurocognitive impairment is small compared to other predictors such as age, income, race, and more importantly, reading level, which is a proxy of cognitive reserve.³⁰ The diminished impact of HIV compared to demographically matched populations is consistent with published work. Although menopausal stage did not exert any detrimental neurocognitive effects, clearly drug use, stress-related factors, insulin resistance and diabetes mellitus, and liver fibrosis (likely a marker of general inflammation) does and may interact with HIV to accentuate or accelerate cognitive aging.

In fact, as this population ages, the prevalence and severity of some conditions will rise; for example, the prevalence of diabetes mellitus occurs in 28.8% of HIV-infected adults 60 and older,⁵⁷ which may further compromise cognitive reserve.⁵⁸ In addition, studies in uninfected adults show that with advancing age, women perceive more stress than men.⁵⁹ Such stress may lead to metabolic disorders such as insulin resistance and diabetes.^{60,61} Furthermore, it is well documented that HIV-infected women experience a high number of stressors. Among HIV-infected women in the WIHS, 31% reported childhood sexual abuse, 66% reported domestic violence within their lifetime, and 21% reported domestic violence within the past 3 months.⁶² With stress exerting a detrimental effect on the aging brain and neurocognition,⁶³ accompanied with a sharp decrease in gonadal hormones in women compared to men,⁶⁴ this may further compromise cognitive reserve, especially for HIV-infected women for which these conditions are common.

Third, as seen in the Maki and colleagues study,³⁰ HIV-infected women with lower cognitive reserve, as measured by lower reading level, were more vulnerable to having neurocognitive impairments. Surprisingly, although age was a predictor of poorer neurocognition in general, an age X HIV interaction was not observed; perhaps this was because of the age of the samples were mainly in the middle 40's before substantial age-related impairments have the opportunity to be expressed with HIV. Models used in the WIHS analysis did not separately examine age X HIV effects among women who have met AIDS diagnostic criteria, a group most vulnerable to these interactions effects in past published work.^{65,66} Age X HIV

interactions were not the primary focus of these WIHS neurocognitive studies, but in general, the larger HIV literature does not show strong interaction effects, although there are strong trends in showing more neurocognitive impairment in older adults with HIV.^{67,68}

As more longitudinal data become available in the WIHS, it may be that such age X HIV interactions or more complex interactions between age X HIV X reading level (i.e., cognitive reserve) will be observed, with probable neurocognitive impairments being observed in verbal learning and verbal memory in HIV-infected women who already have a lower cognitive reserve. The potential interactions may be especially pronounced if these women experience high levels of stress, insulin resistance, and so forth. In addition, other analysis may also examine the impact of poor antiretroviral adherence and lack of sustained viral suppression on neurocognition. Clearly, there are a number of potential factors that may interact with each other to better predict neurocognition over time.

Fourth, the few recent WHIS neuroimaging studies show, compared to uninfected women, reduce neural specificity as well as impairments and/or volume loss in the prefrontal cortex, anterior cingulate, the parahippocampal gyrus, and frontal gyrus were observed in the HIV-infected women. These regional impairments were also associated with greater levels of stress and cocaine use, and correspond to poorer performance with verbal learning and memory.^{11,53} It has been observed in normal aging that such age-related impairments in these regions are also observed,⁶⁹ which may predispose HIV-infected women to additional declines in cognitive reserve. The imaging studies completed in the WIHS also highlights substantial gaps in the examination of brain structure and function among HIV-infected women when comparing the number of studies completed compared to the number published among HIV-infected men.

Conclusion

Our review of the most recent WIHS neurocognitive studies highlights the most comprehensive summary on the literature documenting the impact of HIV and related neurocognitive predictors on the largest cohort of HIV-infected and uninfected women. So far, HIV has shown a consistent pattern in that HIV-infected women are more vulnerable to impairments in verbal memory and verbal learning in particular; these impairments may be exacerbated by drug use, stress, PTSD, insulin resistance, and liver fibrosis. As some of these neurocognitive predictors may become more severe or more prevalent with advancing age, this suggests that such age-related factors may exacerbate such neurocognitive impairment, especially for those with poorer cognitive reserve (i.e., reading level). Yet, these age-related factors when statistically controlled may obscure the independent effect that age itself exerts on neurocognition; it may be for this reason that age X HIV interactions are inconsistency observed in HIV-infected women as well as men.

Future studies in WIHS will use the HAND diagnosis to examine predictors of change over time. Antinori and colleagues³¹ observed that over a 1-year period, classification of HAND can vary as much as 20%. With our neurocognitive battery being administered every 2 years, it will be of particular interest whether this same phenomenon is observed. And more

importantly, discovering what factors predict those who improve or worsen will be vital for developing effective interventions to preserve cognitive reserve as HIV-infected women age.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Papers of special interest, published recently, have been denoted as:

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Table 1
Highlights of the 12 WIHS Neurocognitive and Brain Imaging Studies (2013 to 2016).

WIHS Neurocognitive Comparing HIV-Infected and Uninfected Women				
Study	Participants	Design & Procedure		Major Findings
Maki et al. (2015) ³⁰ Cognitive Function in Women with HIV: Findings from the Women's Interagency HIV Study	•	•	Cross-sectional	• Compared to uninfected women, HIV-infected women performed worse on neurocognitive measures of attention, psychomotor speed, verbal learning, delayed (memory) recall, and recognition.
	•	•	Standardized Neurocognitive Battery	
		•	Unadjusted and adjusted analyses using multivariable regression on raw test scores	• Overall, the greatest HIV neurocognitive impairment was in verbal memory (Cohen $d = -0.13$).
				• The effect size of HIV on neurocognitive performance was relatively small, ranging from 0.05 to 0.09 SD units.
				• Reading level yielded the strongest effect sizes for predicting cognition in nearly all domains, ranging from 0.15 to 0.35 SD units.
				• Although age and HIV were significantly related to neurocognition; an age X HIV interaction was not significantly related to neurocognition.
				• CD4 count, viral load, and prior AIDS-defining illness were predictive of poorer neurocognition in the expected directions.
Rubin et al. (2015) ¹³ The Association of Perceived Stress and Verbal Memory Is Greater in HIV-infected versus HIV-uninfected Women	•	•	Cross-sectional	• HIV-infected women experienced poorer performance on verbal learning, verbal memory, and attention.
	•	•	Standardized Neurocognitive Battery	
	•	•	Stress was measured using the Perceived Stress Scale (PSS-10).	
	•	•	Multivariable linear modeling were used controlling for several variables including	
				• For both HIV-infected and uninfected women, higher stress predicted poorer

WIHS Neurocognitive Comparing HIV-Infected and Uninfected Women

Study	Participants	Design & Procedure	Major Findings
	•	Of the HIV-infected women, 61.7% and 38.3% were classified as either having lower stress or higher stress, respectively.	verbal learning, verbal memory, attention, and executive functioning.
	•	Of the uninfected women, 63.9% and 30.0% were classified as having lower stress or higher stress, respectively.	• An interaction between HIV and stress revealed that those HIV-infected women experiencing more stress exhibited poorer verbal memory.
	•	Uninfected women had a similar amount of perceived stress compared to HIV-infected women.	• Uninfected women had a similar amount of perceived stress compared to HIV-infected women.
Rubin et al. (2015) ²⁷ Post-traumatic Stress Is Associated with Verbal Learning, Memory, and Psychomotor Speed in HIV-infected and HIV-uninfected Women	• 1,004 HIV-infected Women • 496 Uninfected Women • In this sample, 17% of the HIV-infected women and 16% of the uninfected women had probable PTSD.	• Cross-sectional • Standardized Neurocognitive Battery • Probably PTSD was determined using the PTSD Checklist-Civilian version which was used to map symptoms onto the DSM-IV symptom criteria. • Propensity scores of the neurocognitive measures were used as predictors of neurocognition (e.g., hepatitis C, current/former/non-use of illicit drugs, antidepressant use). • Four groups were examined (HIV+/PTSD+; HIV+/PTSD-; HIV-/PTSD+; HIV-/PTSD-) and examined in a two way ANOVA as well as inverse probability weighted linear regression analyses.	• In general, HIV status had little interaction with PTSD status; in fact, compared to women without PTSD, women with PTSD performed worse on measures of memory, verbal learning, and psychomotor speed. • Furthermore, the exposure to violence or sexual abuse was more predictive of poor neurocognitive functioning. • The only significant interaction between HIV and PTSD revealed that uninfected women with PTSD performed worse on a measure of fine motor skills compared to HIV-infected women with PTSD.
Meyer et al. (2013) ¹² HIV and Recent Illicit Drug Use Interact to Affect Verbal Memory in Women	• 952 HIV-infected Women • 443 Uninfected Women • The average age was 42.8 years (<i>SD</i> = 9.5). • In this sample, 10% reported recent drug use (i.e., heroin, powder cocaine, or crack cocaine) within the past	• Cross-sectional • Standardized Neurocognitive Battery • Self-reported drug use was assessed. • Multivariable regression analyses were used controlling for several variables (e.g., study site, age, race, years of education, reading level, depression symptomatology, recent antidepressant medication, etc.). Other	• Recent drug use and HIV infection each contributed to poorer verbal learning and memory. • The interactions between HIV serostatus and recent drug use, compared to non-drug use, was associated with measures of poorer verbal learning and memory.

WIHS Neurocognitive Comparing HIV-Infected and Uninfected Women

Study	Participants	Design & Procedure	Major Findings
Rubin et al. (2014) ⁴⁷ Investigation of Menopausal Stage and Symptoms on Cognition in Human Immunodeficiency Virus-Infected Women	<ul style="list-style-type: none"> 6 months, 47% reported former drug use within their lifetime but not within the past 6 months, and 43% reported non-use in their lifetime. 708 HIV-infected Women ($M_{age} = 44.56$ years; $SD = 7.35$) 278 Uninfected Women ($M_{age} = 42.80$ years; $SD = 7.51$) Of the HIV-infected women, 54% were premenopausal, 15% were early perimenopausal, 5% were late perimenopausal, and 26% were postmenopausal. Of the uninfected women, 62% were premenopausal, 18% were early perimenopausal, 4% were late perimenopausal, and 16% were postmenopausal. 	<ul style="list-style-type: none"> analyses considered marijuana/hash use, smoking, and recent hazardous alcohol use. Cross-sectional Standardized Neurocognitive Battery Menopausal status was categorized as early perimenopausal (change in regularity of menses in the past 3 months), late perimenopausal (some menstrual bleeding in the past 12 month but non menses within the past 3 months), and postmenopausal (no menses in the past 3 months). Multivariable regression analyses were used controlling for several variables (e.g., annual household income, hepatitis C, antidepressant use, etc.). 	<ul style="list-style-type: none"> Yet, there was no HIV X recent drug use interactions on measures of executive functioning and information speed of processing. HIV infection, not menopausal stage, was related to poorer neurocognitive functioning in attention, memory, and executive functioning. In HIV-infected women, greater anxiety was associated with poorer verbal learning and verbal memory; greater depression was associated with poorer attention, executive functioning, and verbal learning and verbal memory; and greater vasomotor symptomatology was associated with poorer attention.
Gustafson et al. (2013) ⁴⁸ Anthropometric Measures and Cognition in Middle-age and HIV-infected and Uninfected Women. The Women's Interagency HIV Study	<ul style="list-style-type: none"> 1,196 HIV-infected Women 484 Uninfected Women In this sample, 69% were considered overweight or obese (BMI ≥ 25.0 kg/m²). Very few (4.1%) participants were considered underweight (BMI < 18.5 kg/m²). Those with a BMI between 20–24.9 kg/m² 	<ul style="list-style-type: none"> Cross-sectional Standardized Neurocognitive Battery Anthropometric measures were taken including waist-to-hip ratio, waist circumference, and body mass index (BMI). Multivariable regression analyses were used controlling for several variables including annual household income, hepatitis C, exogenous insulin, CD4 nadir, HIV viral load, recreational drug use, antidepressant use, etc. 	<ul style="list-style-type: none"> In HIV-infected women, a BMI of < 18.5 kg/m² was associated with poorer executive functioning and speed of information processing. In HIV-infected women, a BMI ≥ 30.0 kg/m² was associated with poorer speed of information processing. In HIV-infected women, a waist circumference greater than 88 cm was associated

WIHS Neurocognitive Comparing HIV-Infected and Uninfected Women				
Study	Participants	Design & Procedure	Major Findings	
		served as the reference group.		with better executive functioning.
			•	In HIV-infected women, those with a waist circumference in the middle category (80–87.9 cm) performed best on Trails B, a measure of executive functioning.
			•	In HIV-infected women, a higher waist-to-hip ratio was associated with better SDMT, a measure of speed of information processing.
			•	In uninfected women, a BMI 30.0 kg/m ² was associated with poorer performance on executive functioning.
			•	In general, these findings are somewhat mixed and may be prone to alpha inflation.
Valcour et al. (2015) ³² Human Immunodeficiency Virus (HIV) Modulates the Associations between Insulin Resistance and Cognition in the Current Combination Antiretroviral Therapy (cART) Era: A Study of the Women's Interagency HIV Study (WIHS)	• 658 HIV-infected Women • 335 Uninfected Women • The average age was 45.1 years (<i>SD</i> = 9.3).	• Cross-sectional • Standardized Neurocognitive Battery • Insulin resistance was measured using the homeostasis model assessment (HOMA). • HOMA was differentiated into quartiles. • Adjusting for several covariates (e.g., study site, income, BMI, waist-to-hip ratio, fasting cholesterol, depressive symptomatology, antidepressant medication, drug use, alcohol use, hepatitis C, prior neurocognitive testing, etc.), multivariate regression analyses were used to determine the effect of HOMA and HIV status on neurocognition.	•	Elevated HOMA (great insulin resistance) predicted poorer attention and verbal fluency.
			•	An HIV X HOMA interaction was observed; HIV-infected women with elevated insulin resistance exhibited poorer attention.
			•	In participants with diabetes mellitus, this metabolic disorder predicted poorer function in attention and psychomotor speed.
Valcour et al. (2016) ³³ Liver Fibrosis Linked to Cognitive Performance in HIV and Hepatitis C	• 770 HIV-infected Women without Hepatitis C • 235 HIV-infected Women with Hepatitis C	• Cross-sectional • Standardized Neurocognitive Battery • Liver fibrosis severity was measured by aspartate aminotransferase to platelet ratio index (APRI).	•	Using APRI, 83% exhibited no/mild liver fibrosis; 14% exhibited moderate liver fibrosis; and 3% exhibited severe liver fibrosis.

WIHS Neurocognitive Comparing HIV-Infected and Uninfected Women

Study	Participants	Design & Procedure	Major Findings
	<ul style="list-style-type: none"> 301 Uninfected Women without Hepatitis C 73 Uninfected Women with Hepatitis C The average age was 46 years ($SD = 9.3$). 	<ul style="list-style-type: none"> A subset ($n = 303$) of the sample were administered a FibroScan (liver transient elastography). Regression models were used controlling for several covariates. 	<ul style="list-style-type: none"> Using APRI, moderate/severe liver fibrosis was associated with poorer fine motor skills, psychomotor speed, verbal learning, verbal memory, verbal fluency, and executive functioning. Using FibroScan, severe liver fibrosis was associated with poorer verbal fluency, attention, and executive functioning.

WIHS Brain Imaging Studies

Study	Participants	Design & Procedure	Major Findings
Liu et al. (2014) ⁵² Reduced Neural Specificity in Middle-aged HIV+ Women in the Absence of Behavioral Deficits	<ul style="list-style-type: none"> 15 HIV-infected women ($M_{age} = 50.1$; $SD = 4.4$) 13 Uninfected women ($M_{age} = 50.2$; $SD = 4.1$) Women were from the WHIS Washington, D.C. site. Women were matched on socioeconomic status, education, drug use, age, depression, and other factors that could impact neurocognition. The HIV-infected women did not have any obvious neurological complications and were medically stable (Mean CD4+ cell count = 702.5; median viral load = 20). 	<ul style="list-style-type: none"> Cross-sectional Face Discrimination Test was conducted outside of the scanner. Conventional fMRI using blood oxygen level-dependent signal served as an index of brain activation during a facial discrimination task in the scanner. 2 advanced fMRI techniques: <ol style="list-style-type: none"> fMRI-Rapid Adaptation, standard technique Local Regional Heterogeneity Analysis (H_{corr}), a novel fMRI technique Using the advanced fMRI techniques, neural specificity was assessed in the fusiform face area (FFA; temporal lobe) during an in-scanner facial discrimination task. A mixed design ANOVA on the behavioral face discrimination test and fMRI data; neuroimaging analyses were conducted. 	<ul style="list-style-type: none"> HIV-infected and uninfected women performed comparably on the behavioral performance of the face discrimination test outside the scanner. Using conventional fMRI responses to the in-scanner facial discrimination task revealed no group differences between the women. As defined as “an earlier recovery from adaptation” and narrow versus a broadened neural activation in the fusiform face area, the advanced fMRI techniques revealed neural specificity was decreased in HIV-infected women. This decreased neural specificity suggests that before behavioral neurocognitive changes or structural changes in the brain emerge, neuronal dysfunction is occurring in HIV-infected women.

WIHS Neurocognitive Comparing HIV-Infected and Uninfected Women

Study	Participants	Design & Procedure	Major Findings
Meyer et al. (2014) ¹¹ Crack Cocaine Use Impairs Anterior Cingulate and Prefrontal Cortex Function in Women with HIV Infection	<ul style="list-style-type: none"> • 10 HIV-infected Women currently using crack cocaine • 11 HIV-infected Women who formerly used crack cocaine • 9 HIV-infected Women who have never used crack cocaine • The average age was 44.1 years ($SD = 7.5$). • Women were from the WIHS Chicago site. • Women were excluded if they had: closed head injury with loss of consciousness, any open head injury, history of dementia, seizure disorder, schizophrenia, taking psychiatric medication that affects cognition, history of AIDS-related diagnosis, severe depressive symptomatology, any factors that would preclude a MRI exam (e.g., metal in the body, claustrophobia), etc. 	<ul style="list-style-type: none"> • Cross-sectional • Hopkins Verbal Learning Test • Standardized Neurocognitive Battery, with a special emphasis on verbal learning and verbal memory (HVLT-R) • fMRI using blood oxygen level-dependent signal served as an index for brain activation along with an in-scanner verbal memory task; neuroimaging analyses were conducted. • Group differences were examined using ANOVAs and chi-square when appropriate. For the neuroimaging analysis, full factorial models on drug use and condition (control/experimental) were run. 	<ul style="list-style-type: none"> • During the encoding task, left anterior cingulate cortex activation was higher in those who never used crack cocaine compared to those who were current and former users. • During the recognition task, bilateral dorsolateral prefrontal cortex and left dorsal medial prefrontal cortex was higher in those who never used crack cocaine compared to those who were current and former users. • Furthermore, poorer performance on the recognition task was correlated with lower activation in the left dorsolateral prefrontal cortex. • Thus, dysfunction in the prefrontal cortex and the anterior cingulate cortex may account for poorer verbal memory and verbal learning associated with crack cocaine use.
Rubin et al. (2015) ⁵³ Prefrontal Cortical Volume Loss Is Associated with Stress-related Deficits in Verbal Learning and Memory in HIV- infected Women	<ul style="list-style-type: none"> • 38 HIV-infected Women from the WIHS Chicago site • The average age was 43.89 years ($SD = 6.88$). • Women were excluded if they had: closed head injury with loss of consciousness, any open head injury, history of dementia, seizure disorder, self-diagnosis of psychosis, taking psychiatric medication that affects cognition, 	<ul style="list-style-type: none"> • Cross-sectional • Standardized Neurocognitive Battery, with a special emphasis on verbal learning and verbal memory (HVLT-R) • Structural MRI was used; neuroimaging analyses were used. • Stress was measured using the Perceived Stress Scale (PSS-10); lower stress levels were categorized by the lowest two tertiles <18, while higher stress levels were categorized by the highest tertile 18. 	<ul style="list-style-type: none"> • HIV-infected women with higher stress levels performed worse on measures of verbal learning and memory and had higher volume loss in the prefrontal cortex, and specifically in superior, medial, and inferior frontal gyrus and the parahippocampal gyrus (bilaterally). • Poorer verbal learning and memory were associated with volume loss in the superior, medial, and

WIHS Neurocognitive Comparing HIV-Infected and Uninfected Women				
Study	Participants	Design & Procedure	Major Findings	
Rubin et al. (2016) ⁵⁴ Elevated Stress Is Associated with Prefrontal Cortex Dysfunction during a Verbal Memory Task in Women with HIV	<ul style="list-style-type: none"> history of AIDS-related diagnosis, current hospitalization, any factors that would preclude a MRI exam (e.g., metal in the body, claustrophobia), etc. 36 HIV-infected Women from the WIHS Chicago site The average age was 43.72 years ($SD = 7.02$). Women were excluded if they had: closed head injury with loss of consciousness, any open head injury, history of dementia, seizure disorder, schizophrenia, taking psychiatric medication that affects cognition, history of AIDS-related diagnosis, current hospitalization, any factors that would preclude a MRI exam (e.g., metal in the body, claustrophobia), etc. 	<ul style="list-style-type: none"> Group differences between high and low stress were examined using multivariable linear regression controlling for age. Cross-sectional Standardized Neurocognitive Battery, with a special emphasis on verbal learning and verbal memory (HVLT-R) fMRI using blood oxygen level-dependent signal served as an index for brain activation along with an in-scanner verbal memory task; neuroimaging analyses were conducted. Stress was measured using the Perceived Stress Scale (PSS-10); lower stress levels were categorized by the lowest two tertiles <18, while higher stress levels were categorized by the highest tertile 18. PTSD Checklist-Civilian version Group differences between high and low stress were examined using multivariable linear regression controlling for age. 	<ul style="list-style-type: none"> HIV-infected women with higher stress levels performed worse on measures of verbal memory including strategic coding. During the verbal recognition task, women with higher stress levels displayed greater deactivation in the posterior cingulate cortex and the medial prefrontal lobe. Similar findings were observed when examining PTSD symptoms. 	inferior frontal gyrus (right hemisphere).

Abbreviations: APRI = Aminotransferase to Platelet Ratio Index; BMI = Body Mass Index; FFA = fusiform face area; fMRI = functional magnetic resonance imaging; HVLT-R = Hopkins Verbal Learning Test – Revised; MRI = magnetic resonance imaging; PSS-10 = Perceived Stress Scale - 10; PTSD = Post-traumatic Stress Disorder; SD, standard deviations; WIHS = Women's Interagency HIV Study.