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REVIEW

HIV, Cognition and Women

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Abstract Although the incidence of HIV in the United States is higher among men compared to women, the global proportion of women versus men who are infected has been approximately 50% since the late 1990s. Women have been under-represented in neuropsychological studies of HIV. A small number of studies have reported a significantly higher prevalence of neurocognitive impairment among HIV+ women compared to HIV− controls regardless of symptom status and with or without an AIDS diagnosis. Impairment was most evident on psychomotor tasks. The risk of neuropsychological impairment was increased among HIV+ women not on antiretroviral therapy. Age and depressive symptoms also increase neurocognitive risk. New neurocognitive studies of ovarian steroid hormones, PTSD and other psychiatric conditions are critical for addressing potential female-specific aspects of HIV-Associated Neurocognitive Disorder. Such studies will also address questions regarding involvement of the hippocampus and verbal memory, which may be of particular significance among HIV+ women.

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Epidemiology of HIV in Women

In the United States, the incidence of HIV is higher in men than women in every ethnic group. A recent report from the Centers for Disease Control indicates that in 2006, the incidence rate of HIV per 100,000 men versus women was 19.6 versus 3.8 among whites, 115.7 versus 55.7 among blacks, and 43.1 versus 14.4 among Hispanic/Latinos (CDC 2006). These estimates indicate that the rate among black women was nearly 15 times higher than that of white women and about four times higher than Hispanic/Latina women. Historically, the incidence of HIV among females increased more slowly than men until the late 1980s, decreased toward the early 1990s, and then remained relatively stable from 2002 (Hall et al. 2008). In 2007 HIV/AIDS rates among adults and adolescents in the United States were 38.8 per 100,000 among males and 12.9 per 100,000 among females, and by 2007 women accounted for 26% of people living with HIV/AIDS (CDC 2007). The Joint United Nations Programme on HIV/AIDS (UNAIDS) estimates that the global proportion of women versus men who are infected has been approximately 50% since the late 1990s, while coverage of antiretroviral treatment for women is higher than or equal to that of men (UNAIDS 2008). The proportion of women affected by HIV varies by global region. In sub-Saharan Africa, nearly 60% of those infected with HIV are women, whereas in Latin America, Eastern Europe/Central Asia, and Asia 30–35% of those infected with HIV are women.

Neurological Function in HIV+ Women Versus Men

It is not altogether surprising that our understanding of neurocognitive complications of HIV is based largely on studies involving men. Higher representation of men in these studies might reflect the higher incidence of HIV among men than women in the United States, the predominance of HIV among men who have sex with men (MSM) throughout most of the epidemic (except in the late 1980s and early 1990s), and the frequency of HIV among MSM and injection drug users (Hall et al. 2008). On the other hand, evidence indicates that women are still under-represented in neuropsychological studies of HIV. A review of 236 studies of neurological and neuropsychological complications of HIV indicated that from 1988 to 1997 only 31% of the studies included women with approximate representational parity, where representational parity meant that the representation of women was greater than or equal to 75% of the proportion of new cases of AIDS involving women (e.g., in 1988, to be classified as comparable, a study sample had to include at least 7.8% women, 7.8% being equal to 75% of new AIDS cases that were diagnosed among women in 1988 [10.4%]) (Fox-Tierney et al. 1999). More recent data on representational parity in HIV research is lacking. Challenges in recruiting minorities, particularly African American women, into research studies further limit our knowledge of neurocognitive complications of HIV/AIDS in women.

There have been some indications that women might be more vulnerable to the development of neuroAIDS. For example, in a retrospective review of 6,548 AIDS cases, the AIDS in Europe Study Group found that the risk of AIDS dementia complex (now termed HIV-associated dementia) in Europe from 1979 to 1989 was twice as high in women than men (Chiesi et al. 1996). On the other hand, a prospective study of 146 adult cases in the southeastern United States found no sex difference in neurocognitive complications (Robertson et al. 2004). Similarly, the Concerted Action on Seroconversion to AIDS and Death in Europe (CASCADE) study found that among 15,380 seroconverters studied from before the introduction of highly active antiretroviral therapy (HAART; pre-1997) to 2006, the risk of HIV-associated dementia was similar in men and women, with a relative risk among men versus women of 1.08 (95% Confidence Interval, 0.75 to 1.55) (Bouwman et al. 1998). Similarly, a small study of 49 HIV-1-seropositive women living in Puerto Rico found that rates of cognitive impairment (77.6%), asymptomatic cognitive impairment (32.7%), minor cognitive motor disorders (16.3%), and HIV-associated dementia (28.6%) were similar to rates found among men in the United States, Europe, and Australia (Wojna et al. 2006). It has been posited that earlier reports of a vulnerability to HIV-related dementia among women may reflect the lower education and higher proportion of injection drug use among HIV+ women than men and access to antiretroviral therapy (Lopez et al. 1999).

HIV-infected women may be at greater risk than HIV-infected men for cognitive decline due to the high prevalence of psychosocial and mental health problems, lower cognitive reserve due to lower education and premorbid intelligence, and increasing age (Basso and Bornstein 2000; Farinpour et al. 2003). Poverty, low literacy levels, substance abuse, poor mental health, barriers to health care services, and several relevant genetic risk factors and environmental exposures prevalent in predominantly minority urban dwelling women can also influence HIV+ women's vulnerability for acquisition and early development of a range of systemic diseases with known or hypothesized CNS effects, such as inflammatory conditions, hepatitis C and other viruses, cardiovascular disease, metabolic disorders including diabetes, and psychiatric illnesses. [See Paul and Martin-Thormeyer (this issue) for a review of effects of drug abuse and hepatitis C disease, two major comorbid conditions with HIV disease].

Neuropsychological Performance in HIV+ Women

Review of Individual Studies

Table 1 shows a summary of published neuropsychological investigations of HIV and neurocognitive performance involving all-female samples of participants. To date, six studies have reported on neuropsychological functioning in HIV+ women compared to controls using standardized clinical neuropsychological tests. Each of these studies involved a cross-sectional design and compared HIV+ women versus seronegative controls. The first of these studies was by Stern and colleagues (Stern et al. 1998), who compared performance of 17 asymptomatic HIV+ women and 14 matched controls on a battery of standardized clinical neuropsychological tests. They found no significant differences in neuropsychological performance, but noted the possibility that the tests administered were not necessarily adequately sensitive to any neurocognitive impairments among this small sample of women with no symptoms of disease. A related study by this team of investigators focused primarily on EEG but also noted no differences between the two groups on a continuous performance test (Costa et al. 1997).

The second study was a preliminary investigation by Mason and colleagues that targeted African American women with a history of drug use (Mason et al. 1998). The sample size included 10 HIV− women, 9 asymptomatic HIV+ women, 13 symptomatic HIV+ women, and 10

Table 1 Summary of neuropsychological studies in HIV+ women

Author (Year)	N (HIV+/−)	Study groups mean age (SD)	Cognitive test	Results
Stern et al (1998)	31 (17/14)	HIV−: 34.7 (6.1) HIV+: 35.7 (6.8)	Adaptive Rate Continuous Performance Test; Performance Assessment Battery; Simple and Choice Reaction Time; Paced Auditory Serial Addition Test; Rey-Osterreith Complex Figure; Color Trails 1 & 2; Grooved Pegboard; CVLT	HIV− = HIV+ All neurocognitive outcomes
Mason et al. (1998)	43 (33/10)[a]	HIV−: 40.1 (6.4) HIV+ asym: 35.8 (7.6) HIV+symp: 39.3 (7.4) AIDS: 35.3 (7.2)	WAIS-R Vocabulary subtest; Digit Span; Trail Making A & B; WMS-R Visual Reproduction; CVLT	HIV+ = HIV− > AIDS[b] Trail Making A and CVLT (lists 1–5, free recall short delay, cued recall short delay, free recall long delay, and cued recall long delay)
Durvasula et al. (2001)	237 (136/91)[c]	HIV-: 35.2 (9.5) HIV+: 36.1 (7.2) AIDS: 38.2 (8.9)	Verbal Memory Factor Score (WHO–AVLT); Psychomotor Factor Score (Symbol Digit Modalities Test; Cal CAP); Motor Factor Score (Grooved Pegboard)	HIV−> HIV+ Psychomotor factor score
Richardson et al. (2002)	231 (149/82)[d]	HIV−: 34.6 (8.8) HIV+: 36.3 (7.5) AIDS: 37.7 (7.2)	Color Trails 1 & 2; WHO/UCLA Auditory Verbal Learning Test; Grooved Pegboard; Symbol Digit Modalities Test; Visual Reproduction Subtest of the Wechsler Visual Memory Scale-Revised; Mental Alternations Test	HIV−> HIV+ Color Trails 2; Grooved Pegboard (nondominant)[T]; Mental Alternations; Symbol Digit
Richardson et al. (2005)	220 (145/75)[e]	HCV−/HIV−: 33.0 (8.6) HCV+/HIV−: 37.3 (9.2) HCV−/HIV+: 33.8 (7.2) HCV+/HIV+: 39.6 (6.5)	Color Trails 1 & 2; WHO/UCLA Auditory Verbal Learning Test; Grooved Pegboard; Symbol Digit Modalities Test; WMS-R Visual Reproduction; Mental Alternations Test	HIV+ > HIV− Risk of neuropsychological impairments
Maki et al. (in press)	63 (51/12)	HIV−: 43.37 (6.79) HIV+: 42.92 (5.52)	Hopkins Verbal Learning Test; Rey Osterreith Complex Figure Task; Stroop; Letter-Number Sequence Test	HIV− > HIV+ HVLT Learning and Delayed Recall; Rey-Osterreith Copy and Immediate and Delayed Recall; Letter-Number Sequence

WAIS-R Wechsler adult intelligence scale-revised; *WMS-R* Wechsler memory scale-revised; *CVLT* California verbal learning test; *WHO-AVLT* world health organization auditory verbal learning test; *Cal CAP* California computerized assessment package; *HCV* hepatitis C virus; *HVLT* Hopkins verbal learning test

[a] Of the 33 HIV+ women, 10 were asymptomatic (CDC category A), 13 were symptomatic (CDC category B) and 10 were diagnosed with AIDS (CDC category C)

[b] Significant differences were found between groups for verbal memory errors, verbal memory recognition, and visual memory but were due to differences between groups on the Beck Depression Inventory

[c] Of the 136 HIV+ women, 91 were without AIDS and 45 were diagnosed with AIDS. See Text for primary analysis, a multivariate analysis of factor scores

[d] Of the 149 HIV+ women, 108 were without AIDS and 41 were diagnosed with AIDS

[e] Of the 75 HIV− women, 48 had hepatitis C virus (HCV) and 27 did not. Of the 145 HIV+ women, 70 had HCV and 75 did not

[T] Statistical trend

women with AIDS. Women with AIDS performed significantly worse than women in the other subgroups on tests of psychomotor speed (Trail Making Test Part A), verbal learning on California Verbal Learning Test (CVLT), and verbal recall on the CVLT (i.e., short- and long-delayed free and cued recall). These impairments were not related to drug use or depressive symptoms. Performance differences were not observed between other groups, and no differences were found on tests of figural memory (Visual Reproduction subtest of the Wechsler Memory Scale-Revised; WMS-R) or immediate or working memory (Digit Span). Although the sample size was small, these preliminary results suggested that there were no detectable cognitive impairments in the early stages of HIV infection, even in relation to drug use or depressive symptoms.

The third study focused on baseline cognitive function among a sample of 237 community-dwelling HIV+ and HIV− women participating in the UCLA/Drew Women and Family Project (WFP)(Durvasula et al. 2001). The sample included 91 HIV− women, 91 HIV+ women without AIDS[1], and 45 women with AIDS. The racial/ethnic distribution of the sample was approximately evenly distributed among African American, White, and Latina women. Alcohol use, drug use, and psychological distress (i.e., depression and anxiety) were used as additional predictors of neuropsychological function. A principal components analysis yielded three factors—verbal memory, psychomotor speed, and motor speed. (See Table 1 for individual tests). Multivariate analyses revealed that HIV+ serostatus was a significant predictor of slower psychomotor speed, but not of the other three factors. Depressive symptoms and African American ethnicity were strong predictors of worse verbal memory, alcohol use and education were strong predictors of psychomotor slowing, and drug use, older age and African American ethnicity were strong predictors of motor slowing. Overall, the finding that that HIV seropositivity predicts psychomotor slowing paralleled studies in men and was consistent with the "subcortical" model of HIV-associated neurocognitive impairment observed prior to the introduction of highly active antiretroviral therapy (HAART).

The fourth study reported on neurocognitive function among 82 HIV− and 149 HIV+ women enrolled in the Women's Interagency HIV Study (WIHS) (Richardson et al. 2002). The HIV+ group included 41 women with AIDS-defining (<200) CD4 counts and 108 women without an immunologic AIDS diagnosis. Consistent with the earlier report by Durvasula and colleagues (2001), deficits among the HIV+ participants were most evident on psychomotor measures such as the Symbol Digit Modalities Test and the Color Trails Test-2, $p<.05$ for each comparison. HIV+ women with or without an AIDS diagnosis showed a significantly higher frequency of abnormal neuropsychological protocols overall compared to controls. Critically, the risk of NP impairment was over two times higher for women not receiving than receiving antiretroviral therapy but no higher for HIV+ women on therapy compared with HIV− controls. These effects survived multivariate analyses controlling for multiple potential confounding factors, including head injury and history of substance dependence. These results support an earlier report by Cohen et al. (2001), who studied longitudinal NP performance among 126 antiretroviral naïve HIV+ women at baseline testing prior to initiation of HAART. They found that neurocognitive performance among women receiving HAART improved significantly at 18 month follow-up compared to baseline testing but neuropsychological performance of an untreated control group declined.

Consistent with Durvasula et al. (2001), Richardson et al. (2002) found that both psychological distress as indexed by the Center for Epidemiological Studies Depression Scale (CES-D) and older age were associated with an increased risk of neuropsychological impairment, and these effects persisted in the multivariate model. Psychological distress does not account completely for neurocognitive impairment among HIV+ individuals (Bornstein et al. 1993; Heaton et al. 1995). However, given the higher prevalence of depression among HIV+ women compared with HIV+ men (Semple et al. 1996; Wisniewski et al. 2005), one might speculate that the effects of depression on neuropsychological function are more pervasive among HIV+ women.

A later study with the WIHS cohort evaluated neurocognitive effects of hepatitis C among HIV+ and HIV− women (Richardson et al. 2005). In that study the risk for cognitive impairment was significantly greater among women coinfected with HIV and hepatitis C virus than in groups of monoinfected or uninfected participants but only among younger subjects.

The sixth study came from the WIHS-Chicago Consortium and was aimed at obtaining preliminary data on the integrity of delayed verbal episodic memory and its neural correlates in 51 HIV infected and 12 matched HIV− controls (Maki et al. in press). Participants completed the Hopkins Verbal Learning Test (HVLT) as part of a longer neurocognitive battery. HIV+ women performed significantly more poorly compared with HIV− controls on learning and delayed recall, as well as measures of visual episodic memory and working memory. A subset of 11 women (7 HIV+) underwent functional magnetic resonance imaging (fMRI) during encoding and recognition phases of a delayed episodic verbal memory task. Neuroimaging findings revealed decreased activation in left hippocampal

[1] The majority of AIDS participants in these studies met criteria for the diagnosis because of a CD4 count of<200 rather than opportunistic conditions such as pneumocystis carinii pneumonia (PCP).

function during verbal encoding and increased activation in the right hippocampal function during verbal retrieval. These functional differences in the hippocampus correlated with performance on the HVLT, such that the alterations observed in HIV+ women at encoding and retrieval were each associated with worse verbal memory on the HVLT. Additionally, self-reported illicit drug use within the previous six months showed a nonsignificant trend ($p<.10$) as an independent predictor of HVLT scores among HIV+ women, raising the possibility of independent and additive effects of drugs of abuse and HIV on verbal memory.

In summary, initial studies of neuropsychological performance among all-female participants reported no evidence of impairment among HIV+ women. However, the sample sizes were small. The larger studies (Durvasula et al. 2001; Richardson et al. 2002) reported a significantly higher prevalence of cognitive impairment among HIV+ women compared to HIV− controls regardless of symptom status and with or without an AIDS diagnosis. Impairment was most evident on psychomotor tasks. Additionally, the Richardson findings showed that although both age and psychological distress contributed to risk of neurocognitive impairment, effects of serostatus on neuropsychological performance were driven primarily by antiretroviral therapy status at testing (Richardson et al. 2002). The risk of neuropsychological impairment among HIV+ women on therapy was no higher than the risk for the control group, while the risk was two and a half times as high for the untreated group.

It must be emphasized that multiple comorbid disorders with potential confounding effects on neuropsychological function, including drug use, head injury and depression, were highly prevalent among both HIV+ and HIV− groups in these studies. Approximately 28% of HIV− participants in the Richardson study showed neuropsychological impairment (Richardson et al. 2002), in contrast with the 17% rate among the higher functioning HIV− controls participating in the HNRC 500 study (Heaton et al. 1995). Consequently, some additional, subtle differences in neurocognitive performance between seronegative and seropositive subjects may be difficult to detect without comprehensive neurocognitive testing of larger sample sizes.

Sex Differences in Cognitive Function in HIV

Only a few published studies directly compared the neurocognitive performance of men and women with HIV. Wisniewski and her colleagues administered two neurocognitive measures to a sample of men and women of varying serostatus and history of injection drug users and reported an interaction between sex and serostatus such that infected men performed the worst, and uninfected women performed the best, on a test of verbal memory (Wisniewski et al. 2005). A recent study reported that HIV+ men ($n=57$) and women ($n=31$) had cognitive impairment rates of 52% and 55% respectively, compared to 0% in HIV− men ($n=18$) and women ($n=16$); however, the serostatus findings were confounded by significantly higher prevalence of substance use disorders among HIV+ participants compared to controls (75% of HIV+ versus 0% of HIV−) (Failde-Garrido et al. 2008). Although there was no direct statistical test comparing the sexes in terms of impairment within select domains of cognitive function, the largest differences between the sexes were in verbal memory for texts, with a higher proportion of females showing impairment (42%) compared to men (<10%). Other studies have not found sex to be a significant predictor of cognitive impairment in HIV+ individuals (Pereda et al. 2000). The literature on sex differences in cognition is limited by small sample sizes.

Importantly, none of the previous studies of HIV and neurocognitive function among all-female or mixed samples of men and women have examined the effects of female-specific characteristics or of highly prevalent comorbid factors on neurocognitive function. In the following section we include known and hypothesized effects of ovarian steroid hormones and post traumatic stress on neurocognitive function that provide unique opportunities to characterize HIV-associated neurocognitive disorder and its potential mechanisms among women.

New Directions for NeuroAIDS Research in Women

Memory and the Hippocampus

Until recently, the functional integrity of medial temporal systems in neuroAIDS has received relatively little attention despite considerable evidence of hippocampal injury associated with human immunodeficiency virus (Fujimura et al. 1997; Wiley et al. 1998). Recent studies of neuroAIDS and cognition have expanded the focus of inquiry beyond integrity of striatal-prefrontal systems to include neurocognitive functions dependent on the integrity of circuitry involving parietal cortex and hippocampus (Castelo et al. 2006; Moore et al. 2006; Olesen et al. 2007). For example, Moore and colleagues reported that postmortem regional neurodegeneration of hippocampus and putamen each contributed unique variance in prediction of antemortem HIV-associated neurocognitive status (Moore et al. 2006). Similarly, an fMRI study by Castelo et al. (2006) reported abnormally lower hippocampal activity during a memory encoding task among HIV+ participants than controls.

Numerous basic science studies demonstrate sex differences in, and sex hormone influences on, hippocampal structure and function and hippocampal-dependent memory,

with better memory and function associated with the female sex and with high levels of estrogen (Bethea et al. 1998; Farr et al. 2000; Gibbs 1999; McEwen and Woolley 1994; Pan et al. 1999; Singh et al. 1994; Toran-Allerand et al. 1992; Woolley et al. 1990; Woolley and McEwen 1994). Human studies also demonstrate a sex difference in favor of women in episodic verbal memory, a hippocampal-dependent cognitive function (Kramer et al. 1988, 2003). There is evidence of enhanced hippocampal metabolism in women compared to men, but after midlife (at the time of menopause) women no longer show this enhancement (Murphy et al. 1996). Estrogen therapy is also associated with enhanced hippocampal blood flow in women (Maki and Resnick 2000). Thus, basic science and clinical studies underscore the importance of considering gender and sex hormones in studies of hippocampal function.

Studies of verbal memory performance have frequently shown deficits in HIV+ individuals compared with HIV− controls (e.g., White et al. 1997; Woods et al. 2005) but typically have not focused specifically on associations with sex or with hippocampal integrity. Findings from the site-specific WIHS study (Maki et al. in press) provide initial evidence that verbal episodic memory deficits are evident in HIV+ women and correlate with impaired left hippocampal activation at encoding and impaired right hippocampal activation at retrieval (Maki et al. in press). There was a nonsignificant trend for illicit drug use predicting poorer verbal memory. Based on these preliminary data, future studies should investigate the individual and interactive effects of HIV infection and drugs of abuse on hippocampal function. Future studies should also focus on the possibility that the hippocampus contributes to the disruption of a larger neural network, possibly involving prefrontal cortex, which drives HIV-associated memory impairments.

Drug and Alcohol Addiction

Questions regarding the integrity of medial temporal memory systems in drug abuse are of critical interest because the hippocampus and amygdala have been implicated as critical neural substrates of the learning and memory component of addiction pathophysiology (Goldstein and Volkow 2002) and in processes underlying drug craving and relapse. Further, there is consistent evidence of sex differences in different components of the addictive process. Compared with men, women escalate their drug use and progress to addiction more rapidly, experience more severe withdrawal, and are more prone to relapse (Becker and Hu 2008). Further, the underlying neural correlates of addictive behavior observed among women are in some cases distinct or even opposite of effects observed in men (e.g., Wang et al. 2007). For example, a recent PET study (Kilts et al. 2004) showed that cue induced craving was associated with increased amygdala activation in males but decreased activity in women, suggesting that new relapse prevention strategies are necessary for effective treatment of addiction in both HIV+ and HIV− women (e.g., Wetherington 2007). These reports provide compelling evidence that studies of drug abuse and HIV+ on neurocognition in women will have critical translational implications for studies of substance abuse treatment as well as management of HIV disease (Cahill 2006).

The relationship between hazardous alcohol use and cognition in HIV+ women is also of interest. According to a recent prospective study from WIHS, the prevalence of hazardous alcohol use in women with HIV is about 1 in 5 (Cook et al. 2009). Neuroimaging studies demonstrate that alcohol abuse and HIV interact to negatively influence both brain structure and neurocognitive performance. For example, a recent diffusion tensor imaging study demonstrated that individuals with AIDS and alcoholism had abnormalities in white matter integrity in the corpus callosum and related fibers that were approximately two standard deviations worse than other HIV-infected subgroups (Pfefferbaum et al. 2007). Alcohol use and HIV also interact to negatively influence structural brain volume outcomes, including ventricular enlargement and callosal dysmorphology (Pfefferbaum et al. 2006), neurocognitive function (Sassoon et al. (2007)) and quality of life (Rosenbloom et al (2007)) , although there are few studies examining the interactive effects of sex and alcohol on cognition in HIV+ individuals,. Evidence from healthy young adults shows either no sex difference in the effects of binge drinking on cognition, or a greater disadvantage among men (Hartley et al. 2004). Evidence from WIHS suggested no impact of alcohol use on episodic memory, mental speed or mental set shifting in HIV+ women, but sample sizes were limited (Maki et al. in press).

Ovarian Steroid Hormones

In healthy women, ovarian steroid hormones influence important aspects of psychological health, including depression (Cohen et al. 2006a, b; Freeman et al. 2004) and cognitive function (Maki 2005). Hormonal fluctuations across the menstrual cycle are associated with changes in cognitive function, particularly on tests that show average sex differences (Maki et al. 2002). The immediate cognitive effects of menopausal declines in ovarian hormones are modest; the transition from premenopausal to perimenopausal stage is associated with slight decreases in verbal fluency (Fuh et al. 2005), but not working memory or perceptual speed (Meyer et al. 2003). Although there is little evidence for an effect of reproductive stage per se on cognition, menopausal symptoms—particularly mood changes, sleep deprivation, and hot flashes—can have a negative impact on cognition. In our studies in healthy

midlife women, vasomotor symptoms (measured objectively with ambulatory monitors) and sleep deprivation, independently predict lower memory performance (Maki et al. 2008). Furthermore, the long-term cognitive consequences of ovarian hormone declines at menopause may be significant, as indicated by increased risk of dementia associated with early surgical menopause (Rocca et al. 2007) and evidence that use of hormone therapy early in the menopause (though not later) may protect against cognitive decline (see Maki 2006, for a review).

The cognitive changes associated with the menopausal transition and onset of menopausal symptoms may be most evident in women with compromised cognitive performance, including HIV+ women. Despite the wealth of literature on normative changes in women's health across the menopausal transition, very little is known about the natural history of menopause in HIV+ women (Kojic et al. 2007), particularly with regard to psychological and cognitive changes. Cross-sectional studies indicate that compared with HIV− women, HIV+ women report more menopausal symptoms (Ferreira et al. 2007; Miller et al. 2005) and may have an earlier age at menopause (Ferreira et al. 2007; Schoenbaum et al. 2005). There are no longitudinal studies tracking symptoms in HIV+ women as they transition through the menopause. A Chicago pilot study indicated that ratings of bothersome hot flashes were negatively associated with visual memory and executive function, and these effects remained significant after controlling for age, education, CD4 count, and depression scores (Sundermann et al. 2007). No significant relationships were found between hormone levels and cognition. These findings provide preliminary insights into the type of cognitive disturbances associated with menopausal symptoms in HIV women and suggest that interventions that lower vasomotor symptoms may confer cognitive benefit.

Stress and Post-Traumatic Stress Disorder

A growing body of research demonstrates that earlier age of trauma, chronic repeated stress exposures, and intensity of acute stressors can lead to profound physiological and psychological consequences (Gunnar and Quevedo 2007). Notably, a history of childhood sexual or physical trauma, intense acute stress, and PTSD are associated with an increased risk of HIV-related morbidity and mortality (Evans et al. 1995; Evans et al. 1997; Leserman 2003a, b, 2002, 2005). PTSD is also a strong predictor of injection drug use and risky sexual behavior, particularly in women (Hutton et al. 2001; Plotzker et al. 2007). Investigations from the Women's Interagency HIV Study have demonstrated that early childhood abuse leads to later domestic violence, which may increase the risk of behaviors leading to HIV infection (Cohen et al. 2000), and that childhood abuse is associated with lack of adherence to HAART (Cohen et al. 2004).

An increasing number of studies identify stress-related structural and functional alterations within the central nervous system, particularly within the corpus callosum, caudate, anterior cingulate, medial prefrontal cortex, and hippocampus (Bossini et al. 2007; Bremner 2007; Cohen et al. 2006a, b; Kitayama et al. 2007, 2006; Shin et al. 2006). These alterations are associated with low verbal and visual learning and memory performance and impaired executive functions (Clark et al. 2003; Jelinek et al. 2006; Kim and Diamond 2002). Structural neuroimaging studies demonstrate thinning of the corpus callosum in non-demented AIDS patients compared to seronegative controls, and CD4 decline is associated with callosal thinning in anterior regions connecting frontal areas with greatest cortical atrophy (Thompson et al. 2006). Therefore, given the cognitive and brain alterations evident in HIV infection, women living with HIV, who also have a history of childhood trauma, acute stress, and/or PTSD as an adult, may be especially susceptible to cognitive and psychological dysfunction due to the additive or synergistic effects of HIV and acute/chronic stress. In men, acute stressful life events are known to contribute to poor executive function, attention, and processing speed (Pukay-Martin et al. 2003), yet the additive or synergistic relationship between HIV and stress on cognition has yet to be systematically examined in women. Thus, an important direction for future HIV studies in women is the impact of stress and PTSD on cognitive function.

Functional Consequences of Cognitive Deficits in HIV

Given the increased survival time for persons living with HIV/AIDS, management concerns have shifted toward issues of daily function and other life tasks in the context of a chronic disease. Recent literature has shown that neurocognitive deficits have significant implications for persons living with HIV/AIDS to maintain employment, manage finances, perform driving tasks safely, adhere with HAART regimens and abstain from high risk sexual and injection risk behaviors (Heaton et al. 1996; Hinkin et al. 2002; Marcotte et al. 1999). Consequently, the significance of neurocognitive functioning continues in the era of HAART. Relatively little is known about the impact of neurocognition on functional outcomes such as caregiving and employment. It is unclear how neurocognitive decline associated with HIV (and/or aging) would affect women's ability to care for children and how the potential stress associated with caregiving within the context of living with a chronic illness might affect these women's lives. This area is ripe for investigation, given the paucity of literature in this area.

Summary

Evidence from initial investigations indicates that HIV+ women are at increased risk for neuropsychological impairment compared to controls. There is a pressing need for more large-scale studies of neuropsychological function in women with HIV. Such studies are needed to address neurocognitive complications of HIV in women, to identify factors that contribute to these complications, and to develop possible treatments for some of the factors contributing to cognitive dysfunction in women with HIV.

The Women's Interagency HIV Study (WIHS) has recently implemented longitudinal neuropsychological testing in a cohort of over 1,600 HIV+ and at-risk, HIV− women. A strength of the WIHS is that the cohort is quite representative of AIDS and HIV cases reported among women in the United States (Barkan et al. 1998). More than half of WIHS participants were living below the federally defined poverty level and 75% are African-American or Hispanic. At entry, women ranged in age from 16 to 73 years. Among HIV+ women, 6% were under age 30, 29% age 20–29, 41% age 40–49 and 25% over age 50. The cohort, therefore, represents an aging cohort, with many women transitioning through the menopause. This study should enable the characterization of patterns of cognitive change in relation to disease progression and investigation of factors that might affect women in particular, including early childhood abuse, post-traumatic stress disorder, and menopausal factors. Further, the WIHS aims to examine the impact of cognitive functioning on functional abilities of particular importance to women, including parenting efficacy. Additional studies could focus on genetic risk factors for cognitive dysfunction in HIV and neuroimaging correlates of cognitive impairments in HIV. Studies such as the WIHS are uniquely positioned to move forward with new questions regarding aspects of HAND that are unique to women.

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